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ERRATA

ERRATA
ARTICLE

Performance of a Career Development and Compensation Program at an Academic Health Science Center

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ABSTRACT

OBJECTIVE. The academic physicians of our department developed a novel Career Development and Compensation Program to outline job expectations, enhance career development, and provide a peer-review process to assess performance. The Career Development and Compensation Program was founded on the principle that sustained achievement in education, clinical care, or research should be valued, supported, and rewarded in an equivalent manner and that reward for clinical work should not be limited by the focus of the university on research and education. The objective of this study was to determine whether the principles of the Career Development and Compensation Program were sustained during the initial 7 years of its implementation.

METHODS. The outcome of the 7 triennial reviews that occurred from 1999 to 2005 was evaluated. For the purposes of some analyses, physicians were classified as predominately clinical (clinician-specialists and clinician-teachers), predominately education (clinician-educators), or predominately research (clinician-investigators and clinician-scientists).

RESULTS. Each of the job profiles had a similar probability to increase a level within the Career Development and Compensation Program at the time of triennial review. Similarly, all 5 job profiles had a similar rate of increase in their level in relation to the total number of years of experience at an academic health science center. Neither the university academic rank nor gender of the physician affected the probability of increasing a level at the time of the triennial review.

CONCLUSION. The peer-reviewed Career Development and Compensation Program recognizes sustained achievement in each area of education, clinical care, and research in an equivalent manner with no detectable effect of academic rank or gender.

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Key Words
career development, education, professional competence, clinical competence, pediatrics

Abbreviations
AHSC—academic health science center
CDCP—Career Development and Compensation Program
PCP—Paediatric Consultants Partnership
AFP—alternative funding plan
JP—job profile
FT—full-time
CAC—Clinical Advisory Committee
MEAC—Medical Education Advisory Committee
RAC—Research Advisory Committee
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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics
In the past decade, we have attempted to answer the following question: How could an academic physician’s career development be supported and rewarded within the setting of an academic health science center (AHSC)? Frequently, an academic physician’s career advancement is linked predominately, if not exclusively, to university-based benchmarks. This presents a significant challenge. Academic physicists at an AHSC must deliver outstanding scholarly clinical care, in addition to research and education, yet research and education usually are the only parameters that are valued by universities and their academic promotion committees. Also, the absence of a formalized career development strategy can hinder the progress of many academic physicists. This may result in the loss of talented and extensively educated physicians who have not been guided in their career development as to how best to meet the expectations of their peers. Our department developed and implemented the Career Development and Compensation Program (CDCP) to enable an academic physician’s career to be developed and rewarded fairly. This CDCP is applicable to all academic medical departments wherein there is a centrally administered financial base that supports a portion or all of the physician’s income.

Our department’s academic physicians work within a single-payer universal health care system that is comparable, in many ways, to a single-payer health maintenance organization. One difference is that the ultimate governance is provided by the Ontario Ministry of Health, which is funded through taxation, and contrasts to a for-profit or not-for-profit private health care organization. In 1990, our partnership (Pediatric Consultants Partnership [PCP]) entered into an alternate funding plan (AFP) wherein its fee-for-service income, obtained from the Ontario Hospital Insurance Plan, was replaced by block funding from the Ontario Ministry of Health. A key component of the AFP agreement was the recognition by the ministry that the fees that previously were received by the PCP not only had resulted in the provision of clinical care but also had supported its research and educational activities. As a result, the PCP, the Hospital for Sick Children, the University of Toronto, and the Ministry of Health agreed that the AFP was to be allocated to clinical care (50%), research (30%), and education (20%). Although the agreement was renewed in 1998 and 2001, with concomitant changes in the level of financial support and some other modifications, the fundamental principles remain intact.

In 1996, the PCP implemented the following job profiles (JP) to define more clearly the role of each physician:

- Clinician-teacher: major (50%–65%) commitment to provide, advance, and promote clinical care; usually significant bedside teaching and some research activities
- Clinician-scientist: major (75%) commitment to research; participate in clinical care and education
- Clinician-investigator: significant (50%) research commitment and contributes to educational and/or research
- Clinician-administrator: major (>50%) administrative responsibilities and contributes to clinical care, education, and research
- Clinician-specialist: predominate (≥70%) commitment to provide, advance, and promote excellence in clinical care with contributions to education and/or research

By 1998, the PCP had established benchmarks to guide career development and a peer-review system to assess the performance of the individual full-time (FT) pediatrician. The development and subsequent implementation of the CDCP in 1998 has been published and is available at www.sickkids.ca/paediatics.

The CDCP was founded on the principle that sustained achievement in education, clinical care, or research should be valued, supported, and rewarded in an equivalent manner and that reward for clinical work should not be limited by the university’s focus on research and education. The goal of this study was to determine whether this principle was sustained during the 7 years during which the CDCP was used to guide and reward career development in our department.

METHODS

Site of the Study

The Hospital for Sick Children is a health care, teaching, and research center that is dedicated exclusively to children and is affiliated with the University of Toronto. Most of its patients are referred for tertiary care. In 2004–2005, there were 13,819 admissions, 99,037 inpatient days, 47,585 emergency department visits, 165,016 outpatient visits, and 127,149 diagnostic visits conducted on site. The Department of Pediatrics provides approximately two thirds of all physician care to these patients, holds approximately $20 million CDN in external research funding, and is responsible for the education of 790 medical students and >200 residents and fellows each year.

The CDCP

At the time of the initial implementation of the CDCP or when hired, the physician was assigned to 1 of the 6 JPs. The assignment was based on the needs of the division and on the individual’s training and achievement and
was subject to final approval by the division head and chief of the department.

The CDCP divides the career of a pediatrician at a leading AHSC into 3 potential phases that are characterized by increasingly sophisticated incremental performance. These different phases of professional growth are divided into 8 levels, each of which is linked to a rate of remuneration that reflects the physician’s stage of career development and the market value of various subspecialties (Table 1). If the physician was just beginning his or her academic career, then he or she was assigned to level I; however, if he or she was recruited at a later stage of his or her career, then he or she was assigned to an appropriate higher level.

The department’s Clinical, Medical Education, and Research Advisory Committees (CAC, MEAC, and RAC, respectively) developed “Categories of Achievement” for clinical care, education, and research, respectively. These became the “benchmarks” that were used both as a guide for career development and for the evaluation of the individual physician’s performance. Evaluations and feedback included the following:

- an annual review, coupled with career development advice from the physician’s division head and department chief
- career development from the CAC, MEAC, RAC, mentors, and advisors
- a major review every 3 years, termed the “triennial review,” that serves as the basis for movement through the levels and additional career guidance

One third of all departmental physicians undergo a triennial review process each year (Fig 1). The physician creates and submits separate clinical, medical education, and research dossiers to the CAC, MEAC, and RAC. Each committee, using a peer-review process that is comparable to a grant review committee, assigns a “category of achievement” on the basis of the previously developed benchmarks. The resultant confidential peer evaluation of their performance then is reviewed by the chief of pediatrics, who places the category of achievement evaluation into context by considering other factors. These factors include the number of years on staff at an academic health science center; his or her JP; the amount of time allocated for clinical, education, and research activities; and other pertinent information to decide whether the pediatrician’s level should be altered.

Study Population
We reviewed the results of all physicians who underwent the 7 triennial reviews that had occurred from 1999 to 2005. Overall, there were 181 physicians (100 male and 81 female) who had 1 or more triennial reviews. For the purposes of some analyses, physicians were classified as predominately clinical (clinician-specialists and clinician-teachers), predominately education (clinician-educators), or predominately research (clini-

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**TABLE 1** Remuneration Grid for Consultant Pediatricians and Subspecialists

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early</th>
<th>Middle</th>
<th>Top 15%</th>
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<tr>
<td></td>
<td>I</td>
<td>I+</td>
<td>I-II</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>W</td>
<td>W+10</td>
<td>W+20</td>
</tr>
<tr>
<td>Subspecialist</td>
<td>X</td>
<td>X+10</td>
<td>X+20</td>
</tr>
<tr>
<td>Hematologist-oncologist</td>
<td>Y</td>
<td>Y+10</td>
<td>Y+20</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>Z</td>
<td>Z+10</td>
<td>Z+20</td>
</tr>
</tbody>
</table>

W, X, Y, and Z refer to different starting base compensation rates in $1000 Canadian and reflect market forces within North America.
cian-investigators and clinician-scientists). Because we had a very small number \((n < 4)\) of clinical administrators at any one time, they were excluded from the analyses.

Although remuneration within the CDCP is not increased on academic promotion within the Faculty of Medicine at the University of Toronto, we determined whether promotion in the CDCP was affected by professorial rank. We also reviewed the “primary platform” for promotion of departmental faculty from 2002 to 2006 inclusive to determine whether the university emphasis on research and education would negatively influence the value that is placed on scholarly clinical care in the CDCP. The primary platform for academic promotion can be 1 of creative professional activities, education, or research (see www.facmed.utoronto.ca/English/Policies-and-Guidelines.html).

**Statistical Analyses**

Descriptive data were summarized using proportions and mean/SD, as appropriate. The probability of advancement in the CDCP across JPs was computed and compared using a \(\chi^2\) test. Furthermore, logistic regression models were used to assess potential relationships between the probability of advancement in the sublevels and demographic and other subject-specific characteristics, such as gender, age, and university academic rank. The relation between the number of years at an AHSC and the level for each JP was quantified using linear regression. Differences between the slopes of the lines for the various JPs were compared by fitting an analysis of covariance model and testing for an interaction effect between JP and number of years at an AHSC. All analyses were conducted using SAS 9.1 (SAS Institute Inc, Carey, NC).

**RESULTS**

A central principle of the CDCP is that achievements in clinical care, education, and research are valued equally. A career development and compensation model that is based on this principle predicts that equivalent achievements in these scholarly domains should result in an equivalent probability of advancement. To investigate whether this principle was sustained during 7 years of implementation of the CDCP, we compared the probability of advancement in the CDCP across JPs. We were unable to detect a statistically significant difference in the probability of physicians who were classified as predominately clinical (clinician-specialists and clinician-teachers), predominately education (clinician-educators), and predominately research (clinician-investigators and clinician-scientists) in their ability to receive an increase in their level at either their first or their second triennial review (Fig 2).

If JPs are equally valued within the CDCP, then each
JP should have a comparable relation between the number of years at an AHSC and the level achieved within the CDCP. In other words, physicians with different JPs should increase their level at the same rate. To determine whether this was true, we reviewed the 103 FT physicians (58 male, 45 female) who worked exclusively at our AHSC, were present in the department during the 2005–2006 academic year, and had undergone at least 1 triennial review. We first calculated the number of years that the physician had spent at any AHSC subsequent to the initial appointment as a FT academic physician (14.6 ± 8.02 SD years). We then determined the relation between the number of years at an AHSC and the level for each JP (clinician-teacher: n = 28; clinician-educator: n = 9; clinician-scientist: n = 30; clinician-investigator: n = 19; clinician-specialist: n = 17). There was no statistically significant difference between the slopes of the lines for the various JPs, which indicated that members of each JP increased their level at the same rate (Fig 3).

Because others have found that gender had effects on academic advancement,4–6 we determined whether advancement in the CDCP was affected by gender. Comparison of rates advancement in either the first or the second triennial review did not reveal a statistically significant difference between male and female members of the department (Fig 4).

Although the CDCP was designed to recognize achievements in clinical care, it is possible that the university emphasis on research and education would negatively influence the value that is placed on scholarly clinical care in the CDCP. Our results, however, demonstrated that the probability of increasing a level at a triennial review was not related to academic rank at either the first (Fig 5A) or the second triennial review (Fig 5B). From 2002 through 2006 inclusive, 43 physicians were promoted from assistant to associate professor or associate professor to professor within the Department of Pediatrics of the Faculty of Medicine. Their primary platforms for promotion (see www.facmed.utoronto.ca/English/Policies-and-Guidelines.html) were education (23%), research (44%), and creative professional activities (32%).
DISCUSSION

An academic department cannot be successful without the requisite financial base and infrastructure. In addition, success will be achieved only when there also is a highly skilled faculty who use the available resources in an effective manner to achieve their own and the department’s goals and objectives. As such, it is our contention that a department must provide mentorship and career development to its faculty, clearly define its goals and objectives, use fair and transparent processes to evaluate the performance of its faculty, provide constructive feedback to the physician, and link the physician’s rewards to these performance measures. The CDCP is our department’s attempt to address some of these issues, and the long-term follow-up evaluation described in this article provides evidence that it has achieved its goal, at least in part. Specifically, regardless of the academic physician’s primary role within the AHSC, his or her career development was supported, successfully developed, and rewarded.

Medical school faculty physicians who work at an AHSC must carry out clinical care, education, research, and administrative activities. A variety of approaches have been taken to document the relative activities, for example assigning a “relative value” to each of these 4 activities or just 1 of these activities, such as education. How this information was used in the long term or how successful this approach has been is uncertain, because we are unaware of outcome studies using this relative-value approach.

Our department developed the CDCP from 1996 to 1997, and the present study provides outcome information for our faculty who were evaluated by our department’s various parameters. Similar to other groups, we included both quantitative and qualitative outcomes measures. One of the key design principles was that each of the JPs would be rewarded equally. This not only should encourage excellence in each of the clinical, education, and research arenas but also should enhance the morale of the department. As such, we designed the CDCP so that the rate of remuneration did not depend on the JP but rather on 2 other factors. One is the specialty or subspecialty area that reflects market forces (Table 1) and the second is the achievements of the physician relative to similarly challenging, albeit different, performance measures for the physicians whose roles are predominately clinical, education, or research. Only under rare circumstances did department members obtain changes to their remuneration outside the triennial review process. This outcome study of the CDCP provides evidence that the CDCP does value and reward equally each JP. There are physicians from each JP in within the 2 top levels (II–III and III; unpublished observations) of the CDCP and an individual physician to increase their level within the CDCP is similar for each JP (Fig 2 and 3). The findings of our study also indicate that, in contrast to documented gender bias in peer-review or academic advancement, male and female physicians had a similar probability of success within the CDCP (Fig 4).

This outcome study that demonstrates that the CDCP satisfied its design principles from the department’s perspective is in agreement with our previous qualitative research study that evaluated the departmental physician’s perception of the CDCP. That previous study found that our physicians thought that the CDCP was an

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<th>No.</th>
<th>Assessed</th>
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<tr>
<td>A</td>
<td>37</td>
<td>30</td>
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<td>B</td>
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<td>26</td>
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FIGURE 5
The probability of increasing a level was not related to academic rank at either the first (A; $\chi^2$ probability $= 0.90, P = NS$) or second triennial review (B; $\chi^2$ probability $= 0.70, P = NS$). All physicians who held level III before the triennial review were excluded from these analyses.
improvement over previous methods, that they still were in agreement with the CDCP’s purpose and design principles, and that they did not want the CDCP to undergo a major redesign. Taken together, these 2 outcomes studies of our CDCP should provide useful information and/or strategies to other academic departments, for example, to promote the career development and excellence of their physicians or to use as 1 parameter whereby departmental budgets might be aligned with desired academic outputs.10,11

ACKNOWLEDGMENTS

The CDCP represents the work of many members of our Department of Pediatrics. Special acknowledgment is made to the Department of Pediatrics’ Clinical, Medical Education, and Research Advisory Committees.

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Multidrug-Resistant Bacteria in Hospitalized Children: A 5-Year Multicenter Study

Josette Raymond, MD, PhD, Patrice Nordmann, MD, PhD, Catherine Doit, MD, Hoang Vu Thien, MD, Michèle Guibert, MD, Agnès Ferroni, MD, Yannick Aujard, MD

Objective. The objective of this study was to determine the incidence of multidrug-resistant bacteria in hospitalized children

Methods. This multicenter study was conducted in 5 hospitals in the Paris area from 1999 to 2003. We recorded all isolations of multidrug-resistant bacteria from clinical samples that were obtained from hospitalized children. Strains that were isolated during systematic screening for carriers were excluded.

Results. The mean incidences were 0.9 per 1000 hospitalization-days for methicillin-resistant Staphylococcus aureus, 0.45 for extended-spectrum β-lactamase–producing Klebsiella pneumoniae, 0.32 for extended-spectrum β-lactamase–producing Enterobacteriaceae other than Klebsiella pneumoniae, 0.40 for Enterobacter species with derepressed cephalosporinase, and 0.01 for vancomycin-resistant Enterococcus. The incidences per 1000 hospitalization-days of methicillin-resistant Staphylococcus aureus, extended-spectrum β-lactamase–producing Klebsiella pneumoniae, extended-spectrum β-lactamase–producing Enterobacteriaceae other than Klebsiella pneumoniae, and Enterobacter species with derepressed cephalosporinase decreased significantly from 1999 to 2003, whereas the incidence of vancomycin-resistant Enterococcus remained very low. The proportion of resistant strains within the species did not vary significantly for methicillin-resistant Staphylococcus aureus (11% to 9.6%), extended-spectrum β-lactamase–producing Enterobacteriaceae other than Klebsiella pneumoniae (1.1%), and vancomycin-resistant Enterococcus (0.03% to 0.023%). In contrast, the frequency of extended-spectrum β-lactamase–producing Klebsiella pneumoniae decreased from 31.6% to 7.4%, and that of Enterobacter species with derepressed cephalosporinase decreased from 38.8% to 18.5%.

Conclusions. We report significant decreases in the incidence of methicillin-resistant Staphylococcus aureus, extended-spectrum β-lactamase–producing Klebsiella pneumoniae, extended-spectrum β-lactamase–producing Enterobacteriaceae other than Klebsiella pneumoniae, and Enterobacter species with derepressed cephalosporinase in hospitalized children during a 5-year period.
MULTIDRUG-RESISTANT BACTERIA (MDRB) present an emerging threat worldwide in hospitalized children as in adult patients.1,2 They are responsible of an increase in mortality rate and additional financial costs.3 The most clinically relevant MDRB include methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum cephalosporin-resistant Gram-negative bacilli, and vancomycin-resistant enterococci (VRE).1 MDRB colonization occurs as a result of patient-to-patient transmission and/or the selective effects of antimicrobial therapy.4 MDRB colonization/infection can be used as an indicator of compliance with hygiene measures.

Incidence of MDRB is widely known in hospitalized adults. MRSA strains accounted for 5% to 20% of the S. aureus that was isolated from adult patients who were hospitalized in ICUs in Europe5 and 64.4% of those who were isolated in similar situations in the United States in 2006.6 In Europe, >20% of the Klebsiella strains that were isolated from adult patients in ICUs were found to produce an extended-spectrum β-lactamase (ESBL; ESBL-producing Klebsiella pneumoniae [ESBLKp]) in 19987 and often are responsible of outbreaks.8 The frequency of VRE ranges from <1% in Europe to >20% in ICUs in the United States.9 However, few data are available concerning the incidence of MDRB in hospitalized children. In a study by Cosseron et al,10 11% of the S. aureus strains that were isolated from NICUs and PICUs were MRSA. Kim et al11 reported that ESBLKp strains accounted for 52.9% of the Klebsiella strains that were isolated from bacteremic patients in Korea. In a previous multicenter study that was conducted in pediatric units in 8 European countries, we found that 18% of the S. aureus strains were MRSA and 14% of the Klebsiella strains were ESBLKp.2 We report the results of a multicenter study that was conducted to determine the frequency of MDRB and the incidence of infections with these bacteria in hospitalized children during a 5-year period in 5 university hospitals in the Paris area.

METHODS

Patients

This prospective study was conducted from January 1, 1999, to December 31, 2003, by the microbiology laboratories of 5 teaching hospitals. Three of them were exclusively pediatric hospitals, with 480, 250, and 350 beds, respectively. Two other pediatric departments included, respectively, 200 and 350 pediatric beds in “mixed” hospitals that admit both children and adult patients. Five PICUs and 3 NICUs were included. All of these hospitals were part of the same network, and the French National Guidelines for Control Measures were applied at each hospital.

Nosocomial bloodstream infections, catheter-related infections, and urinary tract infections (UTIs) were defined as previously reported.12,13 Clinical signs of bacteremia, such as fever and chills, were always present. Urine was collected using sterile bags in children who were younger than 2 years.

The antimicrobial treatments that were administered before infection were not analyzed. Antibiotic treatment protocols for suspected nosocomial sepsis was a combination of vancomycin, a third-generation cephalosporin, and an aminoglycoside was given when the patient had an indwelling catheter; vancomycin was omitted from this combination for the treatment of suspected sepsis in patients without an indwelling catheter. The use of carbapenem was restricted to children who previously were identified as carriers of MDRB. These empiric treatment recommendations were maintained throughout the study and were applied in all hospitals.

Bacteria

All MRSA, ESBLKp, ESBL-producing Enterobacteriaceae other than K pneumoniae (ESBLE), Enterobacter species with derepressed cephalosporinase, and VRE that were isolated from clinical specimens in cases of suspected or confirmed infection were recorded. Only strains that were cultured from clinical samples that were taken 48 hours after admission were counted. Strains that were isolated during systematic screening for carriage were not considered. When multiple strains of the same species with the same antimicrobial susceptibility were recovered from a single patient, only the first isolate was included. We also recorded the sampling site of each strain.

We did not systematically record cases of bacteremia that was caused by non-MDRB. The overall frequency of MDRB among all bacteria that were isolated from patients with infection therefore was not known.

Infection Control Measures

The French National Guidelines for Control Measures that were published in 1999 were applied at each hospital.14 They included recommendations (1) to identify reservoirs of MDRB by systematic screening for MDRB in newly hospitalized patients; briefly, samples from nose and anus were taken at admission from patients in ICUs; (2) for the early notification of the clinician by the laboratory and notification of the new hospital if the patient is transferred (3) to prevent transmission between patients by means of barrier precautions for colonized and infected patients, such as antiseptic handwashing, the wearing of gloves, and keeping infected patients isolated in single rooms or keeping patients who are infected with the same bacterium together in the same room; and (4) to organize systematic detection and monitoring of carriers. In case of an extended hospitalization, samples from nose and anus were taken each week to search MDRB.
Microbiologic Methods
The Kirby-Bauer disk diffusion method, microbroth dilution, and E-tests (AB Biodisk, Solna, Sweden) were performed according to National Committee for Clinical Laboratory Standards guidelines, using the recommended thresholds to define resistance.\textsuperscript{15} \textit{S aureus} strains were considered to be resistant to methicillin when a diameter of inhibition of <20 mm was observed around a 5-\textmu g oxacillin disk after 24 hours to 48 hours of incubation at 35°C. We used the double-disc synergy method to assess ESBL production in Enterobacteriaceae isolates as previously described.\textsuperscript{16} The derepression of cephalosporinase in \textit{Enterobacter} (\textit{Enterobacter} expressing chromosomal \textit{ampC} \textit{\beta}-lactamases) was detected on the basis of cefotaxime resistance (minimum inhibitory concentration $\geq$16 \textmu g/mL). For detection of a possible \textit{\beta}-lactamase, each cefotaxime-resistant \textit{Enterobacter} was tested on an MH medium (Mérieux, Marcy l’Etoile, France) with 100 mg/L of cloxacillin as was tested on an MH medium (Mérieux, Marcy l’Etoile, France) with 100 mg/L of cloxacillin.

Data Analysis
We used 3 different surveillance indicators: (1) percentage of MRSA strains among isolated strains of \textit{S aureus}, of ESBL Klebsiella strains among isolated \textit{Klebsiella} species strains, of cefotaxime-resistant \textit{Enterobacter} strains among \textit{Enterobacter} species, and of VRE strains among \textit{Enterococcus} species; (2) the incidence of MDRB infection per 1000 hospitalization-days (HD); and (3) the incidence of MDRB infection per 100 admissions. Changes over time in incidence per 1000 HD and per 100 admissions were analyzed from 1999 to 2003 for bacteremia, catheter-related infections, and UTI.

Statistical Analysis
Time trends were analyzed by $\chi^2$ tests for linear trend on proportions and goodness of fit, comparing the observed and expected incidence rate distributions. For all tests, $P < .05$ was considered significant.

RESULTS
During the 5-year study, 34 5150 admissions were recorded: 73 911 in 1999, 70 922 in 2000, 69 299 in 2001, 69 973 in 2002, and 69 865 in 2003. A total of 3856 multidrug-resistant pathogens were isolated from 1999 to 2003: 1665 MRSA (10.1% of all isolated \textit{S aureus} strains), 832 ESBLKp (23.2% of isolated \textit{K pneumoniae} strains), 594 ESBLE (1.4%), 743 \textit{Enterobacter} species with derepressed cephalosporinase (24.6% of isolated \textit{Enterobacter} species), and 22 VRE (0.28% of isolated \textit{Enterococcus} species; Table 1). The global incidence of MDRB was 2.8 cases per 1000 HD, corresponding to 1.4 cases per 100 admissions.

MDRB incidence per 1000 HD decreased during the course of the study: from 1.06 to 0.75 (mean: 0.9) for MRSA, from 0.71 to 0.12 (mean: 0.45) for ESBLKp, from 0.45 to 0.21 (mean: 0.32) for ESBL-producing Enterobacteriaceae, and from 0.74 to 0.24 (mean: 0.40) for derepressed \textit{Enterobacter} species. The incidence of VRE was 0.01 per 1000 HD and 0.01 per 100 admissions (Table 1).

The percentages of MRSA, ESBLE, and VRE strains in the corresponding species did not vary significantly during the course of the study. Conversely, the proportion of ESBLKp decreased considerably, from 31.6% to 7.4% ($P < .0001$), and that of derepressed \textit{Enterobacter} species decreased from 38.8% to 18.5% ($P < .0001$; Table 1).

The global incidences of MRSA, ESBLKp, ESBLE, and derepressed \textit{Enterobacter} infections per 1000 HD decreased significantly from 1999 to 2003 ($P < .001$). Similarly, incidences per 100 admissions of ESBLKp, ESBLE, and derepressed \textit{Enterobacter} infections decreased significantly during the same period except for MRSA.

Between 1999 and 2003, incidence per 100 admissions of ESBLKp decreased significantly in 3 centers but not significantly in 2 centers, probably in relation with the low number of isolated bacteria. The incidence of derepressed \textit{Enterobacter} decreased significantly in 3 centers and not significantly in 2 centers; incidence of ESBLE decreased in 3 centers, increased in 1 (with a low number of isolated strains), and was stable for the last 1. Finally, global trend of MRSA incidence did not decrease because bacterial evolution was different according to the centers (Table 2).

The incidence per 1000 HD of MDRB infection was determined as a function of the site of infection. The mean incidence of primary MDRB bacteremia was 0.11 per 1000 HD (0.12–0.08), and that of catheter-related infections was 0.08 per 1000 HD (0.1–0.06). The incidence of UTI as a result of MDRB was 0.34 per 1000 HD (0.39–0.31). The incidences of bacteremia, catheter-related infections, and UTI as a result of MDRB did not vary significantly during the study period ($P = 1.0$).

Of the 3856 MDRB isolated, 176 (4.6%) were responsible for primary septicemia: 88 (51.2%) MRSA, 34 (19.3%) ESBLKp, 21 (11.9%) ESBLE, and 33 (18.7%) derepressed \textit{Enterobacter} species. For catheter-related infections, 119 (3%) MDRB were isolated: 52 (43.7%) MRSA, 29 (24.4%) ESBLKp, 17 (14.3%) ESBLE, and 21 (17.6%) derepressed \textit{Enterobacter}. For UTI, 492 (12.8%) MDRB were isolated: 54 (11%) MRSA, 137 (27.8%) ESBLKp, 131 (26.6%) ESBLE, 170 (34.5%) derepressed \textit{Enterobacter}, and 1 VRE. The other 3069 MDRB were isolated from various sites, including respiratory samples and wounds, but it was not possible to differentiate between colonization and infection. No case of meningitis as a result of MDRB was recorded.

DISCUSSION
The rate of nosocomial infections that are caused by MDRB is a good indicator of compliance with prevention...
control measures and antibiotic policy. It also is used to optimize the empiric treatment that is administered by clinicians. The incidence and bacterial epidemiology of nosocomial infections in children differ from those in adults, confirming the need for specific evaluation.14 MRSA strains are endemic in adults in many American and European hospitals, accounting for 5% to 65% in ICUs.5,6,17 Previous pediatric studies that included all hospitalized children have reported proportions of 18% to 27% for MRSA.2,18 However, the incidence of MRSA infection in children also was reported to be closer to that for adults (1.06 vs 0.81 per 1000 HD and 0.52 vs 0.63 per 100 admissions in 1999).14 As reported earlier for adults in other countries,19 we report here a significant decrease in the incidence per 1000 HD of MRSA during the 5-year period studied, contrasting with the increase in incidence, from 0.71 to 0.96 per 1000 HD in adults during the 1996–2001 period.14 The incidence per 100 admissions of MRSA decreased, but the proportion of MRSA was not significantly different from that in adults.14,19 Numerous outbreaks of ESBLKp have been reported in several countries in adults as well as in children.20–24 The prevalence of ESBLKp in adult patients is higher in Latin America (45%) and Europe (16.7% to 2%) than in the United States (8%).25,26 We found a higher proportion of ESBLKp in children than in the adult population. The prevalence of ESBLKp in French children (23.2%) was higher than that in French adults (11.4%).27 However, incidence of ESBLKp infection in children was also reported to be closer to the incidence of ESBLKp in adults.27 Cefotaxime use also may select Enterobacteriaceae with naturally derepressed cephalosporinase. Resistance of the antibiotic use can lead to a selection pressure that promotes ESBL-producing bacteria.28 Colonization with resistant Gram-negative bacilli has been shown to be associated with the use of broad-spectrum antibiotics in the pediatric units. Because this prospective study was conducted in the microbiology laboratories, data from PICUs and NICUs could not be differentiated from the pediatric units.

<table>
<thead>
<tr>
<th>Year</th>
<th>MRSA</th>
<th>ESBLKp</th>
<th>ESBLE</th>
<th>Cefotaxime-Resistant Enterobacter</th>
<th>VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (N)</td>
<td>Incidence per 1000 HD</td>
<td>Incidence per 100 Admissions</td>
<td>% (N)</td>
<td>Incidence per 1000 HD</td>
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<td>1.06</td>
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<td>31.6(809)</td>
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<td>1.50</td>
<td>0.50</td>
<td>34.8(866)</td>
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<td>1.50</td>
<td>0.50</td>
<td>36.5(558)</td>
<td>0.19</td>
</tr>
<tr>
<td>2002</td>
<td>113 (1179)</td>
<td>0.92</td>
<td>0.51</td>
<td>22.1 (706)</td>
<td>0.40</td>
</tr>
<tr>
<td>2003</td>
<td>96 (829)</td>
<td>1.20</td>
<td>0.39</td>
<td>17.6 (601)</td>
<td>0.12</td>
</tr>
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<td>Mean</td>
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<td>0.47</td>
<td>23.2</td>
<td>0.45</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>0.04</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>
decrease in MDRB colonization.\textsuperscript{32,33} During the study, no changes in antimicrobial drug use, which could explain the MDRB decreased incidence, were observed in the various pediatric departments.

The major reservoir of MDRB is colonized/infected adult or pediatric patients. The hand carriage accounts for the major mechanism for patient-to-patient transmission.\textsuperscript{34} Wendt et al\textsuperscript{35} stated that bacterial overgrowth in the gut of patients in the ICU is a relevant mechanism to acquire carriage of MDRB during a nonoutbreak situation.\textsuperscript{35} Therefore, barrier precautions are important to avoid patient-to-patient transmission. The national guidelines, including recommendations similar to those of the US Hospital Infection Control Practices Advisory Committee, were distributed to all hospitals.\textsuperscript{36} However, no external audit was conducted to assess the validity of hygiene control procedures.

Methicillin-resistant coagulase-negative \textit{Staphylococcus}, the pathogen that most commonly is responsible for systemic infection that is associated with a central venous catheter in children, was excluded from this analysis. The inclusion of methicillin-resistant coagulase-negative \textit{Staphylococcus} in future studies of MDRB infections in children would be of clinical relevance.

**CONCLUSIONS**

The epidemiologic characteristics of MDRB differ in children and adults. We report in 5 pediatric centers a decrease in the frequency of MDRB isolation that needs to be confirmed. Evidence-based effective measures, including greater compliance with hand hygiene rules that are based on the use of alcohol-based hand rubs,\textsuperscript{37} restrictions on antibiotic use, early communication, and isolation, probably are effective in pediatric units, but additional prospective evaluations are required.

**REFERENCES**


ABSTRACT

OBJECTIVE. The objective of this study was to examine the relation of factors that are present at birth to subsequent hospitalization for childhood pneumococcal disease.

METHODS. We conducted a cohort study of all singletons born in 3 counties in western Denmark from 1980 through 2001, using population-based registries to obtain data on pregnancy- and birth-related variables and hospitalizations through age 12. We calculated incidence rates of pneumococcal disease hospitalization overall and within strata of study variables and used Poisson regression to estimate rate ratios for pneumococcal disease hospitalization while accounting for other birth characteristics.

RESULTS. Among 338,504 eligible births, 1,052 children were later hospitalized for pneumococcal disease. Pneumonia accounted for most hospitalizations (81.9%). The pneumococcal disease hospitalization rate was highest among 7- to 24-month-olds, followed by 0- to 6-month-olds and 25- to 60-month-olds. The highest rates, typically over 200 hospitalizations per 100,000 person-years, were in 0- to 6- and 7- to 24-month-old children who were born preterm or with low birth weight, a low 5-minute Apgar score, or birth defects. The hospitalization rate was lower for first-born children at 0 to 6 months but not at older ages. At older ages, hospitalization rates were not substantially different for children whose mothers smoked during pregnancy, but at 0 to 6 months, the rate was higher for children of multiparous nonsmokers than for others. Adjusted rate ratios were elevated across all age categories for several variables, including low birth weight, presence of birth defects, and low 5-minute Apgar. For several others, including preterm birth, maternal multiparity, age <20 years, and non-Danish/European Union citizenship, adjusted rate ratios were elevated only for 0- to 6-month-olds.

CONCLUSIONS. This large cohort study of hospitalization for childhood pneumococcal disease clarifies the roles of some gestation and birth factors while raising new questions about how these factors work.
Pneumococcal Disease (PD)—Meningitis, Septicemia, Pneumonia, and Other Infections

Neumococcal disease (PD)—meningitis, septicaemia, pneumonia, and other infections that are caused by *Streptococcus pneumoniae*—is a leading cause of serious illness and death, causing an estimated 1.6 million deaths worldwide annually, most of them in children. Although most children become colonized with *S. pneumoniae* during early childhood, for reasons that are not entirely clear, few develop PD. Postnatal risk factors for childhood PD include factors such as out-of-home child care, which likely increase the risk for exposure to pneumococci, as well as factors such as exposure to environmental tobacco smoke, and underlying illnesses such as hemoglobinopathies, immune deficiencies, and chronic pulmonary or cardiac disease that likely increase the risk for invasion once colonization has occurred. The role of prenatal and perinatal risk factors in susceptibility to childhood PD is incompletely understood. The only controlled study to examine the roles of preterm birth and low birth weight (LBW) in childhood PD reported that they were strongly associated with increased risk. The risk ratio was 1.6 for infants who were born before 38 weeks’ gestation and 9.1 for those who were born before 32 weeks; similarly, the rate ratio (RR) was 2.6 for infants who weighed <2500 g at birth and 6.7 for those who weighed <1500 g. This study was limited by a small number of preterm and LBW infants with PD, however. Preterm birth, LBW, and maternal smoking during pregnancy have been associated with increased risk for a variety of other infectious outcomes in childhood, so examining their role in PD may lead to improved understanding of susceptibility and contribute to better prevention of this serious disease. We used data from the Danish National Birth Registry and the hospital discharge registries in western Denmark to conduct a large, population-based, cohort study of the relationship of birth weight, gestational age, maternal smoking during pregnancy, and other factors that are present at birth with subsequent hospitalization for childhood PD.

**METHODS**

**Study Population**

The study population consisted of all singleton live births in North Jutland, Aarhus, and Viborg counties (total population: 1.4 million), Denmark, from 1980 through 2001. In this area, pneumococcal conjugate vaccine has never been used for routine childhood vaccination but was available for children with high-risk medical conditions for part of 2001. Since 1968, a unique National Civil Registration number has been assigned to all Danish residents at birth and has been used in all public records, allowing records in various systems to be linked. For this study, the study population was identified in the Danish National Birth Registry, disease outcomes were determined from the counties’ local hospital discharge registries, and death and emigration were determined from the Danish Civil Registration System, which is updated daily. Because the study was based on de-identified data that were extracted from publicly available records, it was exempt from human subjects review.

**Birth Registry Data**

Pregnancy- and birth-related data were extracted from the Danish Medical Birth Registry and classified as follows. Gestational age was classified as preterm (≤37 completed weeks), term (38–41 completed weeks), and postterm (≥42 completed weeks). Preterm infants were subclassified as very preterm (≤31 completed weeks) or moderately preterm (32–36 weeks). Birth weight was classified as <2500 g, 2500 to 3000 g, 3001 to 3500 g, and >3500 g. Infants with birth weight <2500 g were subclassified as very low birth weight (<2000 g) or moderately low birth weight (2000–2499 g). Mothers were classified as primiparous or multiparous, and maternal age at delivery as ≤20 years, 21 to 35 years, and >35 years. Fetal presentation was classified as cephalic or breech/other, and mode of delivery was classified as vaginal, cesarean, or other (including forceps and vacuum extraction). Five-minute Apgar score was classified as low (0–6) or normal (7–10), and birth defects were classified as present or absent. The mother’s citizenship was dichotomized as Danish/original European Union states or any other country, and the infant’s county of birth also was recorded. Information on whether the mother smoked during pregnancy, based on self-report at the first antenatal visit, and whether she cohabited with a partner at the time of delivery was available for births that occurred from 1991 through 2001.

**Hospital Discharge Registry Data**

Information on hospitalizations for PD that occurred through 2004 was obtained from each country’s hospital discharge registry, using *International Classification of Diseases, Eighth Revision* (ICD-8) codes 320.19 (pneumococcal meningitis), 038.29 (pneumococcal septicemia), and 481.xx (pneumococcal pneumonia) before 1994 and ICD-10 codes G00.1 (pneumococcal meningitis), A40.3 (pneumococcal septicemia), and J13.9 (pneumococcal pneumonia) subsequently. Osteomyelitis and arthritis were not included because pathogen-specific ICD codes did not exist for either diagnosis in ICD-8 or for osteomyelitis in ICD-10. Children whose diagnoses were coded as inpatient were considered to have been hospitalized. When >1 of these discharge diagnoses were given during an episode of hospitalization for PD, meningitis had priority over septicemia, which had priority over pneumonia. PD hospitalizations were categorized by the admission date as having occurred at 0 to 6, 7 to 24, 25 to 60, or 61 to 144 months of age. For validation of discharge diagnoses of pneumococcal pneumonia, 31 discharge summaries were selected at random from the 334 available for North Jutland county and reviewed for
microbiologic, radiologic, treatment, and clinical information. Patients were considered to have definite PD when a blood culture was positive for *S pneumonieae*. They were considered to have probable PD when lobar consolidation was present on chest radiograph together with sputum that was culture positive for *S pneumonieae* and clinical response to penicillin or, in those who previously were treated with antibiotics, clinical response to penicillin alone. They were considered to have possible PD when (1) chest radiography showed consolidation, C-reactive protein was >100 mg/L, and symptoms resolved rapidly with penicillin or (2) radiologic changes were not present but C-reactive protein >100 mg/L, a positive sputum culture for *S pneumonieae*, and clinical response to penicillin were present.

**Civil Registration System Data**

Data on emigration and death came from the Civil Registration System. Follow-up time for each child in the birth cohort was measured from birth to the date of hospital admission for PD; emigration; death; 12th birth-day or December 31, 2004, whichever came first.

**Statistical Analysis**

We excluded records with birth weight <500 g or gestation <25 or >45 completed weeks. We also excluded records with the implausible combination of gestational age <28 weeks and birth weight >2500 g.

For the defined follow-up periods, we computed incidence rates of hospitalization for PD overall and within strata of study variables. Incidence rates for each type of PD diagnosis (meningitis, sepsisemia, and pneumonia) were calculated by recording the other 2 diagnoses as nonevents and treating them as censoring variables. We similarly computed incidence rates stratified by both maternal smoking and parity. To examine the joint effects of birth and maternal variables on the risk for hospitalization for PD, we used Poisson regression to model rates of hospitalization for PD at different follow-up times as a function of the birth and maternal variables. We analyzed the data with SAS 9.01 (SAS Institute, Inc, Cary, NC).

**RESULTS**

**Descriptive Data**

In all, 338 633 singleton live births occurred during the study period. After 129 records were excluded (5 with birth weight <500 g, 60 with gestation <25 completed weeks, 48 with gestation >45 completed weeks, 9 with implausible combination of birth weight and gestational age, and 7 that met >1 of the exclusion criteria), 338 504 were included in analysis. The median follow-up period was 12.0 years (interquartile range: 7.8–12.0), and the mean was 9.8 years. Table 1 shows characteristics of the study population as well as rates of hospitalization for PD overall and within age categories. No trend toward increasing or decreasing incidence was seen during the study period. In general, this population had a high proportion of normal pregnancies, with 81.5% delivered vaginally, 85.9% delivered at term, 96.2% with birth weight ≥2500 g, 99.1% with a normal 5-minute Apgar score, and 94.2% with no birth defect noted. For births after 1991, 26.9% of mothers smoked. The prevalence of smoking during pregnancy decreased steadily from 34% in 1991 to 21% in 2001.

Among the 338 504 children in the study population, 1052 were hospitalized for PD during the follow-up period. Table 1 presents age-specific and overall rates of hospitalization for each PD diagnosis. Pneumonia accounted for the majority of hospitalizations (81.9%), and most hospitalizations occurred at either 7 to 24 months (46.4%) or 25 to 60 months (26.0%).

**Stratified Analysis**

Table 1 also shows the crude age-specific rate of hospitalization for PD for various strata of birth-related variables. Overall, the rate was highest among 7- to 24-month-olds (97 hospitalizations per 100 000 person-years [PY]), followed by 0- to 6-month-olds (65 hospitalizations per 100 000 PY) and 25- to 60-month-olds (28 hospitalizations per 100 000 PY). Children who were 61 to 144 months of age had the lowest rate, 11 hospitalizations per 100 000 PY. The highest rates were in 0- to 6- and 7- to 24-month-old children who were born preterm for all preterm births, 212 hospitalizations per 100 000 PY at 0–6 months, 196 at 7–24 months; for very preterm births, 710 hospitalizations per 100 000 PY at 0–6 months, 436 at 7–24 months) or with LBW (for all LBW, 221 at 0–6 months, 214 at 7–24 months; for very low birth weight, 413 at 0–6 months, 275 at 7–24 months), a low 5-minute Apgar score (157 at 0–6 months, 236 at 7–24 months), or birth defects (212 at 0–6 months, 190 at 7–24 months). Table 2, which is restricted to term infants, shows that age-specific PD hospitalization rates were higher in LBW infants independent of preterm birth.

The PD hospitalization rate was substantially lower for first-born children at 0 to 6 months but not at older ages (Table 1). Rates were higher in all age categories for children whose mothers were ≤20 years of age at delivery. Rates also were higher in all age categories for children whose mothers lived in North Jutland county during pregnancy. For the subset of children for whom information about maternal smoking was available, the crude rate of hospitalization for PD was lower for children of smokers than of nonsmokers (39 vs 68 cases per 100 000 PY) at 0 to 6 months and higher (104 vs 97 hospitalizations per 100 000 PY) at 7 to 24 months. This pattern applied only to children with a diagnosis of pneumonia; for those with meningitis or bacteremia, rates were similar regardless of maternal smoking his-
<table>
<thead>
<tr>
<th>Parameter</th>
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<th>165 858</th>
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<th>488</th>
<th>504 543</th>
<th>97</th>
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<th>1 700 927</th>
<th>11</th>
<th>1052</th>
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<td>Overall</td>
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<td>165 858</td>
<td>12</td>
<td>79</td>
<td>504 543</td>
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* The original 15 members of the European Union (EU-15) are Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, and United Kingdom.

* Pertains to 183,832 births that occurred after 1990, when maternal smoking in pregnancy and cohabitation status became recordable to the Birth Registry. Of those, 7282 (4%) records had missing data on smoking and 1226 (0.7%) had missing data on cohabitation.

The overall PD rate for the 1991–2001 birth cohort was 34/100,000 PY.

* Among the 338,504 total births, 6350 (1.9%) had data missing on birth presentation, 3236 (1%) on 5-minute Apgar score, 913 (0.3%) on birth weight, and 223 (0.1%) on gestational age.
tory (data not shown). Table 3, which presents age-specific PD hospitalization data stratified by both maternal smoking and parity, shows that a substantially increased rate of PD hospitalization in 0- to 6-month-olds who were born to nonsmokers was limited to children of multiparous women. Except for maternal smoking, as noted, the patterns that were seen in these stratified analyses did not change when the PD outcome was restricted to diagnoses of septicemia and meningitis (data not shown).

Regression Analysis
Table 4 presents adjusted RRs from the Poisson regression model including all variables for which data were available for the whole study period. Although confidence intervals were broad, the adjusted RR for hospitalization for PD was elevated in children with LBW in all age categories. Similarly, adjusted RRs were elevated in all age categories for children who were born with birth defects or a 5-minute Apgar score and for those who were born in North Jutland county. For several other variables, including preterm birth, maternal multiparity, age ≤20 years, and non-Danish/European Union citizenship, RRs were elevated only for 0- to 6-month-olds. A similar model, limited to births from 1991 through 2001 for which data on maternal smoking was available, had results consistent with the stratified and regression analyses presented previously (data not shown).

Validation of Discharge Diagnosis of Pneumococcal Pneumonia
Among the 31 patients who had a discharge diagnosis of pneumococcal pneumonia and whose discharge summaries were reviewed, 6 (19%) had definite PD, 14 (45%) had probable PD, and 11 (36%) had possible PD.

DISCUSSION
This large cohort study of hospitalization for childhood PD clarifies the roles of some major gestation and birth factors in conferring risk for hospitalization for PD while raising new questions about how these factors work. Children with preterm birth, LBW, low 5-minute Apgar score, or a birth defect had higher PD hospitalization rates later in infancy and childhood than did children who were born without these factors. These factors, as well as maternal parity and smoking, are discussed further. Other findings—the increased rates in boys, in children of younger mothers, and in children from an area with lower socioeconomic status (North Jutland county)—in this study confirm the results of previous studies8,10,11,21,22 and are not discussed further.

Our study comprised a large population with complete follow-up. The independent and thorough collection of data on predictor and outcome variables and the universal health care system that serves the study population minimize the risk for several types of selection and information bias. In focusing on hospitalizations, we captured the most severe and costly infections. Nevertheless, as is typical for studies that use existing data, we do not have all of the information that we would wish for a comprehensive analysis. Specifically, we do not know which children in our study had comorbid conditions such as congenital heart or lung diseases, immunodeficiency syndromes, or hemoglobinopathies that would have increased their risk for invasive PD. These comorbidities have been reported in only ~7% to 16% of childhood invasive PD in other northern European countries,23,24 however, and they generally are not associated with preterm birth, LBW, or the other birth factors that we studied. Fewer than 20 cases of pediatric HIV infection were reported in the study area during the

### Table 2

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### Table 3

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Moreover, invasive PD accounted for a minority of hospitalizations in our study, so it is unlikely that the inclusion of comorbidity data would change our findings in important ways. Similarly, our inability to include diagnoses of uncommon invasive pneumococcal infections such as osteomyelitis, arthritis, and pericarditis is not likely to affect our findings substantially, because these outcomes are so rare.26 Our study relies on discharge diagnoses, which were not confirmed independently. Our validation study, as well as a previous evaluation of the Hospital Discharge Registry System,17 suggests that a discharge diagnosis of PD has reasonably high specificity. However, cases of PD could have been missed if the illness were mild, if cultures were falsely negative, or for other reasons.

Other large studies found that children who are born preterm or with LBW are at greater risk for infectious disease hospitalization and mortality than children who are born at term or with normal birth weight.8–11 Several uncontrolled studies have shown that infants who are born with these risk factors make up a higher proportion of cases of invasive PD in infancy and childhood than might be expected from the relative rarity of these conditions.27–31 We are aware of only 1 other study that compared childhood PD occurrence in preterm and LBW infants with normal infants. In that study, consistent with ours, children who had been born preterm or with LBW had increased risk for invasive PD. That study was not large enough to assess the independent contribution of these factors or their role at various ages, however.6 Our study extends this literature in 2 ways. First, our data clearly demonstrate increased rates of hospitalization for PD in children who were born with either of these risk factors. These rates are increased markedly for children who were born very preterm or with very low birth weight. Second, our data show that, although the

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CI indicates confidence interval.
effect of these risk factors is most marked in the youngest age groups, increased hospitalization rates for LBW children persist well into childhood.

The increased rates of hospitalization for PD in the first year or so in infants who are born preterm might be expected, given that pneumococcal type–specific antibody is protective and that maternal antibody is transferred across the placenta to the fetus late in gestation. Even in term infants, pneumococcal antibody concentrations and opsonic activity usually are lower than in their mothers, and preterm infants have even lower relative levels. Preterm infants also may be more likely to be hospitalized than term infants because they are perceived by parents and physicians to be more vulnerable. However, we doubt that either of these reasons fully explains preterm infants’ higher rate of hospitalization for PD in the second year of life. The persistently increased rates of hospitalization for PD across all age groups in children with LBW, independent of preterm birth, also are intriguing and not explained easily. The “programming” hypothesis suggests that inadequate prenatal nutrition, manifested as LBW, may affect organ system function permanently, increasing risk for infectious and other diseases later in life. Immunologic studies have found decreased transplacental antibody transfer in infants with intrauterine growth retardation as well as impaired immune system function that persisted well into childhood or even adolescence. Epidemiologic studies of other infectious outcomes have had varying results: similar findings for LBW infants were reported from a large Danish case-control study of risk factors for childhood meningococcal disease but not from a US study of childhood infectious disease mortality. Therefore, our findings suggest that LBW increases both short-term and long-term susceptibility to PD but do not explain how this effect is mediated.

Factors that increase the risk for exposure to S pneumoniae will increase the risk for PD regardless of whether these factors are associated with susceptibility. Of note, in Denmark, most children are cared for at home for the first 6 to 12 months of life. Thereafter, tax-supported child care centers and kindergartens are available for most children, a system that changed little during the study period. Our data show that infants who are born to multiparous women have increased rates of hospitalization for PD at 0 to 6 months of age but not at older ages; infants who are born to multiparous women usually have older siblings, who may increase their risk for exposure to S pneumoniae. This interpretation is supported by the observation that having older siblings is associated with antimicrobial-resistant PD. After 6 months of age, most infants and young children likely have substantial contact with other young children, regardless of whether they have siblings. Children with birth defects or low 5-minute Apgar scores also may have increased exposure to S pneumoniae if these children have more contact with the health care system than children without these factors. Of course, these factors also could act by other mechanisms to increase risk.

We found no substantial effect of maternal smoking in older age groups but a considerably higher rate of hospitalization for PD in 0- to 6-month-old infants who were born to multiparous mothers who did not smoke during pregnancy. This finding may be attributable to chance but still merits discussion. This result is surprising, because maternal smoking during pregnancy was associated previously with hospitalization for infectious diseases. Moreover, women who smoke during pregnancy also are likely to smoke after delivery, and postnatal exposure to environmental tobacco smoke has been associated with childhood invasive PD at all ages. However, immunoglobulin levels are higher in pregnant smokers than in nonsmokers, suggesting that infants who are born to women who smoked during pregnancy might have higher protective immunoglobulin levels in early life. Because many studies have shown clearly that maternal smoking increases the risk for LBW, among other health issues, and because invasive PD rates in LBW infants are so high, we do not wish to suggest that maternal smoking provides any net benefit to infants.

CONCLUSIONS

Our most important findings emphasize the heightened risk for hospitalization for PD in children who are born preterm or with LBW, a low 5-minute Apgar score, or a birth defect. For those who are born preterm, rates of PD hospitalization seem to be elevated only in the first 2 years of life, whereas increased hospitalization rates persist for older children who are born with the other risk factors. Our data also suggest that infants who are born to primiparous mothers are relatively protected in early infancy and that the role of maternal smoking during pregnancy may be more complex than previously realized.

ACKNOWLEDGMENTS

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REFERENCES

ARTICLE

Patient and Hospital Characteristics Associated With Length of Stay and Hospital Charges for Pediatric Sports-Related Injury Hospitalizations in the United States, 2000–2003

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\textsuperscript{a}Injury Prevention Research Center, Departments of \textsuperscript{b}Community and Behavioral Health, \textsuperscript{c}Occupational and Environmental Health, \textsuperscript{d}Health Management and Policy, and \textsuperscript{e}Biostatistics, and \textsuperscript{c}Department of Pediatrics, Roy J. & Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. The objectives of this study were to describe the patient and hospital characteristics of pediatric sports injury hospitalization and to determine the hospital characteristics that are associated with length of stay and total hospital charges (per discharge).

METHODS. Children who were aged 5 to 18 years and had a diagnosis of a sports injury in the Nationwide Inpatient Sample between 2000 and 2003 were included. National estimates of pediatric sports injury hospitalization, including the average and median of length of stay and total hospital charges, were computed. The relationship of hospital characteristics to length of stay and total hospital charges were assessed using linear regression, adjusting for patient characteristics and sample weight.

RESULTS. A total of 7979 pediatric sports injury hospitalizations among children who were aged 5 to 18 were identified during 4 years, approximately 10 000 per year, nationwide. More than half of the hospitalizations were attributed to fractures. The mean and median of length of stay for pediatric sports injuries was 2.4 and 1.1 days, respectively. When weighted, the estimated total hospital charges for sports injury hospitalizations among 5- to 18-year-olds were $485 million during 4 years, with a steady increase each year. Urban hospitals had 46.1% higher total hospital charges than rural hospitals. Hospitals in the western United States had significantly greater total hospital charges than those in other regions.

CONCLUSIONS. The findings provide an empirical basis for future research on the magnitude of sports-related injuries that result in hospitalization among children. More research is needed to identify contributing factors that are associated with length of stay and total hospital charges for sports injury hospitalization. Intervention efforts also should be directed toward preventing severe sports injuries and to reducing the hospitalization and cost.
Youth sports injuries pose a serious threat to the health and well-being of young people. At least 4.3 million sports and recreational injury episodes occur each year to school-aged children in the United States. For people who are aged 5 to 24 years, sport- and recreation-related injuries account for 1 of every 5 injury episodes. Although the number of sports-related injuries that result in hospitalization is relatively small compared with those that are treated in emergency departments (EDs) or outpatient clinics, it represents the more serious end of the spectrum of injuries. These injuries can have profound negative consequences for young people in terms of their physical, mental, and emotional health. They also can place a tremendous burden on the patient’s family, the health care system, and society as a whole. A study of Massachusetts children ranked sports injuries second only to falls in per capita treatment expenditures. It is estimated that one fifth of school children are absent from school at least 1 day a year as a result of sports injuries, and annual treatment costs for youth sports injuries are estimated to be $1.8 billion dollars.

Much of the previous research on sports-related injuries in children focused on injuries that were treated in emergency departments (ED) or outpatient clinics because most of these injuries do not require hospitalization. Little has been reported in the literature about the characteristics of pediatric sports injuries that result in hospitalization. There are no published national data describing patient and hospital characteristics related to hospital length of stay (LOS) and total hospital charges that result from sports-related injuries in the pediatric population.

In this study, we describe the patient and hospital characteristics of sports-related injuries that resulted in hospitalization among children who were aged 5 to 18 years in the United States between 2000 and 2003. We also examine the hospital characteristics that were associated with LOS and total hospital charges for sports-related injuries that resulted in hospitalization in this population.

METHODS

Data Source
This study was a retrospective analysis of 4 years (2000–2003) of pediatric sports injuries that resulted in hospitalizations and was based on data from the Nationwide Inpatient Sample (NIS) of the Health Care Utilization Project provided by the Agency for Healthcare Research and Quality. The NIS is the largest all-payer inpatient care database in the United States. Each year, the NIS provides information on 5 to 8 million inpatient stays from ~1000 hospitals located in 35 states. The NIS was designed to approximate a 20% sample of US hospitals, defined as “all nonfederal, short-term, general, and other specialty hospitals, excluding hospital units of institutions.” A stratified probability sample of hospitals was used with sampling probabilities proportional to the number of US hospitals in each stratum. The 5 hospital characteristics that were used to define the strata were ownership/control, bed size, teaching status, urban/rural location, and region.

Sample of Patients
All patients who were aged 5 to 18 years and had a diagnosis of a sports-related injury in the NIS between 2000 and 2003 were selected. Three International Classification of Diseases, 9th Revision, Clinical Modification, external cause of injury codes (E-codes) that were used for the patient selection were as follows: E886.0, tackles in sports that cause fall on same level from collision, pushing, or shoving, by or with other person; E917.0, striking against or struck accidentally by objects or persons in sports without subsequent fall; and E917.5, striking against or struck accidentally by objects or persons in sports with subsequent fall. Although other injuries may have been sports related, only these 3 E-codes were used specifically to identify sports injuries in this study. After 5 inpatient deaths were excluded, the sample included a total of 7979 pediatric sports injury hospitalizations.

Analysis
From the NIS sample, national estimates, along with 95% confidence intervals, were calculated using patient and hospital characteristics to identify the number of hospitalizations that met the study definition. The top 10 principal diagnoses and top 10 principal procedures were described for pediatric sports injuries that resulted in hospitalization. The discharge-level weights that were provided by the Health Care Utilization Project were applied in the calculation to account for sampling weights.

The average and median of LOS and total hospital charges (per discharge) for the top 10 principal diagnoses were computed, excluding patients who were transferred to another hospital after being admitted to a hospital (n = 76; 0.95%). Hospital charges were adjusted to the year 2003 (last quarter) levels, using the consumer price index for inpatient hospital services that were provided by the Bureau of Labor Statistics.

Linear regression models were used to assess hospital characteristics that were associated with LOS and total hospital charges per discharge, adjusting for patient characteristics including age, gender, type of injury, body site of injury, and admission source. For modeling total hospital charges per discharge, LOS was adjusted in addition to other covariates because LOS was a confounding variable that influenced the relationship between total hospital charges and patient’s characteristics. A log transformation was performed on LOS and hospi-
tal charges per discharge to deal with the skewed distribution of these variables and to stabilize the variability of residuals from the regression models. Cook’s D statistics were used in the model diagnostics to identify influential observations. The cutoff $D_i > 4/n$ was used, where $n$ was the sample size, to exclude the observations that do not fit with regression model. The results reported from the linear regression models were based on reduced samples that removed outliers. For LOS and total hospital charges per discharge, respectively, 5.46% and 5.51% of observations were identified through model diagnostics as outliers that affected model fitting and reduced the degree of model interpretability. All of the analyses were conducted using SAS callable SUDAAN 9.0, accounting for cluster sampling and sample weights.\textsuperscript{12}

RESULTS

Characteristics of Sports-Related Injuries That Resulted in Hospitalization

A total of 7979 hospitalizations for pediatric sports injuries were identified in the sample of NIS data. When weighted, these represent an estimated total of 39 010 pediatric sports injury hospitalizations nationwide among children who were aged 5 to 18 years between 2000 and 2003, with approximately 10 000 pediatric sports injury hospitalizations each year (Table 1). Of all patients hospitalized for pediatric sports injuries, approximately one half (49.0%) were 15 to 18 years of age. Boys accounted for 86.5% (95% confidence interval: 85.7–87.3) of pediatric sports injury hospitalizations, or 6 times the number of comparable hospitalizations that occurred among girls. More than half (54.9%) of the pediatric sports injury hospitalizations were attributed to fractures. The most frequently injured body sites were the lower extremities (38.6%), the head and neck (24.2%), and the upper extremities (15.2%).

The number of hospitalizations for pediatric sports injuries was higher in urban hospitals (86.5%), hospitals with high bed volume (59.9%), and teaching hospitals (54.3%). Most hospitalizations for sports-related injuries were admitted through the ED (73.3%) and discharged routinely after 24 to 48 hours of hospitalization (96.8%). The majority of the patients paid hospital charges through private insurance, including health maintenance organizations (78.3%). A total of 347 (4.4%) sampled patients, an estimated 1699 patients nationwide, were uninsured and paid hospital charges by themselves.

Top 10 Principal Diagnoses and Top 10 Principal Procedures

The most common principal diagnosis was lower extremity fracture, which accounted for nearly one third (31.7%) of all hospitalizations for sports-related injuries in this study, followed by upper extremity fractures (13.5%) and abdominal internal organ injuries (9.9%; Table 2). Five of the top 10 principal diagnoses were attributed to fractures. In addition, 4 of the top 10 principal diagnoses involved definite or possible traumatic brain injury.

More than two thirds (68%) of patients underwent at least 1 procedure during their hospitalization. The most common principal procedure performed was open reduction and internal fixation of a lower leg fracture (11.4%; Table 2). The top 10 principal procedures performed accounted for a total of 2948 procedures, which translated to a weighted total of 14 416 top 10 principal procedures performed nationwide from 2000 to 2003. Of these, approximately half (49%) were done for patients who were aged 15 to 18 and almost 9 (87%) of 10 for boys. Six of the top 10 procedures involved the lower extremities, and 3 involved the upper extremities. At least 4 of the top 10 principal procedures required surgery.

LOS and Total Hospital Charges

Overall, the average LOS for all pediatric sports injuries was 2.4 days with a median of 1.1 day (Table 3). For the top 10 principal diagnoses, the average hospitalization ranged from a little more than 1 day (eg, internal organ with possible traumatic brain injury, sprain and strain of lower extremity) to 4 days (eg, abdominal internal organ injury). Injury to the abdominal organs had a longer LOS compared with the other top 10 principal diagnoses, with a mean of 4.0 days and a median of 2.9 days.

Nationwide, the estimated total hospital charges for sports injury hospitalizations among 5- to 18-year-olds was almost $0.5 billion dollars for 4 years (Table 3). The average hospital charges per discharge ranged from $7621 (eg, internal organ with possible traumatic brain injury) to $18 814 (eg, fracture with definite traumatic brain injury) for the top 10 principal diagnoses. The total hospital charges for each of the top 10 principal diagnoses ranged from $7.4 million (eg, fracture with possible traumatic brain injury) to $167 million (eg, fracture of lower extremity). The total hospital charges for lower extremity fractures were more than one third of all hospital charges, as a result of a large number of hospitalizations.

Hospital Characteristics Associated With LOS and Total Hospital Charges

Overall, the average LOS for pediatric sports injury hospitalizations remained steady during the 4 study years. In contrast, the total hospital charges per discharge went up steadily and significantly during the 4 years even after adjustment for inflation rates in hospital care. Compared with the year 2000, the total hospital charges per discharge were 18.2% higher for the year 2002 and 20.4% higher for the year 2003 ($P < .0001$; Table 4). Children who were admitted into urban hospitals had 46.1% higher total hospital charges per discharge than those who were admitted into rural hospitals ($P <
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<th>Sample</th>
<th>National Estimation</th>
<th>National Estimation, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 7979), n</td>
<td>(N = 39,010), n*</td>
<td>(95% CI)*</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>2078</td>
<td>10,185</td>
<td>26.1 (22.9–29.6)</td>
</tr>
<tr>
<td>2001</td>
<td>1924</td>
<td>9,690</td>
<td>24.8 (21.8–28.1)</td>
</tr>
<tr>
<td>2002</td>
<td>1968</td>
<td>9,476</td>
<td>24.3 (21.4–27.4)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6841</td>
<td>33,427</td>
<td>86.5 (85.7–87.3)</td>
</tr>
<tr>
<td>Female</td>
<td>1065</td>
<td>5,213</td>
<td>13.5 (12.7–14.3)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>722</td>
<td>3,536</td>
<td>9.1 (8.3–9.9)</td>
</tr>
<tr>
<td>10–14</td>
<td>3,349</td>
<td>16,352</td>
<td>41.9 (40.4–43.4)</td>
</tr>
<tr>
<td>15–18</td>
<td>3,908</td>
<td>19,122</td>
<td>49.0 (47.2–50.8)</td>
</tr>
<tr>
<td>Admission source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>5,831</td>
<td>28,578</td>
<td>73.3 (71.1–75.3)</td>
</tr>
<tr>
<td>Transfer from a hospital/health care facility</td>
<td>411</td>
<td>1,983</td>
<td>5.1 (4.3–6.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1,737</td>
<td>8,449</td>
<td>21.7 (19.8–23.7)</td>
</tr>
<tr>
<td>Disposition of patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine</td>
<td>7,719</td>
<td>37,744</td>
<td>96.8 (96.3–97.2)</td>
</tr>
<tr>
<td>Short-term hospitals</td>
<td>76</td>
<td>378</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>Nursing facility/home/other</td>
<td>180</td>
<td>868</td>
<td>2.2 (1.8–2.9)</td>
</tr>
<tr>
<td>Hospital location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1,025</td>
<td>5,275</td>
<td>13.5 (11.2–16.3)</td>
</tr>
<tr>
<td>Urban</td>
<td>6,949</td>
<td>33,712</td>
<td>86.5 (83.8–88.8)</td>
</tr>
<tr>
<td>Hospital bed size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>1,284</td>
<td>5,988</td>
<td>15.4 (12.0–19.5)</td>
</tr>
<tr>
<td>Medium</td>
<td>1,985</td>
<td>9,640</td>
<td>24.7 (21.9–27.8)</td>
</tr>
<tr>
<td>Large</td>
<td>4,705</td>
<td>23,359</td>
<td>59.9 (55.8–63.9)</td>
</tr>
<tr>
<td>Teaching status of hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonteaching</td>
<td>3,681</td>
<td>17,829</td>
<td>45.7 (41.8–49.7)</td>
</tr>
<tr>
<td>Teaching</td>
<td>4,293</td>
<td>21,159</td>
<td>54.3 (50.3–58.2)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>1,934</td>
<td>9,828</td>
<td>25.2 (21.2–29.6)</td>
</tr>
<tr>
<td>Midwest</td>
<td>1,706</td>
<td>8,484</td>
<td>21.7 (19.1–24.7)</td>
</tr>
<tr>
<td>South</td>
<td>2,498</td>
<td>11,756</td>
<td>30.1 (26.5–34.0)</td>
</tr>
<tr>
<td>West</td>
<td>1,841</td>
<td>8,943</td>
<td>22.9 (19.9–26.3)</td>
</tr>
<tr>
<td>Payer information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>14</td>
<td>71</td>
<td>0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>1,134</td>
<td>5,472</td>
<td>14.1 (12.8–15.4)</td>
</tr>
<tr>
<td>Private including HMO</td>
<td>6,202</td>
<td>30,402</td>
<td>78.3 (76.6–79.8)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>347</td>
<td>1,699</td>
<td>4.4 (3.8–5.1)</td>
</tr>
<tr>
<td>No charge</td>
<td>14</td>
<td>68</td>
<td>0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>236</td>
<td>1,139</td>
<td>2.9 (2.5–3.5)</td>
</tr>
<tr>
<td>Injured body site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head/neck</td>
<td>1,923</td>
<td>9,432</td>
<td>24.2 (22.8–25.6)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>178</td>
<td>866</td>
<td>2.2 (1.8–2.7)</td>
</tr>
<tr>
<td>Vertebral column</td>
<td>175</td>
<td>866</td>
<td>2.2 (1.8–2.7)</td>
</tr>
<tr>
<td>Torso</td>
<td>1,105</td>
<td>5,429</td>
<td>13.9 (13.0–14.9)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>1,214</td>
<td>5,936</td>
<td>15.2 (14.1–16.4)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>2,095</td>
<td>15,061</td>
<td>38.6 (37.0–40.3)</td>
</tr>
<tr>
<td>Other/unspeicified</td>
<td>289</td>
<td>1,420</td>
<td>3.6 (3.2–4.1)</td>
</tr>
<tr>
<td>Type of injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td>4,395</td>
<td>21,407</td>
<td>54.9 (53.0–56.7)</td>
</tr>
<tr>
<td>Dislocation</td>
<td>191</td>
<td>949</td>
<td>2.4 (2.1–2.8)</td>
</tr>
<tr>
<td>Sprains/strains</td>
<td>382</td>
<td>1,893</td>
<td>4.9 (3.8–6.1)</td>
</tr>
<tr>
<td>Internal organ</td>
<td>1,936</td>
<td>9,056</td>
<td>24.4 (22.9–26.0)</td>
</tr>
<tr>
<td>Open wounds</td>
<td>112</td>
<td>545</td>
<td>1.4 (1.2–1.7)</td>
</tr>
<tr>
<td>Superficial/contusion</td>
<td>313</td>
<td>1,525</td>
<td>3.9 (3.4–4.5)</td>
</tr>
<tr>
<td>Other/unspeicified</td>
<td>650</td>
<td>3,186</td>
<td>8.2 (7.4–9.0)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HMO, health maintenance organization.

* Weighted to discharges from all US community, nonrehabilitation hospitals.

# Sums <7979 are because of missing values.
.0001). Hospitals that are located in the western United States had significantly higher total hospital charges compared with hospitals in other regions ($P < .0001$). In particular, hospitals that are located in the western United States had 36.1% greater total hospital charges than hospitals in the Northeast.

After adjustment for patient characteristics and injury type and site, children who were admitted into large or medium bed volume hospitals had longer LOS compared with those who were admitted into small bed volume hospitals, with a 9.5% and 7.7% increase in LOS, respectively ($P = .0001$). Children who were admitted into teaching hospitals also had significantly longer LOS, with a 7.9% ($P < .0001$) increase in LOS compared with children who were admitted to nonteaching hospitals. Uninsured patients tended to have shorter LOS ($P < .0001$) compared with insured patients even after adjustment for other patient characteristics.

**DISCUSSION**

In this study, we analyzed the NIS data and found, nationwide, an estimated 39,010 hospitalizations for sports-related injuries among children who were aged 5 to 18 years between 2000 and 2003. This translates into nearly 10,000 sports injury hospitalizations for this age group each year, resulting in annual charges of $113 to $133 million. Although most sports-related injuries are minor, the NIS data demonstrate that a significant number of sports-related injuries have a major impact on the health and well-being of children. These injuries also constitute a substantial economic burden to the health care system as well as the patient’s family. We found that

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Principal Diagnoses for Sports Injury Hospitalization Among Children Aged 5 to 18: NIS, 2000–2003 ($N = 7979$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Diagnoses</td>
<td>Sample, n</td>
</tr>
<tr>
<td>Fracture of lower extremity</td>
<td>2544</td>
</tr>
<tr>
<td>Fracture of upper extremity</td>
<td>1079</td>
</tr>
<tr>
<td>Internal organ, abdomen</td>
<td>787</td>
</tr>
<tr>
<td>Internal organ, possible traumatic brain injury</td>
<td>623</td>
</tr>
<tr>
<td>Fracture of face</td>
<td>346</td>
</tr>
<tr>
<td>Internal organ, definite traumatic brain injury</td>
<td>326</td>
</tr>
<tr>
<td>Sprain and strain of lower extremity</td>
<td>283</td>
</tr>
<tr>
<td>Fracture, possible traumatic brain injury</td>
<td>136</td>
</tr>
<tr>
<td>Fracture, definite traumatic brain injury</td>
<td>131</td>
</tr>
<tr>
<td>Dislocation of lower extremity</td>
<td>111</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

$^a$ Weighted to discharges from all US community, nonrehabilitation hospitals.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Principal Procedures for Sports Injury Hospitalization Among Children Aged 5 to 18: NIS, 2000–2003 ($N = 7979$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Procedures</td>
<td>Sample, n</td>
</tr>
<tr>
<td>Open reduction of fracture with internal fixation (tibia and fibula, leg NOS)</td>
<td>906</td>
</tr>
<tr>
<td>Closed reduction of fracture without internal fixation (tibia and fibula, leg NOS)</td>
<td>372</td>
</tr>
<tr>
<td>Open reduction of fracture with internal fixation (radius and ulna, arm NOS)</td>
<td>336</td>
</tr>
<tr>
<td>Closed reduction of fracture with internal fixation (femur)</td>
<td>256</td>
</tr>
<tr>
<td>Open reduction of fracture with internal fixation (femur)</td>
<td>239</td>
</tr>
<tr>
<td>Other repair of joint of lower extremity, cruciate ligaments</td>
<td>205</td>
</tr>
<tr>
<td>Closed reduction of fracture without internal fixation (radius and ulna, arm NOS)</td>
<td>202</td>
</tr>
<tr>
<td>Closed reduction of fracture with internal fixation (tibia and fibula, leg NOS)</td>
<td>161</td>
</tr>
<tr>
<td>Open reduction of fracture with internal fixation (humerus)</td>
<td>152</td>
</tr>
<tr>
<td>CAT of head</td>
<td>119</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NOS, not otherwise specified.

$^a$ Weighted to discharges from all US community, nonrehabilitation hospitals.
### TABLE 4
LOS and Total Hospital Charges for Sports Injury Hospitalization Among Children Aged 5 to 18: NIS, 2000 –2003 (N = 7903)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>National Estimate, N (%)</th>
<th>Total Hospital Charges (per discharge), $</th>
<th>LOS, d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Total estimated casesa</td>
<td>38,632</td>
<td>12,777</td>
<td>9,299</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>10,086 (26.1)</td>
<td>11,345</td>
<td>8,443</td>
</tr>
<tr>
<td>2001</td>
<td>9,605 (24.9)</td>
<td>12,340</td>
<td>9,250</td>
</tr>
<tr>
<td>2002</td>
<td>9,378 (24.3)</td>
<td>13,236</td>
<td>9,820</td>
</tr>
<tr>
<td>2003</td>
<td>9,563 (24.8)</td>
<td>14,304</td>
<td>10,007</td>
</tr>
<tr>
<td>Principal diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture of lower extremity</td>
<td>12,189 (31.6)</td>
<td>13,884</td>
<td>11,484</td>
</tr>
<tr>
<td>Fracture of upper extremity</td>
<td>5,138 (13.3)</td>
<td>10,394</td>
<td>8,710</td>
</tr>
<tr>
<td>Internal organ, abdomen</td>
<td>3,687 (9.5)</td>
<td>15,975</td>
<td>9,992</td>
</tr>
<tr>
<td>Internal organ, possible traumatic brain injury</td>
<td>2,955 (7.6)</td>
<td>7,621</td>
<td>4,906</td>
</tr>
<tr>
<td>Fracture of face</td>
<td>1,643 (4.3)</td>
<td>11,426</td>
<td>9,654</td>
</tr>
<tr>
<td>Internal organ, definite traumatic brain injury</td>
<td>1,510 (3.9)</td>
<td>17,214</td>
<td>7,700</td>
</tr>
<tr>
<td>Sprain and strain of lower extremity</td>
<td>1,325 (3.4)</td>
<td>16,980</td>
<td>14,336</td>
</tr>
<tr>
<td>Fracture, possible traumatic brain injury</td>
<td>654 (1.7)</td>
<td>11,424</td>
<td>6,514</td>
</tr>
<tr>
<td>Fracture, definite traumatic brain injury</td>
<td>625 (1.6)</td>
<td>18,814</td>
<td>11,560</td>
</tr>
<tr>
<td>Dislocation of lower extremity</td>
<td>519 (1.3)</td>
<td>10,003</td>
<td>6,195</td>
</tr>
</tbody>
</table>

a Patients who were transferred to a short-term hospital were excluded.

b Weighted to discharges from all US community, nonrehabilitation hospitals.

c Total hospital charges were weighted for national estimates of total charges and adjusted to the year 2003 inflation rates for in-hospital care.

### TABLE 5
Hospital Characteristics Associated With LOS and Total Hospital Charges for Sports Injury Hospitalization Among Children Aged 5 to 18: NIS, 2000 –2003 (N = 7903)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LOS, d</th>
<th>Total Hospital Charges, $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Change (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2000</td>
<td>0.0 (0.0 to 0.0)</td>
<td>0.0 (0.0 to 0.0)</td>
</tr>
<tr>
<td>2001</td>
<td>2.48 (−3.42 to 8.73)</td>
<td>7.30 (0.61 to 14.43)</td>
</tr>
<tr>
<td>2002</td>
<td>3.89 (−2.25 to 10.41)</td>
<td>18.24 (11.04 to 25.92)</td>
</tr>
<tr>
<td>2003</td>
<td>5.68 (−0.43 to 12.16)</td>
<td>20.42 (12.39 to 29.03)</td>
</tr>
<tr>
<td>Hospital location</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Rural</td>
<td>0.0 (0.0 to 0.0)</td>
<td>0.0 (0.0 to 0.0)</td>
</tr>
<tr>
<td>Urban</td>
<td>5.61 (−5.40 to 17.89)</td>
<td>5.75 (−1.46 to 17.39)</td>
</tr>
<tr>
<td>Hospital bed size</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Small</td>
<td>0.0 (0.0 to 0.0)</td>
<td>0.0 (0.0 to 0.0)</td>
</tr>
<tr>
<td>Medium</td>
<td>7.66 (2.80 to 12.75)</td>
<td>0.21 (−8.86 to 10.18)</td>
</tr>
<tr>
<td>Large</td>
<td>9.49 (4.96 to 14.23)</td>
<td>2.96 (−7.62 to 1.93)</td>
</tr>
<tr>
<td>Teaching status of hospital</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Nonteaching</td>
<td>0.0 (0.0 to 0.0)</td>
<td>0.0 (0.0 to 0.0)</td>
</tr>
<tr>
<td>Teaching</td>
<td>7.86 (4.12 to 11.73)</td>
<td>36.07 (23.60 to 49.80)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Northeast</td>
<td>0.0 (0.0 to 0.0)</td>
<td>0.0 (0.0 to 0.0)</td>
</tr>
<tr>
<td>Midwest</td>
<td>9.20 (4.15 to 14.50)</td>
<td>−2.58 (−10.49 to 6.03)</td>
</tr>
<tr>
<td>South</td>
<td>4.78 (0.21 to 9.55)</td>
<td>−0.71 (−9.55 to 8.76)</td>
</tr>
<tr>
<td>West</td>
<td>−1.77 (−8.60 to 5.57)</td>
<td>36.07 (23.60 to 49.80)</td>
</tr>
<tr>
<td>Payer information</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Medicare/Medicaid</td>
<td>0.0 (0.0 to 0.0)</td>
<td>0.0 (0.0 to 0.0)</td>
</tr>
<tr>
<td>Private including HMO</td>
<td>−9.59 (−13.15 to −5.88)</td>
<td>−2.96 (−7.62 to −1.93)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>−10.83 (−16.43 to −4.23)</td>
<td>−8.05 (−15.39 to −0.08)</td>
</tr>
<tr>
<td>Other</td>
<td>−4.14 (−8.83 to 3.05)</td>
<td>−0.16 (−7.50 to 7.77)</td>
</tr>
</tbody>
</table>

a Patients who were transferred to a short-term hospital were excluded.

b Weighted to discharges from all US community, nonrehabilitation hospitals.

c Total hospital charges was weighted for national estimates of total charges and adjusted to the year 2003 inflation rates for in-hospital care. The model for total hospital charge per discharge was based on 7135 observations after the potentially influential observations were removed. The results listed were adjusted for LOS, age, gender, type of injury, injury body site, and admission source.
although the number of hospitalizations did not increase during the study period, the total hospital charges increased significantly. This disparity indicates an increase in costs to families and third-party payers. To our knowledge, this is the first study to describe the extent and characteristics of pediatric sports injuries that result in hospitalization nationwide. Our findings provide an empirical basis for future research on the magnitude of sports-related injuries that result in hospitalization and suggest priorities for future intervention strategies. These findings are an underestimation of the total number of hospitalizations because only 3 E-codes that are very specific to sports injuries were used; many other sports injuries may have codes that do not specify the injury as being sports related.

Consistent with previous findings from ED studies, boys and teenagers were more likely to sustain sports-related injuries. Our data also showed that the number of children who were admitted to hospitals for sports-related injuries was 6 times higher for boys than for girls. In addition, children in either the 10- to 14- or 15- to 18-year age groups had approximately 5 times as many hospitalizations for sports-related injuries than those who were aged 5 to 9. The age and gender differences that were observed in this study suggest that teenage boys not only may be at a greater risk for injury when playing sports but also tend to be more severely injured compared with girls and boys of younger ages. The higher sports exposure of a teenage boy may be partly responsible for such an elevated risk, although other behavioral (eg, willingness to take risks, thrill seeking) and physical (eg, increased muscle mass, larger force of impact) factors also may contribute to the observed differences. Additional investigation into why teenage boys are at an increased risk for pediatric sports injury hospitalization is warranted.

Although the proportion of all sports-related injuries that result in hospitalization is small, the absolute number of hospitalizations was high. Nationwide, at least 10 000 children and adolescents aged 5 to 18 years are hospitalized each year as a result of sports-related injuries. This equates to daily averages of 23 boys, 8 new lower extremity fractures, and 4 new traumatic brain injuries that result in hospitalization from sports-related injuries from only the 3 E-codes included.

Our findings showed that children with sports injuries were more likely to be admitted to large, urban, teaching hospitals, and children in these hospitals also had longer hospital LOS and higher hospital charges. Participation of greater numbers of urban youth in organized sports may explain in part the larger proportion of urban hospitalizations. Other possible explanations may include the greater availability of medical resources, including trauma centers, in large urban hospitals; the referral of more severe injuries to large urban hospitals for treatment; the concentration of advanced diagnostic equipment and treatment techniques, including image testing and orthopedic surgeries, in large urban hospitals; and the limited sideline care at sporting events in rural communities. Another potential factor is increased use of E-codes that specifically identify sports injuries in large, teaching hospitals.

The average hospital LOS was 2.4 days, which likely represents more missed school days for the child and work days for the parents during hospitalization and recovery. A hospitalization can add tremendous stress to the patient’s family and/or caregiver, both financially and psychologically. This could be even more burdensome for the rural family who must travel to a large urban hospital for necessary treatment of their injured child.

Our findings revealed that the most frequent injury diagnoses for pediatric sports injury hospitalizations involved fractures, a cause of serious physical damage and potentially permanent disability. The average hospital charges per fracture were almost $14 000. Such charges may be devastating for a family without adequate health insurance, and even for those with insurance coverage, copayments may be high enough to be financially damaging.

It is not uncommon that an injured child has to modify his or her level of sporting activity after hospitalization. In some cases, the child may not be able to play a particular sport any more and may have to choose another sport. For many children, their participation in sports serves as, at least, a significant source of peer interaction, if not a major construct for their self-identity. The stress of removal from sports participation as a result of a severe injury likely compounds that of hospitalization and treatment.

Approximately half of all American children who are aged 5 to 18 years participate in organized sports. With the epidemic of obesity in the population, sports participation can be a valuable tool to promote physical activity and healthful living. Although participation in sports activities involves an inherent risk for injury, research has demonstrated that most of these injuries are preventable. Existing injury prevention programs have been successful in preventing the occurrence of sports injuries or reducing the severity of the injury, through the development and enforcement of safety rules, protective gear, and changes in sporting equipment and environments. This research objectively demonstrates the need for more investigation into the prevention of sports-related injuries. Other authors have suggested that without adequate sports safety measures, sports-related injuries and hospitalizations may become more widespread. Our research validates these concerns by illustrating the significant number of severe sports-related injuries that occur each year.

This study has several limitations. NIS data are derived from hospital discharge data, which lack informa
tation on sports exposure. Therefore, we could not determine the rate of pediatric sports injury hospitalizations or compare the risk among different sports. The financial charge information provided by the NIS is based on hospital charges, not actual costs. In general, hospital charges are greater than actual costs. However, several charges (eg, physician professional fees, emergency transportation costs, subsequent rehabilitation costs) are not included as part of the hospital charge. Therefore, our estimation of total hospital charges may not reflect fully the financial impact of sports injury hospitalization on the patients and their families. Our case definition of sports injury hospitalization relied on 3 E-codes, which had high specificity but low sensitivity. In addition, not all hospitals in the United States were included in the NIS. Therefore, our projection of the number of sports injury hospitalizations could have been underestimated.

Despite these limitations, findings from our study demonstrate the significant morbidity and economic consequences that are associated with pediatric sports injury hospitalizations. Our findings will help to create a better understanding of the scope of and outcomes that are associated with pediatric sports injury hospitalizations so that intervention strategies can be developed to improve the quality of care, to maximize the recovery process, and to direct an effort to prevent future injuries.

CONCLUSIONS
This study analyzed characteristics of sports-related injuries that resulted in hospitalization in children. The findings of the study are important because the physical damage and financial burden that result from such an injury could have a lifelong impact on the children and their families.

Because participation in sports activity is widely promoted as part of a healthful lifestyle, pediatricians and other child health care providers can play a critical role in educating children, parents, and policy makers about injury prevention. More research is needed to identify risk factors that are associated with sports injury hospitalization. Prevention efforts also should address the severity of sports injury to reduce injury-related morbidity and the economic costs of treating these injuries.

REFERENCES
Preventive Health Care for Children With and Without Special Health Care Needs

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ABSTRACT

OBJECTIVE. The objective of this study was to compare the receipt of preventive health services for children with and without special health care needs and to identify predictors of these health services for children with special health care needs using nationally representative data.

METHODS. Data from the 2002 and 2003 Medical Expenditure Panel Surveys were analyzed. A total of 18,279 children aged 3 to 17 years were included in our study. The Child Preventive Health Supplement was used to identify caregiver recall of specific health screening measures and anticipatory guidance during the previous 12 months. Odds ratios were calculated for predictive factors of preventive services for children with special health care needs.

RESULTS. The prevalence of special health care needs in children aged 3 to 17 years was 21.6%. Based on caregiver reports, 87.5% of children with special health care needs had ≥1 health screening measure checked in the past year compared with 73.1% of children without special health care needs. Receipt of ≥1 topic of anticipatory guidance was reported for 69.8% of children with special health care needs compared with 55.2% of children without special health care needs. Black and Hispanic caregivers of children with special health care needs were more likely than others to report receipt of all 6 categories of anticipatory guidance measured in this study.

CONCLUSIONS. We found that caregivers of children with special health care needs were more likely to report receipt of anticipatory guidance and health screening than were caregivers of children without special health care needs. Although a majority of these caregivers reported receiving some health screening and anticipatory guidance on an annual basis, there are clear gaps in the delivery of preventive health services. This study identifies areas for improvement in the delivery of preventive health services for children with special health care needs and children in general.
A long with immunizations, anticipatory guidance and health monitoring are the cornerstones of well-child care for both healthy children and children with special health care needs (CSHCN). The American Academy of Pediatrics (AAP) provides recommendations for pediatric health supervision visits through their Guidelines for Health Supervision III. In addition, the Maternal and Child Health Bureau (MCHB) launched a major initiative to improve the quality of health promotion and preventive services for infants, children, and adolescents through the sponsorship of Bright Futures. These recommendations call for periodic monitoring, screening, and guidance for all children. Furthermore, preventive care is an essential part of the AAP’s Medical Home policy statement. Specifically, the AAP states that primary care services should include “growth and developmental assessments, appropriate screening, health care supervision, and patient and parent counseling about health, nutrition, and safety.” Many recent studies have focused on access to and use of preventive health care and anticipatory guidance for children in general, but there is a paucity of such data for CSHCN. Instead, most previous research for CSHCN focused on access to selected components of the medical home, excluding preventive care. At this point, there is little research regarding general health care maintenance and the quality of these services for CSHCN.

A recent study that was presented as an abstract at the Pediatric Academic Society Meeting 2006 found no difference between children with and without special health care needs in terms of preventive health topics discussed. Unpublished data from the 2000 Iowa Child and Family Household Health Survey indicated that CSHCN received more anticipatory guidance than their healthy age-matched peers. Specifically, that survey found that 39% of families with CSHCN reported anticipatory guidance about seat belts, car seats, bicycle safety, or nutritional counseling compared with 26% of families with healthy children. At this point, there is little research regarding general health care maintenance and the quality of these services for CSHCN.

The MCHB defines CSHCN as children who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or an amount beyond that required by children generally. Excluding children who are at risk for developing a special health care need, CSHCN make up 13% to 18% of the pediatric population, depending on the data source. These children tend to use more health care services than other children and have higher health care expenditures. Anecdotal evidence suggests that CSHCN receive less preventive health care than their healthy peers, because their special health care needs dominate clinical encounters. Care for these children is dynamic, and many health care providers find their energies consumed by time-intensive chronic condition or disability-related issues.

The purpose of this study was to determine how frequently children with and without special health care needs are receiving some of the preventive health screening and anticipatory guidance that are recommended by the AAP. Our study is the first to evaluate preventive health care and identify predictors for the receipt of these services for CSHCN using nationally representative data: the 2002 and 2003 Medical Expenditure Panel Surveys (MEPS).

**METHODS**

MEPS provides national estimates of health care use, expenditures, and insurance coverage for the US civilian, noninstitutionalized population, including children. MEPS is composed of 4 components: the Household Component, the Medical Provider Component, the Insurance Component, and the Nursing Home Component. In 2002 and 2003, a total of 18 445 children who were aged 3 to 17 years were surveyed by MEPS. Valid response data were available for 18 279 of those children and were included in our study. An adult caregiver, usually a parent, answered questions about health and health services use for all children.

The screening instrument that was used in MEPS to identify CSHCN, the CSHCN Screener, identified children who had a medical, behavioral, or other health condition that had lasted or was expected to last ≥1 year, and reported ≥1 of the following consequences of the condition: (1) using or needing more medical care, mental health services, or education services than other children of the same age; (2) using or needing prescription medication; (3) having limitations in their ability to do the things that most children of the same age do; (4) using or needing special therapies, such as physical, occupational, or speech therapy; or (5) using or needing emotional, developmental, or behavioral treatment or counseling. Children were classified as having or not having special health care needs based on data from the CSHCN Screener. Children who were at risk for having a special health care need were not identified by this questionnaire. The prevalence of CSHCN then was calculated, and classification of children from the CSHCN Screener stratified the population for the rest of the measures.

We calculated the number of health care visits for children with and without special health care needs from questions that were included in the MEPS Child Preventive Health Supplement. On the basis of caregiver recall, additional questions identified whether sample children had their height, weight, and/or blood pressure checked during the past 12 months or ever had their vision evaluated. For anticipatory guidance, parents were asked whether their provider gave advice about dental care, passenger automobile safety, bicycle helmet...
use, exercise, healthful eating, and secondhand smoke exposure during the past 12 months.

We also created the categories of all, any, or none by calculating the percentages of caregivers who reported receipt of all, any, or none of the health screening parameters or anticipatory guidance topics. For example, if caregivers recalled the receipt of anticipatory guidance for 1 or more topics (but not all), then the data were classified in the any category. Likewise, data from caregivers who reported receipt of all of the measured anticipatory guidance topics were classified in the all category, whereas data from caregivers who reported receipt of 0 topics were classified in the none category. The same all, any, and none categories were calculated separately for health screening measures. We then identified predictive factors for the receipt of health screening and anticipatory guidance for CSHCN. Although the measures of health screening and anticipatory guidance that were identified in this study do not encompass all of the health screening parameters and anticipatory guidance topics that are recommended by the AAP, they provide a representative cross-section.

Estimates that are presented in the tables and text were statistically weighted to reflect national population totals. The weights, provided by the MEPS, are equal to the inverse of the sampling probability for each case, adjusted for nonresponse. We present results from bivariate and multivariate statistics. Our multivariate analyses used logistic regression methods to control for possible confounding. Standard errors and test statistics were derived using Stata software that takes into account the complex sample design of the survey.

### RESULTS

A total of 18,279 children who were between 3 and 17 years of age were included in our analysis (Table 1). Of these children, 3,660 were CSHCN. The prevalence of special health care needs was 21.6% and was found to be higher in non-Hispanic white (23.7%) and black children (21.4%) than in Hispanic children (16.1%; $P < .001$ for all comparisons). Among children who were aged 3 to 17 years and had health insurance, 22.3% were CSHCN; in contrast, only 13.3% of children without health insurance were identified as CSHCN ($P < .001$). A higher percentage of boys (23.4%) were CSHCN than girls (19.7%; $P < .001$). There were significant regional differences in the prevalence of CSHCN ($P < .01$): the Midwest had the highest prevalence of CSHCN (23.4%), and the West had the lowest prevalence rate (18.5%). No significant difference was found when children were stratified by poverty status.

The vast majority (89.6%) of all survey respondents reported that their child had a usual source of care. However, CSHCN more frequently had a usual source of care (94.8%) compared with children without special health care needs (88.1%; $P < .001$). In the 12 months preceding the interview, children averaged 2.8 health care provider office visits. CSHCN made a significantly higher number of office visits than children without special health care needs (6.1 vs 1.9 per year; $P < .001$).

As shown in Table 2, caregivers of CSHCN were significantly more likely than other caregivers to report that their child had their height and weight checked in the 12 months before the survey administration (Table 2). Similarly, they were more likely to

### TABLE 1 Prevalence and Characteristics of CSHCN

<table>
<thead>
<tr>
<th>Population</th>
<th>$n$</th>
<th>Sample No. of CSHCN</th>
<th>Estimated Total Population, $\times 1000$</th>
<th>Estimated Total Population of CSHCN, $\times 1000$</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 3–17 y</td>
<td>18,279</td>
<td>3,660</td>
<td>61,023</td>
<td>13,175</td>
<td>21.6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9,363</td>
<td>2,056</td>
<td>31,225</td>
<td>7,295</td>
<td>23.4</td>
</tr>
<tr>
<td>Female</td>
<td>8,916</td>
<td>1,604</td>
<td>29,798</td>
<td>5,880</td>
<td>19.7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>7,631</td>
<td>1,879</td>
<td>36,638</td>
<td>8,698</td>
<td>23.7</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>3,370</td>
<td>724</td>
<td>9,251</td>
<td>2,083</td>
<td>21.4</td>
</tr>
<tr>
<td>Other non-Hispanic</td>
<td>1,179</td>
<td>199</td>
<td>4,131</td>
<td>727</td>
<td>17.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6,099</td>
<td>858</td>
<td>11,003</td>
<td>1,767</td>
<td>16.1</td>
</tr>
<tr>
<td>Income level, % FPL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>9,785</td>
<td>2,081</td>
<td>22,981</td>
<td>4,863</td>
<td>21.2</td>
</tr>
<tr>
<td>200–399</td>
<td>5,237</td>
<td>1,030</td>
<td>20,772</td>
<td>4,339</td>
<td>20.9</td>
</tr>
<tr>
<td>$\geq$400</td>
<td>3,257</td>
<td>749</td>
<td>17,270</td>
<td>3,973</td>
<td>23.0</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insured</td>
<td>16,501</td>
<td>3,474</td>
<td>56,538</td>
<td>12,579</td>
<td>22.6</td>
</tr>
<tr>
<td>Uninsured</td>
<td>1,778</td>
<td>186</td>
<td>4,485</td>
<td>96</td>
<td>13.3</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>2,720</td>
<td>658</td>
<td>10,874</td>
<td>2,519</td>
<td>23.2</td>
</tr>
<tr>
<td>Midwest</td>
<td>3,366</td>
<td>793</td>
<td>13,675</td>
<td>3,206</td>
<td>23.4</td>
</tr>
<tr>
<td>South</td>
<td>6,894</td>
<td>1,367</td>
<td>21,639</td>
<td>4,712</td>
<td>21.8</td>
</tr>
<tr>
<td>West</td>
<td>5,299</td>
<td>842</td>
<td>14,835</td>
<td>2,738</td>
<td>18.5</td>
</tr>
</tbody>
</table>

report blood pressure monitoring (69.5% vs 50.7%; \( P < .001 \)). Of children who were between the ages of 3 and 6 years, 60.5% reportedly had their vision screened by a health care provider at least once in their lifetime; no statistical difference was noted between children with and without special health care needs.

On the basis of caregiver reports, 41.5% of children without special health care needs had all health screening parameters checked compared with 60.8% of CSHCN (\( P < .001 \)). CSHCN also were more likely than other children to have had \( \geq 1 \) parameter checked (87.5% vs 73.1%; \( P < .001 \)). This means that 12.5% of caregivers of CSHCN did not recall having any screening parameters checked in the 12 months preceding the study and neither did 26.9% of caregivers of children without special health care needs (\( P < .001 \)). Among the subset of children with \( \geq 1 \) office visit in the previous 12 months, 90.7% of CSHCN received \( \geq 1 \) type of health screening compared with 85.1% of children without special health care needs (\( P < .001 \)). In addition, caregivers of CSHCN were more likely than the caregivers of children without special health care needs to report that \( \geq 1 \) topic of anticipatory guidance was discussed (69.8% vs 55.2%; \( P < .001 \)). The statistical difference persisted when presentation to a health care provider in the year before the survey was accounted for. Of the CSHCN who made an office visit, 72.5% of caregivers reported being given advice about \( \geq 1 \) of the anticipatory guidance topics compared with 63.5% of caregivers of children without special health care needs (\( P < .001 \)). Only 8.6% of caregivers reported having all 6 anticipatory guidance topics discussed, and there was no significant difference between caregivers of CSHCN and caregivers of children without special health care needs. In addition, 41.7% of all caregivers did not recall having received any anticipatory guidance in the 12 months preceding the study. Caregivers of children without special health care needs were significantly more likely than the caregivers of CSHCN to report having 0 anticipatory guidance topics discussed in the past year by a health care provider (44.8% vs 30.2%; \( P < .001 \)).

Predictive factors for receipt of health screening for dental checkups (40.1% vs 33.8%; \( P < .001 \)), healthful eating (47.6% vs 36%; \( P < .001 \)), wearing a helmet (30.6% vs 25.6%; \( P < .001 \)), secondhand smoke exposure (35.1% vs 27%; \( P < .001 \)), and exercise (36.6 vs 25.3%; \( P < .001 \)). In addition, caregivers of CSHCN were more likely than the caregivers of children without special health care needs to report that \( \geq 1 \) topic of anticipatory guidance was discussed (69.8% vs 55.2%; \( P < .001 \)). The statistical difference persisted when presentation to a health care provider in the year before the survey was accounted for. Of the CSHCN who made an office visit, 72.5% of caregivers reported being given advice about \( \geq 1 \) of the anticipatory guidance topics compared with 63.5% of caregivers of children without special health care needs (\( P < .001 \)). Only 8.6% of caregivers reported having all 6 anticipatory guidance topics discussed, and there was no significant difference between caregivers of CSHCN and caregivers of children without special health care needs. In addition, 41.7% of all caregivers did not recall having received any anticipatory guidance in the 12 months preceding the study. Caregivers of children without special health care needs were significantly more likely than the caregivers of CSHCN to report having 0 anticipatory guidance topics discussed in the past year by a health care provider (44.8% vs 30.2%; \( P < .001 \)).

### Table 2: Percentages of Health Screening in the Past Year According to Special Needs Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSHCN</th>
<th>Children Without Special Health Care Needs</th>
<th>All Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height and weight checked</td>
<td>82.3 (0.79)</td>
<td>66.6 (0.75)</td>
<td>70.0 (0.64)</td>
</tr>
<tr>
<td>Blood pressure checked</td>
<td>69.4 (0.97)</td>
<td>50.7 (0.74)</td>
<td>54.8 (0.67)</td>
</tr>
<tr>
<td>Vision checked</td>
<td>62.8 (2.66)</td>
<td>60.0 (1.26)</td>
<td>60.5 (1.16)</td>
</tr>
<tr>
<td>All parameters checked</td>
<td>60.8 (1.00)</td>
<td>41.5 (0.75)</td>
<td>45.6 (0.69)</td>
</tr>
<tr>
<td>Any parameter</td>
<td>87.5 (0.67)</td>
<td>73.1 (0.69)</td>
<td>76.2 (0.59)</td>
</tr>
<tr>
<td>None of the parameters</td>
<td>12.5 (0.67)</td>
<td>26.9 (0.69)</td>
<td>23.8 (0.59)</td>
</tr>
</tbody>
</table>

Data are presented as % (SE).

* \( \chi^2 \) significant at .001 level.

Asks whether ever performed, not necessarily in the past 12 months; only 3- to 6-year-olds.


### Table 3: Percentages of Anticipatory Guidance in the Past Year by Special Needs Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSHCN</th>
<th>Children Without Special Health Care Needs</th>
<th>All Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advice about dental checkups</td>
<td>40.1 (1.21)</td>
<td>33.8 (0.76)</td>
<td>35.2 (0.71)</td>
</tr>
<tr>
<td>Advice about healthful eating</td>
<td>47.6 (1.29)</td>
<td>36.0 (0.75)</td>
<td>38.5 (0.70)</td>
</tr>
<tr>
<td>Advice about passenger automobile safety (car seats, booster seats, and seat belts)</td>
<td>26.3 (1.13)</td>
<td>24.5 (0.64)</td>
<td>24.9 (0.65)</td>
</tr>
<tr>
<td>Advice about wearing a helmet</td>
<td>30.6 (1.19)</td>
<td>25.6 (0.73)</td>
<td>26.7 (0.70)</td>
</tr>
<tr>
<td>Advice about secondhand smoke exposure</td>
<td>35.1 (1.20)</td>
<td>27.0 (0.72)</td>
<td>28.8 (0.71)</td>
</tr>
<tr>
<td>Advice about exercise</td>
<td>36.6 (1.08)</td>
<td>25.3 (0.74)</td>
<td>27.8 (0.69)</td>
</tr>
<tr>
<td>All 6 topics discussed</td>
<td>9.2 (0.73)</td>
<td>8.4 (0.46)</td>
<td>8.6 (0.45)</td>
</tr>
<tr>
<td>Any topic</td>
<td>69.8 (1.10)</td>
<td>55.2 (0.77)</td>
<td>58.4 (0.72)</td>
</tr>
<tr>
<td>None</td>
<td>30.2 (1.10)</td>
<td>44.8 (0.77)</td>
<td>41.7 (0.72)</td>
</tr>
</tbody>
</table>

Data are presented as % (SE).

* \( \chi^2 \) significant at .001 level.

CSHCN are shown in Table 4. Caregivers of CSHCN who had fair or poor health status were more likely to recall having had at least 1 health screening parameter checked in the previous 12 months than those with children with excellent health status (odds ratio [OR]: 1.81; 95% confidence interval [CI]: 1.03–3.16), but health status did not predict recall of receipt of all parameters. When compared with those who were living above 400% of the federal poverty level (FPL), caregivers of CSHCN who were living below 200% of the FPL were significantly less likely to recall having had any parameters checked (OR: 0.76; 95% CI: 0.60–0.96). Caregivers of CSHCN in the middle family income category of 200% to 399% of the FPL were less likely to recall having had any health screening parameter checked (OR: 0.66; 95% CI: 0.48–0.92) but not significantly different in recall of having had all parameters checked. In addition, caregivers of uninsured CSHCN were significantly less likely than their insured peers to recall having had any or all parameters checked (OR: 0.50 [95% CI: 0.30–0.84] and 0.60 [95% CI: 0.38–0.96], respectively. Compared with residence in the Northeast, living in the Midwest, South, and West decreased the likelihood of recalling having had any health screening (OR: 0.38 [95% CI: 0.23–0.65], 0.38 [95% CI: 0.23–0.63], and 0.32 [95% CI: 0.19–0.53]), respectively. Race was not a significant predictor of health screening.

Table 5 shows predictive factors for the receipt of anticipatory guidance. Caregivers of Hispanic and black CSHCN were more likely than caregivers of white children to report receipt of ≥1 topic of anticipatory guidance (OR: 1.37 [95% CI: 1.06–1.76] and 1.48 [95% CI: 1.12–1.96]), respectively. Caregivers of Hispanic and black CSHCN also were more likely to recall having had all items addressed than caregivers of white children (OR: 2.09 [95% CI: 1.40–3.12] and 2.24 [95% CI: 1.42–3.51]), respectively. Having a child with special health care needs in fair/poor or good health increased the likelihood of recalling that ≥1 anticipatory guidance topic was covered compared with those with CSHCN in excellent health (OR: 1.77 [95% CI: 1.19–2.62] and 1.32 [95% CI: 1.05–1.66]), respectively. In contrast, health status was not a predictor for any subgroup of having all anticipatory guidance topics discussed. Caregivers of CSHCN who were living below 400% of the FPL were significantly less likely than those above to recall having had any anticipatory guidance topic discussed (OR: 0.64; 95% CI: 0.49–0.84). Caregivers of CSHCN with incomes between 200% and 399% of the FPL also were less likely

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds of Having All Health Screening Measures in the Past 12 mo</th>
<th>Odds of Having Some (at Least 1) Health Screening Measures in the Past 12 mo</th>
<th>Odds of Having No Health Screening Measures in the Past 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Reference</td>
<td>1.95 (1.63–2.33)</td>
<td>0.75 (0.57–1.00)</td>
</tr>
<tr>
<td></td>
<td>3–10</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>11–17</td>
<td>1.26 (0.89–1.78)</td>
<td>1.81 (1.03–3.16)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.07 (0.86–1.34)</td>
<td>1.32 (1.05–1.66)</td>
</tr>
<tr>
<td>Race</td>
<td>White non-Hispanic</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Black non-Hispanic</td>
<td>1.29 (0.82–2.04)</td>
<td>1.10 (0.56–2.16)</td>
</tr>
<tr>
<td></td>
<td>Other non-Hispanic</td>
<td>1.07 (0.86–1.34)</td>
<td>1.31 (0.97–1.76)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Income level, % FPL</td>
<td>0.65 (0.48–0.96)</td>
<td>0.66 (0.48–0.92)</td>
</tr>
<tr>
<td></td>
<td>≥400</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>200–399</td>
<td>0.76 (0.60–0.96)</td>
<td>0.77 (0.52–0.97)</td>
</tr>
<tr>
<td></td>
<td>&lt;200</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Insurance</td>
<td>Insured</td>
<td>0.60 (0.38–0.96)</td>
<td>0.50 (0.30–0.84)</td>
</tr>
<tr>
<td></td>
<td>Uninsured</td>
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<td>Reference</td>
</tr>
<tr>
<td>Health status</td>
<td>Excellent</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>1.03 (0.82–1.31)</td>
<td>1.37 (0.99–1.89)</td>
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<tr>
<td></td>
<td>Fair/poor</td>
<td>1.26 (0.89–1.78)</td>
<td>1.81 (1.03–3.16)</td>
</tr>
<tr>
<td>Region</td>
<td>Northeast</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Midwest</td>
<td>0.69 (0.51–0.92)</td>
<td>0.38 (0.23–0.65)</td>
</tr>
<tr>
<td></td>
<td>South</td>
<td>0.68 (0.52–0.88)</td>
<td>0.38 (0.23–0.63)</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>0.65 (0.48–0.89)</td>
<td>0.32 (0.19–0.53)</td>
</tr>
</tbody>
</table>

Data are presented as adjusted OR (95% CI).
to recall having had all 6 anticipatory guidance topics discussed (OR: 0.49; 95% CI: 0.32–0.74) than CSHCN in families with incomes above 400% of the FPL, whereas caregivers of CSHCN who were living below 200% of FPL did not differ significantly from those above 400% of the FPL for recall of receipt of all 6 anticipatory guidance topics. Residence in the Northeast was a predictor of anticipatory guidance. Compared with the Northeast, caregivers of CSHCN who were living in the Midwest, South, and West were significantly less likely to recall having received any anticipatory guidance (OR: 0.55 [95% CI: 0.35–0.87], 0.62 [0.40–0.97], and 0.55 [0.34–0.89], respectively. Age, gender, and insurance status were not significant predictors for receipt of anticipatory guidance.

**DISCUSSION**

Our study examined how frequently caregivers recall receipt of preventive health care screening and anticipatory guidance. We note that caregiver recall is a proxy measure for receipt of services in the discussion that follows. We found that, consistent with previously published results, nearly two thirds of all children received ≥1 anticipatory guidance topic at their office visit.\(^6\)\(^{25,26}\) Nelson et al\(^25\) found that families reported that anticipatory guidance topics were discussed for 62% of relevant recommended topics. Schuster et al\(^6\) found that for 6 recommended anticipatory guidance topics, coverage ranged from 23% to 62%. The Agency for Healthcare Research and Quality (AHRQ) detailed in its 2004 National Healthcare Quality/Disparities Reports that 36% of parents were counseled about healthful eating for their child.\(^26\) Results from the Physicians’ Practice Survey found that 80% of pediatricians reported discussing ≥1 anticipatory guidance topic during routine office visits.\(^8\) With respect to health screening, the AHRQ found that 71% of children had their height and weight measured by a health care professional in 2001.\(^26\) Our results are consistent with the data from the AHRQ. No other studies were available for additional comparison of health screening.

Our study also compared the rates of health care screening and anticipatory guidance between CSHCN and children without special health care needs. Some­what surprising, we found that CSHCN were more likely than their peers to receive anticipatory guidance and were more likely to receive preventive health screening.

### TABLE 5 Predictors of Anticipatory Guidance Among CSHCN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds of Having All Areas of Anticipatory Guidance Covered in the Past 12 mo</th>
<th>Odds of Having Some (At Least 1) Areas of Anticipatory Guidance Covered in the Past 12 mo</th>
<th>Odds of Having No Anticipatory Guidance Covered in the Past 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–10</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>11–17</td>
<td>0.87 (0.66–1.14)</td>
<td>0.89 (0.72–1.10)</td>
<td>1.12 (0.91–1.39)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>0.92 (0.71–1.20)</td>
<td>1.06 (0.87–1.29)</td>
<td>0.95 (0.78–1.15)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>2.09 (1.40–3.12)</td>
<td>1.37 (1.06–1.76)</td>
<td>0.73 (0.57–0.95)</td>
</tr>
<tr>
<td>Other non-Hispanic</td>
<td>0.38 (0.15–0.98)</td>
<td>1.17 (0.77–1.78)</td>
<td>0.86 (0.56–1.30)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.24 (1.42–3.51)</td>
<td>1.48 (1.12–1.96)</td>
<td>0.67 (0.51–0.89)</td>
</tr>
<tr>
<td>Income level, % FPL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥400</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>200–399</td>
<td>0.49 (0.32–0.74)</td>
<td>0.64 (0.49–0.85)</td>
<td>1.56 (1.18–2.06)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>0.73 (0.50–1.08)</td>
<td>0.64 (0.49–0.84)</td>
<td>1.55 (1.19–2.03)</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insured</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Uninsured</td>
<td>0.77 (0.33–1.80)</td>
<td>0.67 (0.44–1.03)</td>
<td>1.49 (0.97–2.29)</td>
</tr>
<tr>
<td>Health status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Very good</td>
<td>0.89 (0.62–1.27)</td>
<td>1.18 (0.94–1.49)</td>
<td>0.85 (0.67–1.06)</td>
</tr>
<tr>
<td>Good</td>
<td>0.85 (0.57–1.27)</td>
<td>1.52 (1.05–1.96)</td>
<td>0.76 (0.60–0.95)</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>1.12 (0.70–1.79)</td>
<td>1.77 (1.19–2.62)</td>
<td>0.57 (0.38–0.84)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Midwest</td>
<td>0.55 (0.35–0.87)</td>
<td>0.60 (0.43–0.84)</td>
<td>1.66 (1.19–2.32)</td>
</tr>
<tr>
<td>South</td>
<td>0.62 (0.40–0.97)</td>
<td>0.59 (0.44–0.87)</td>
<td>1.70 (1.28–2.26)</td>
</tr>
<tr>
<td>West</td>
<td>0.55 (0.34–0.89)</td>
<td>0.48 (0.35–0.66)</td>
<td>2.09 (1.52–2.87)</td>
</tr>
</tbody>
</table>

Data are presented as adjusted OR (95% CI).

than children without special health care needs. This contradicts anecdotal evidence and the perception that CSHCN may not receive adequate anticipatory guidance and health screening compared with children without special health care needs. Notably, our results are consistent with the unpublished data from the 2000 Iowa Child and Family Household Health Survey.12

Our study adds to the existing literature in several substantive ways. First, we were able to describe, using a nationally representative sample, the frequency of anticipatory guidance and preventive health care screening in CSHCN for the areas surveyed in the Child Preventive Health Supplement of the MEPS. Second, we were able to show that CSHCN were more likely to receive both anticipatory guidance and preventive health screening when compared with their peers without special health care needs. We also identified some disparities within the population of CSHCN. CSHCN who were living below 200% of the FPL were significantly less likely than those from higher income families to have any health screening parameters checked. They also were less likely to have all screening parameters checked. This suggests that family income was positively associated with having health screening parameters checked by a provider regardless of health status. In addition, uninsured CSHCN were significantly less likely to have any or all health screening parameters checked compared with their insured peers. Insurance coverage for CSHCN not only enables medical care for the child’s specific disease-related needs but also enables preventive services and health screening. One encouraging finding was that almost all CSHCN had an identified usual source of care. Given the increased need and complexity of their health care needs, having a usual source of care should improve the process of care for CSHCN.

In addition to the information about CSHCN, our results highlight that for children in general, there are deficits in the receipt of anticipatory guidance and health screening. Besides the strides that have been made by the pediatric community as a whole, we still have more work to do to ensure that children receive the recommended preventive services. Our results also showed that despite their increased need and perhaps more issues to address at any particular visit, CSHCN do receive anticipatory guidance and preventive screening measures. It seems that increased exposure to providers through increased number of office visits may contribute, in part, to more preventive services being provided to CSHCN. Our data support this conclusion. With increasing time pressure at every clinical encounter, it is important to ensure that all children receive the recommended number of visits and services, regardless of their health status.

Our study has several limitations. First, the data were derived from retrospective caregiver self-reports and therefore are susceptible to recall bias. Recall of receipt of services does not equate to actual receipt of those services. Averaging more visits per year, caregivers of CSHCN may be more likely to report anticipatory guidance, even if they could not recall the event explicitly in relation to a particular health care encounter. Second, given that CSHCN are a very heterogeneous group, encompassing various disease processes, it is possible that for CSHCN with greater functional limitation or different disease states and severity, our findings may not persist. We did not perform additional analysis on the basis of disease-specific data, which may have illuminated interesting and relevant findings. In addition, our data do not allow us to evaluate explicitly the quality of services given or the appropriateness of care at each encounter. There may be appropriate reasons for deferring an AAP-recommended screening or anticipatory guidance at any particular visit. Last, our study did not evaluate all of the various types of health screening and anticipatory guidance that are recommended by the AAP; therefore, the generalizability of our results is diminished.

CONCLUSION

Although a majority of children with and without special health care needs receive some of the recommended health screening and anticipatory guidance on an annual basis, there are clear gaps in the delivery of preventive health services for both groups. All 6 of the anticipatory guidance items identified in this study are rarely provided to families. This study identifies areas for improvement in the delivery of preventive health services for CSHCN and children in general. Given the importance that health professionals and the public place on preventive health services, pediatricians and other health care professionals who provide care to children should strive to provide the recommended health screening and anticipatory guidance for all of their pediatric patients.22 Programs to improve the efficiency of the delivery of preventive health care should be sought. On the basis of our data, additional research is necessary to evaluate disparities in the receipt of preventive health services and determine the significance of these disparities. Lastly, research is necessary to evaluate how preventive health services can contribute to improvements in health and health care quality.

ACKNOWLEDGMENTS

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ARTICLE

Association Between Parental Depression and Children’s Health Care Use

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^Department of Pediatrics and ^Primary Care Research Unit, University of Colorado at Denver and Health Sciences Center, Denver, Colorado; ^Clinical Research Unit, Kaiser Permanente, Denver, Colorado

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. The objective of this study was to determine the association between parental depression and pediatric health care use patterns.

METHODS. We selected all children who were 0 to 17 years of age, enrolled in Kaiser Permanente of Colorado during the study period July 1997 to December 2002, and linked to at least 1 parent/subscriber who was enrolled for at least 6 months during that period. Unexposed children were selected from a pool of children whose parents did not have a depression diagnosis. Outcome measures were derived from the child’s payment files and electronic medical charts and included 5 categories of use: well-child-care visits, sick visits to primary care departments, specialty clinic visits, emergency department visits, and inpatient visits. We compared the rate of use per enrollment month for these 5 categories between exposed and unexposed children within each of the 5 age strata.

RESULTS. Our study population had 24,391 exposed and 45,274 age-matched, unexposed children. For the outcome of well-child-care visits, teenagers showed decreased rates of visits among exposed children. The rate of specialty department visits was higher in exposed children in the 4 oldest age groups. The rates of both emergency department visits and sick visits to primary care departments were higher for exposed children across all 5 age categories. The rate of inpatient visits was higher among exposed children in 2 of the 5 age groups.

CONCLUSIONS. Overall, having at least 1 depressed parent is associated with greater rate of emergency department and sick visits across all age groups, greater use of inpatient and specialty services in some age groups, and a lower rate of well-child-care visits among 13- to 17-year-olds. This pattern of increased use of expensive resources and decreased use of preventive services represents one of the hidden costs of adult depression.
Numerous studies have shown a high prevalence of depression among parents, ranging as high as 47% in some pediatric settings.1–6 Prevalence is highest in parents who care for a chronically ill family member.7–9 Studies of the impact of parental depression on child health outcomes have found positive associations with adverse child behavioral,10–19 developmental,20–23 psychological,14,24–28 and physiologic outcomes.29 Studies that have examined the association between parental depression and child health care use outcomes have been inconsistent in their findings. Two studies found lower rates of well-child-care (WCC) visits among children of depressed parents31; other studies found no association with WCC indicators.32–35 Studies have found an association between parental depression and child acute-care use indicators, including hospitalization,29,32,34,36,37 and emergency department (ED) visits.35,36,38 Only 2 studies found no association between a parent’s depression and ED visits.33,37

Most of these previous studies were limited by small sample sizes, by studying only 1 type of use, by studying use in only 1 type of setting (eg, clinic, nursery), or by relying on the parent’s report of use to measure outcomes. No previous studies combined a wide array of use outcomes in the context of a large sample size, and none did this in the context of a closed-model health maintenance organization (HMO) setting, which allows nearly total capture of all health care use.

Closing these literature gaps has important implications for families and their health care providers. By strengthening and broadening our understanding of the association between parental depression and child health care outcomes, we can improve clinicians’ assessment and management of the pediatric patient in the context of the child–parent dyad. By demonstrating the magnitude of this association, we provide additional impetus to improve mental health services for parents and help policy-makers understand more about the hidden costs of adult depression. The objective of this study was to assess the association between parental depression and pediatric health care use. We hypothesized that children of depressed parents would have lower use of preventive care and higher use of emergent services than children of nondepressed parents. This association was hypothesized to be present for both maternal and paternal depression and across all age strata of children.

**METHODS**

**Data Source**
The data for this study were drawn from the Kaiser Permanente of Colorado (KPCO) membership system. The study period for these analyses was July 1997 to December 2002. Our study design was a retrospective, matched-cohort design.

**Subjects**
We identified all children who were 0 to 17 years of age and enrollees of KPCO during the study period July 1997 to December 2002. Children were linked to “parents” by identifying subscribers through whom the child received eligible care. Over time, many children had >1 subscriber. We considered any subscriber who was linked to a child’s record to be a “parent.” This method missed parents who were not primary subscribers to KPCO, such as spouses who consistently were dependents during the entire study period, and may have included nonparents, including grandparents or unrelated subscribers. We included only those children who were linked to at least 1 parent/subscriber who had been a member for at least 6 continuous months during this time. Only 1 child was randomly selected from each family within each predefined age group (3–11 months, 1–2 years, 3–5 years, 6–12 years, and 13–17 years).

Children who had any parent with a depression diagnosis were classified as exposed for these analyses. Parents’ diagnoses were obtained from the visit records and outside claim records. A parent was considered to have depression when their records contained any of the International Classification of Diseases, Ninth Revision (ICD-9) depression codes in Table 1.

Unexposed children were selected from a pool of children whose parents did not have a depression diagnosis and whose parents also did not have any other mental health condition or prescription antidepressant use. Other mental health conditions were identified using the ICD-9 codes between 290 and 316. Excluded codes were the depression codes listed in Table 1 and codes that commonly are used in primary care for non–mental health issues: 302.7 psychosexual dysfunction (impotence), 305 nondependent drug use (includes tobacco use), 307.81 tension headache, and 315 developmental disorders. Pharmacy records provided information on prescription antidepressant use.

For each child, we defined an index date indicating the start of the period of captured use data. For exposed children, we defined this starting point as the latter of 2 dates: (1) the first captured parental depression date or (2) the 90th day after the child’s KPCO enrollment date.

**TABLE 1 ICD-9 Code–Based Definition of Depression**

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>296.2</td>
<td>Major depression, single episode</td>
</tr>
<tr>
<td>296.3</td>
<td>Major depression, recurrent episode</td>
</tr>
<tr>
<td>296.82</td>
<td>Atypical depression disorder</td>
</tr>
<tr>
<td>298.0</td>
<td>Depressive type psychosis</td>
</tr>
<tr>
<td>300.4</td>
<td>Neurotic depression</td>
</tr>
<tr>
<td>308.0</td>
<td>Predominant disturbance of emotions</td>
</tr>
<tr>
<td>309.0</td>
<td>Adjustment reaction, brief depressive</td>
</tr>
<tr>
<td>309.1</td>
<td>Adjustment reaction, prolonged depressive</td>
</tr>
<tr>
<td>309.4</td>
<td>Adjustment reaction, with mixed disturbance-emotions</td>
</tr>
<tr>
<td>311</td>
<td>Depressive disorder not otherwise classified</td>
</tr>
</tbody>
</table>
Children were required to be members for at least 3 months before the index date to avoid capturing use during initial months when a new member’s use often is inflated. This matching requirement resulted in exclusion of all children who were 0 to 3 months from our sample. We excluded children whose membership duration was <1 month after the index date; this was a relatively rare finding (<3%). A total of 24,413 exposed children met these eligibility criteria.

Up to 2 unexposed children were matched to each exposed child by age and membership eligibility criteria. We chose to match by age because of the great age-related variability in health care use, fostered, in part, by nationally endorsed childhood immunization and WCC visit schedules. We chose to match by enrollment period to align the timing of use data capture for exposed and unexposed children, to minimize problems that changes in administrative data elements over time might introduce. First, we selected unexposed children with birth dates within a 2-week window of the exposed child’s birth date. We then set the index dates for the unexposed children to the date for the matched exposed child and applied the same membership eligibility minimum requirements of 3 months before and 1 month after the index date.

Of the 24,413 exposed children, 24,391 were matched to at least 1 unexposed child by age and membership eligibility criteria. Two control matches were found for 85.6% (20,883). This produced a total $N$ of 69,665 for these analyses.

Measures

Outcome measures were derived from the KPCO use database and included 5 categories of use: WCC visits, sick visits to primary care departments, specialty clinic visits, ED visits, and inpatient visits. Primary care department providers include Family medicine, internal medicine, pediatrics, and obstetrics/gynecology practitioners. All visits to other departments were classified as “specialty” visits.

We included a risk adjustment variable to control for possible morbidity differences between exposed and unexposed children. We used a pharmacy-based disease score that was developed by Fishman and Shay and applied this to pharmacy dispensings during the 12 months after the index date. The 33 disease indicator groups include both physical and mental health categories. We evaluated several different variables for possible morbidity adjustment: (1) the risk score (RxRisk) as it was originally developed and weighted to predict costs in the following year; (2) a summed count of the 33 disease indicators used in the score; (3) a summed count of the disease indicators excluding (a) sickle cell disease, which needed reprogramming to capture appropriately only penicillin use with concurrent folic acid use and which is low prevalence in our region, and (b) the liver disease indicator, which contained a drug that often is used to treat pediatric constipation at KPCO; and (4) selected individual disease indicators entered as separate variables. The count of diseases excluding the 2 questionable indicators (modified RxRisk count) provided the most consistent adjustment across the various use outcomes in this study and also decreased exposed versus unexposed differences to the greatest degree. We selected this morbidity adjustment as the best and most conservative adjustment for the analyses presented here.

Analysis

Frequencies of categorical variables were contrasted by $\chi^2$ statistics. Wilcoxon rank sum tests were used for the chronic disease score and membership months variables because of the skewness of their distributions. We performed bivariate comparisons of characteristics of exposed and unexposed children within each age group.

We calculated a visit rate for each group by dividing the total number of each type of visit during the children’s captured use period by the duration of that period. We compared rates of use for each of the 5 visit categories between exposed and unexposed children within each of the 5 age strata, yielding 25 comparisons. We estimated confidence intervals for these person-time rates using Fisher’s exact method in PEPI software version 4.0. These rate contrasts provide magnitudes of visit differences between exposed and unexposed children while accounting for varying enrollment periods in the denominator calculations but do not adjust for matching.

Incidence rate ratios were estimated using conditional Poisson models. These models used counts of visits over time as the primary outcome, adjusted for varying enrollments by an offset variable and additionally accounted for matching with a stratum identifier. Both ratios of the descriptive rates and the incidence rate ratios from univariate conditional Poisson models were presented. Adjusted incidence rate ratios also are presented controlling for the child’s gender, number of parents, and the pediatric RxRisk risk-adjustment variable described.

We estimated the excess visit rate that was attributable to having depressed parent(s) by multiplying the adjusted rate ratio by the unadjusted visit rate for unexposed children. For example, for infants, the exposed versus unexposed sick visit adjusted rate ratio is 1.14. This suggests that exposed infants have 14% more sick visits than unexposed infants, so the excess would be $0.14 \times 487.1$ (the unadjusted rate of sick visits for unexposed infants), which equals 68.2 visits per 100 person-years.

Analyses were completed using SAS 9.1. This study was approved by the institutional review boards of the Children’s Hospital of Denver and KPCO.
RESULTS

Our study population had 24,391 exposed and 45,274 unexposed children. Table 2 shows the comparison of gender, number of linked parents, number of chronic diseases, and membership duration between exposed and unexposed children within each age group. There were slightly more girls in the unexposed group, although this difference was not significant. The number of parents who were linked to the child’s KPCO record was higher among exposed than unexposed children. Exposed children had longer periods of enrollment after the index date. The differing enrollment times are accounted for in the Poisson models. As expected, exposed children had a higher mean number of chronic diseases.8

Of the exposed children, 88.2% had 1 depressed parent, 11.7% had 2, and 0.1% had 3. Gender of depressed parents was 79.7% female and 31.7% male; these figures include the 11.4% of children with depressed parents of both genders. Of all depressed parents, 83.9% were on antidepressant medications.

Unadjusted use rates are presented in Table 3, which presents the visit rate for exposed and unexposed children. Sick visits to primary care sites were the most common visit type across all age groups, even in the infant age category, when frequent WCC visits are the standard of care. ED visit rates were higher than specialty visit numbers in the youngest ages, but this pattern reversed among older children.

The most common departments in the specialty visits, by percentage of all subspecialty visits, were mental health (23.9%), optometry (18.6%), orthopedics (10.7%), head and neck surgery (9.6%), ophthalmology (6.6%), dermatology (5.6%), and allergy (5.5%). Mental health, optometry, and orthopedics visits increased with increasing age, with >80% of visits in each of these 3 categories among 6- to 17-year-olds.

Differences in visit counts for exposed and unexposed children were apparent for several types of visits in these unadjusted numbers (Table 3). WCC visit rates for exposed children were either similar to or slightly lower than those of unexposed children, although none of these differences was significant. In contrast, exposed children had higher rates of sick visits and ED visits in all ages. Univariate rates of specialty visits also generally were higher among exposed children, although confidence intervals were nonoverlapping only for children who were 3 years or older. Hospital rates were higher for exposed children who were 6 years and older.

Table 4 improves the statistical comparison of exposed and unexposed children through the use of conditional Poisson models to add control of matching as well as adjusting for possible confounders, including gender, number of parents, and disease history counts. In Table 4, univariate rate ratios showed patterns of significance and direction that generally mirrored those seen in Table 3. Adding adjustment for possible confounders generally lowered the exposed versus unexposed differences primarily as a result of adjustment for the higher disease counts among exposed children.

For the outcome of WCC visits, our adjusted model showed a decreased rate of WCC visits among exposed children in the teenage category. The rates of both ED

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Characteristics of Exposed and Unexposed Children by Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>3–11 mo (2445 [34.6%] of 7072)</td>
</tr>
<tr>
<td>Girls, %</td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>47.0</td>
</tr>
<tr>
<td>Unexposed</td>
<td>49.2</td>
</tr>
<tr>
<td>No. of parents, % with 1, 2, or 3</td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>78.7</td>
</tr>
<tr>
<td>3</td>
<td>80.0</td>
</tr>
<tr>
<td>Unexposed</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>77.8</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>Mean No. of chronic diseases</td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>0.32</td>
</tr>
<tr>
<td>Unexposed</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean No. of membership months</td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>9.59</td>
</tr>
<tr>
<td>Unexposed</td>
<td>8.34</td>
</tr>
</tbody>
</table>

a Estimates are percentages for % girls and number of parents and means for number of chronic disease and membership months.
b P value from t test for % girls and number of parents and from Wilcoxon rank sum test for number of chronic disease and membership months.
visits and sick visits to primary care departments were higher for exposed children in the adjusted models across all 5 age categories, and the rate of specialty department visits was higher in exposed children in the 4 oldest age groups. The rate of inpatient visits was higher among exposed children in the 2 oldest age groups.

Table 5 shows the excess visit rate, in visits per 100 person-years, that was attributable to having a depressed parent. The difference is greatest for sick visits to primary care departments, particularly in the youngest age group, in which exposed infants had 68 more visits per 100 person-years than did unexposed infants. For both sick visits and ED visits, the age-related trend was similar, with greater excesses in the youngest age groups. In contrast, the greatest excesses in specialty visit rates were among the older age groups.

### DISCUSSION

In this study, children with at least 1 depressed parent had higher use of costlier forms of health care—using more ED, sick visit, specialty department, and inpatient services—than did children of parents without depression. Findings from our study, in general, support previous studies, although our study strengthens the evidence for these findings, because no previous studies combined a wide array of use outcomes in the context of a large sample size, and none did this in the context of a closed-model HMO setting. Ours also is only the second study to consider paternal as well as maternal depression as a predictor of health care use.

Our finding of no association between parental depression and a child’s WCC visits in the 4 youngest age groups is consistent with previous findings. However, our finding that 13- to 17-year-olds had fewer WCC

### TABLE 3: Estimated Visit Rates Per 100 Person-Years for Exposed and Unexposed Children by Age, With Excess Visits Among Exposed Children

<table>
<thead>
<tr>
<th>Use Outcome</th>
<th>Age Group</th>
<th>Rate (95% CI)</th>
<th>Rate (95% CI)</th>
<th>Rate (95% CI)</th>
<th>Rate (95% CI)</th>
<th>Rate (95% CI)</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3–11 mo</td>
<td>1–2 y</td>
<td>3–5 y</td>
<td>6–12 y</td>
<td>13–17 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 7072)</td>
<td>(n = 7771)</td>
<td>(n = 10 767)</td>
<td>(n = 23 544)</td>
<td>(n = 20 511)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCC visits</td>
<td>Exposed</td>
<td>204.1 (197.8–210.5)</td>
<td>72.0 (68.5–75.6)</td>
<td>45.7 (43.4–48.1)</td>
<td>24.5 (23.4–25.7)</td>
<td>16.5 (15.5–17.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unexposed</td>
<td>210.3 (203.3–215.4)</td>
<td>76.1 (73.3–79.0)</td>
<td>45.3 (43.4–47.2)</td>
<td>24.0 (23.1–24.9)</td>
<td>17.2 (16.5–18.0)</td>
<td></td>
</tr>
<tr>
<td>Sick visits: primary care departments</td>
<td>Exposed</td>
<td>563.2 (552.8–573.9)</td>
<td>331.6 (324.1–339.3)</td>
<td>214.4 (209.4–219.5)</td>
<td>189.1 (185.9–192.3)</td>
<td>214.3 (210.6–218.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unexposed</td>
<td>487.1 (479.5–494.8)</td>
<td>277.7 (272.3–283.2)</td>
<td>173.6 (170.0–177.4)</td>
<td>140.9 (138.7–143.1)</td>
<td>157.0 (154.7–159.4)</td>
<td></td>
</tr>
<tr>
<td>Specialty department visits</td>
<td>Exposed</td>
<td>39.5 (36.7–42.3)</td>
<td>34.8 (32.4–37.3)</td>
<td>35.7 (33.7–37.8)</td>
<td>64.7 (62.8–66.6)</td>
<td>103.3 (101–106)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unexposed</td>
<td>36.4 (34.3–38.5)</td>
<td>28.6 (26.8–30.4)</td>
<td>26.2 (24.8–27.7)</td>
<td>35.6 (34.5–36.7)</td>
<td>59.3 (57.8–60.7)</td>
<td></td>
</tr>
<tr>
<td>ED visits</td>
<td>Exposed</td>
<td>50.4 (47.3–53.6)</td>
<td>34.1 (31.7–36.7)</td>
<td>17.6 (16.2–19.2)</td>
<td>14.4 (13.5–15.3)</td>
<td>20.9 (19.7–22.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unexposed</td>
<td>41.4 (39.3–43.7)</td>
<td>26.4 (24.8–28.2)</td>
<td>14.6 (13.6–15.8)</td>
<td>10.0 (9.4–10.6)</td>
<td>13.5 (12.8–14.2)</td>
<td></td>
</tr>
<tr>
<td>Inpatient visits</td>
<td>Exposed</td>
<td>4.5 (3.6–5.5)</td>
<td>2.4 (1.7–3.1)</td>
<td>1.1 (0.7–1.5)</td>
<td>2.3 (1.9–2.6)</td>
<td>4.8 (4.3–5.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unexposed</td>
<td>3.7 (3.1–4.4)</td>
<td>1.5 (1.1–1.9)</td>
<td>1.0 (0.7–1.3)</td>
<td>0.7 (0.5–0.9)</td>
<td>2.5 (2.2–2.8)</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

**TABLE 4: Use Rate Ratios from Conditional Poisson Models Comparing Exposed and Unexposed Children**

<table>
<thead>
<tr>
<th>Use Outcome</th>
<th>Model</th>
<th>3–11 mo (n = 7072)</th>
<th>1–2 y (n = 7771)</th>
<th>3–5 y (n = 10 767)</th>
<th>6–12 y (n = 23 544)</th>
<th>13–17 y (n = 20 511)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate Ratio</td>
<td>Rate Ratio</td>
<td>Rate Ratio</td>
<td>Rate Ratio</td>
<td>Rate Ratio</td>
<td>Rate Ratio</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>WCC visits</td>
<td>Univariatea</td>
<td>0.97 (0.93–1.01)</td>
<td>0.95 (0.89–1.01)</td>
<td>1.01 (0.95–1.08)</td>
<td>1.03 (0.97–1.10)</td>
<td>0.96 (0.89–1.04)</td>
</tr>
<tr>
<td></td>
<td>Adjusteda</td>
<td>0.96 (0.92–1.00)</td>
<td>0.94 (0.88–1.01)</td>
<td>0.99 (0.93–1.06)</td>
<td>0.99 (0.93–1.06)</td>
<td>0.92 (0.85–0.99)</td>
</tr>
<tr>
<td>Sick visitsb</td>
<td>Univariatea</td>
<td>1.15 (1.12–1.18)</td>
<td>&lt;0.0001</td>
<td>1.22 (1.18–1.26)</td>
<td>1.36 (1.33–1.39)</td>
<td>1.36 (1.33–1.39)</td>
</tr>
<tr>
<td></td>
<td>Adjusteda</td>
<td>1.14 (1.11–1.17)</td>
<td>&lt;0.0001</td>
<td>1.19 (1.15–1.23)</td>
<td>1.24 (1.21–1.27)</td>
<td>1.21 (1.18–1.24)</td>
</tr>
<tr>
<td>ED visitsc</td>
<td>Univariatea</td>
<td>1.22 (1.12–1.33)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.05–1.32)</td>
<td>1.41 (1.29–1.54)</td>
<td>1.55 (1.44–1.68)</td>
</tr>
<tr>
<td></td>
<td>Adjusteda</td>
<td>1.23 (1.13–1.34)</td>
<td>&lt;0.0001</td>
<td>1.15 (1.02–1.30)</td>
<td>1.28 (1.16–1.41)</td>
<td>1.35 (1.24–1.46)</td>
</tr>
<tr>
<td>Inpatient visitsd</td>
<td>Univariatea</td>
<td>1.21 (0.91–1.61)</td>
<td>0.19</td>
<td>1.19 (0.75–1.89)</td>
<td>3.55 (2.69–4.69)</td>
<td>1.99 (1.68–2.35)</td>
</tr>
<tr>
<td></td>
<td>Adjusteda</td>
<td>1.18 (0.84–1.66)</td>
<td>0.33</td>
<td>1.35 (0.81–2.25)</td>
<td>0.87 (0.47–1.61)</td>
<td>2.02 (1.22–3.34)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

a Visit rate ratio (exposed/unexposed) from univariate conditional Poisson model.

b Adjusted visit rate ratio from conditional Poisson model controlling for the child’s gender, number of parents, and the pediatric ReRisk risk-adjustment variable.

c Sick visits to primary care department.
visits when they had a depressed parent is the first report that we could find of a significant association between parental depression and WCC visit rates in adolescents. This does not contradict previous studies, because all 4 previous analyses of the association between parental depression and WCC visits studied infants\cite{32,34,35} or pre-school children only.\cite{33}

Our finding of an association between parental depression and higher rates of sick visits to the primary care site is consistent with the 1 previous study of this association, authored by Mandl et al.\cite{35} That study found that women were twice as likely to exhibit depressive symptoms when their infant had >1 sick visit. We found no comparison studies that assessed the association between specialty visits and parental depression.

Regarding ED visits, previous literature is mixed, with some studies showing increased ED visits among children of depressed parents\cite{36} and others showing no association.\cite{33,37} By showing a strong association between ED visits and parental depression. The literature is more consistent regarding the association between parental depression and the child’s likelihood of inpatient visit, with previous studies finding an odds ratio of 1.5 to 3.0.\cite{32,34,36-38} Our study found an association only in the 2 oldest age groups. Of the previous 5 analyses, 3 studied children who were younger than 2 years.\cite{32,34,36} Our finding of no association in the 3 youngest age groups is inconsistent with these previous findings and may be related to selection bias: the 2 US studies selected their subjects from families who attended primary care clinics, which may select for a population with a greater tendency to use services.\cite{32,36} Of the 2 previous analyses that involved older children, 1 studied 4- to 9-year-old children with asthma,\cite{38} and the other studied 6- to 23-year-olds; the latter study found higher rates of surgery-related inpatient visit among children of depressed parents but no difference in the rate of nonsurgical inpatient visits.\cite{37}

The finding of higher excess visit rates for ED and sick visits among the youngest age groups may reflect the greater difficulty that depressed parents encounter confronting the challenge that is presented by figuring out the anatomic site and the severity of distress among preverbal children. It also may reflect the influence of ongoing postpartum depression, which can last up to 1 year after delivery. Because we used the adjusted rate ratio in calculating excess visits, we accounted for the effect of chronic illness; this is corroborated further by the finding that no excess inpatient visits were noted in these youngest age groups despite their higher excesses of emergent and urgent visit rates. The clinical significance of the excess bed days depends to some degree on perspective. None of our rates exceeded 1 extra visit per patient per year, so the average impact of excess visits on families may not be clinically significant. However, even the smallest significant excess in visits—an excess of 1.3 inpatient visits per 100 patients in the 13- to 17-year age group—is significant from a health care financing standpoint.

The limitations of this study are related to limitations that are inherent in using medical chart databases. Several factors limit the accuracy of medical charts for disease identification in general, including incomplete or erroneous charts submitted by providers and limited clinical detail in the ICD-9 system. The use of administrative data for depression identification in particular presents additional challenges.\cite{42} Social stigma may discourage individuals from reporting mental health diagnoses, and suboptimal health care screening practices by providers may limit further individuals’ ability to know and report mental illness.\cite{43,44} The limitations would result in misclassification of exposed children as unexposed children and would be expected to dilute the effect reported. The identification of “parents” by subscriber match also led to inexact linking of parents and children. This, too, likely would result in misclassification of exposed children as unexposed, which would bias our results to the null. Another set of limitations are related to dissimilarities between the exposed and unexposed groups. We found a higher number of parents linked to the child’s KPCO record among exposed children than unexposed. This finding may result, in part, from the fact that having more parents gives a child more opportunity to have at least 1 depressed parent.

| TABLE 5: Excess Number of Visits per 100 Person-Years Among Exposed Children |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Use Outcome                  | Age Group                  | 3–11 mo (n = 7072) | 1–2 y (n = 7771) | 3–5 y (n = 10 767) | 6–12 y (n = 23 544) | 13–17 y (n = 20 511) |
| WCC visits                  | NS                          | NS                          | NS                          | NS                          | −1.4                         |
| Sick visits to primary care departments | 68.2                      | 44.4                        | 33.0                        | 33.8                        | 33.0                        |
| Specialty department visits | NS                          | 3.7                         | 6.3                         | 19.9                        | 25.5                        |
| ED visits                   | 9.5                        | 8.2                         | 2.2                         | 2.8                         | 4.7                         |
| Inpatient visits            | NS                          | NS                          | NS                          | 1.4                         | 1.3                         |

We estimated the excess visit rate that was attributable to having depressed parent(s) by multiplying the adjusted rate ratio (Table 4) by the unadjusted visit rate (Table 3) for unexposed children. NS indicates nonsignificant.
We also found longer enrollment periods among exposed children. This may reflect a phenomenon that is similar to the effect of having more parents linked to one's file; namely, children with longer enrollments had more opportunity to have a parent receive a diagnosis of depression. Finally, because this is a retrospective analysis, we cannot make assumptions about causality. Despite adjusting for chronic illness, we cannot assume that causality starts with the parent's depression; perhaps it is the child's genuine need for more visits that has contributed to the parent's depression. In either causality scenario, efforts that are directed at improving the parent's depression are likely to be associated with improved outcomes for the parent–child dyad.

This study confirms previously reported associations in a large, closed-model HMO setting. The costlier patterns of health care use that are associated with parental depression raise important issues both for pediatric health care providers and for health care policy-makers. For pediatric providers, our study supports the conclusions of previous reports, which have called for increased screening and treatment of depression in the parents of pediatric patients. Conducting routine, brief, maternal depression screening during WCC visits has been found to be feasible, successful, and well accepted and has resulted in specific pediatrician actions. For policy-makers, our findings suggest that interventions that are directed at improving rates of detection and treatment of parental depression will result in less costly health care use patterns for children of depressed parents.

ACKNOWLEDGMENTS

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Breastfeeding and Hospitalization for Diarrheal and Respiratory Infection in the United Kingdom Millennium Cohort Study

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. The objective of this study was to measure the effect of breastfeeding on hospitalization for diarrheal and lower respiratory tract infections in the first 8 months after birth in contemporary United Kingdom.

METHODS. The study was a population-based survey (sweep 1 of the United Kingdom Millennium Cohort Study). Data on infant feeding, infant health, and a range of confounding factors were available for 15,890 healthy, singleton, term infants who were born in 2000–2002. The main outcome measures were parental report of hospitalization for diarrhea and lower respiratory tract infection in the first 8 months after birth.

RESULTS. Seventy percent of infants were breastfed (ever), 34% received breast milk for at least 4 months, and 1.2% were exclusively breastfed for at least 6 months. By 8 months of age, 12% of infants had been hospitalized (1.1% for diarrhea and 3.2% for lower respiratory tract infection). Data analyzed by month of age, with adjustment for confounders, show that exclusive breastfeeding, compared with not breastfeeding, protects against hospitalization for diarrhea and lower respiratory tract infection. The effect of partial breastfeeding is weaker. Population-attributable fractions suggest that an estimated 53% of diarrhea hospitalizations could have been prevented each month by exclusive breastfeeding and 31% by partial breastfeeding. Similarly, 27% of lower respiratory tract infection hospitalizations could have been prevented each month by exclusive breastfeeding and 25% by partial breastfeeding. The protective effect of breastfeeding for these outcomes wears off soon after breastfeeding cessation.

CONCLUSIONS. Breastfeeding, particularly when exclusive and prolonged, protects against severe morbidity in contemporary United Kingdom. A population-level increase in exclusive, prolonged breastfeeding would be of considerable potential benefit for public health.

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The views in this article are those of the authors and do not necessarily represent the views of the Department of Health.

Key Words
breastfeeding, hospitalization, diarrhea, respiratory infection

Abbreviations
CI—confidence interval
LRTI—lower respiratory tract infection
OR—odds ratio
PAF—population-attributable fraction

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics
The World Health Organization recommends that all infants be exclusively breastfed for 6 months. In developing countries, exclusive breastfeeding has a large protective effect on infant mortality and severe morbidity. However, the public health importance of breastfeeding in healthy, term infants in developed countries rarely has been quantified. Few studies have assessed the effect of breastfeeding on hospitalization rates in such settings.

Hospitalization is a marker of disease severity that is associated with large and measurable costs. One United Kingdom study conducted in the 1980s observed significantly less hospitalization for diarrheal disease in infants who were breastfed for ≥13 weeks compared with those who never were breastfed. A meta-analysis estimated a significant reduction in risk for hospitalization for respiratory disease in healthy, term infants in developed countries associated with exclusive breastfeeding for ≥4 months compared with no breastfeeding (unadjusted risk ratio: 0.28; 95% confidence interval [CI]: 0.14–0.54). However, there was limited adjustment for confounders in the meta-analysis, with adjustment only for smoking in 1 model and socioeconomic status in another model. Moreover, some of the studies that were included in the meta-analysis did not analyze the timing of the outcome in relation to breastfeeding exposure. Therefore, some infants were classified according to their breastfeeding duration rather than whether the outcome occurred during breastfeeding (which would measure the effect of current breastfeeding) or after breastfeeding cessation (which would measure the effect of past breastfeeding). It is plausible that the effect of past breastfeeding is weaker than the effect of current breastfeeding, and combining the 2 effects may distort the interpretation of the effect of both current and past breastfeeding.

The present study aimed to measure the effect of breastfeeding on hospitalization for diarrheal and lower respiratory tract infections (LRTI) in 15 980 infants who were born in the United Kingdom who were born in the United Kingdom. A random 2-stage sample of all infants who were born in England and Wales between September 2000 and August 2001 and in Scotland and Northern Ireland between November 2000 and January 2002 and were alive and living in the United Kingdom at 9 months of age were drawn from Child Benefit registers. Child Benefit claims in the United Kingdom cover virtually all children except those who are ineligible as a result of recent or temporary immigrant status. Stratified sampling by electoral ward (defined geographic area), with over sampling of ethnic minority and disadvantaged areas, ensured adequate representation of such areas. The interview response rate was 85%.

Parents were interviewed for the first time (sweep 1) when most infants were aged 9 months, and detailed information was collected on a range of socioeconomic and health factors. The Millennium Cohort Study does not cover births in which the infant died within the first 9 to 10 months after birth, but these constituted <1% of all births.

Exclusions

The analysis focused on the effects of breastfeeding in term, singleton infants who did not have major problems at birth. Hence, 2839 infants (15% of the original 18819) were excluded for the following reasons: twins and higher order multiples (n = 522; 2.8%), singleton infants who were born at <37 completed weeks’ gestation (n = 1290; 6.8%), singleton infants who were born at ≥37 weeks’ gestation and were admitted to ICUs at birth (n = 975; 5.2%); the most common reasons were for breathing difficulties/delay in breathing, n = 353; jaundice that required hospital treatment, n = 154; and infection/suspected infection, n = 103), main respondent not natural mother (n = 50; 0.3%), consent withdrawn (n = 1; 0.005%), and infant’s age missing (n = 1; 0.005%). The analysis was based on the remaining 15980 infants.

Breastfeeding

Breastfeeding initiation was assessed by the question, “Did you ever try to breastfeed your infant?” Breastfeeding duration was estimated using the questions about the age of the infant when last given breast milk and when first given formula, other types of milk, and solids. Infant feeding was categorized per month into the following groups, which refer to the previous month: (1) not breastfed; (2) partially breastfed (received some breast milk but also received other milk and/or solids); (3) exclusively breastfed (received only breast milk and no other milk, solids, or fluids other than water).

Hospitalization for Diarrhea and LRTI

Hospitalized morbidity was assessed by the questions, “Has your infant ever been admitted to a hospital ward because of an illness or health problem?” and, “How...
many months old was your infant when admitted?” Among the possible reasons for admission that were listed on the questionnaire were “gastroenteritis” and “chest infection or pneumonia.” In our analysis, diarrhea was defined as “gastroenteritis” (n = 201); this did not include “other persistent or severe diarrhea” (n = 14), “other severe or persistent vomiting” (n = 43), “other reflux or other vomiting” (n = 73) or “other gastrointestinal abnormalities” (n = 7). LRTI was defined as “chest infection or pneumonia” (n = 552) and did not include those with a diagnosis of “wheezing or asthma” (n = 139).

Statistical Methods
All analysis was restricted to the first 8 months after birth, for which all but 1 infant had complete follow-up. The data for each infant were analyzed per month of age to incorporate time-changing variables. Hence, variables at each month of age indicated whether the infant had been admitted to the hospital for diarrhea or LRTI during that month, whether they had been exclusively/partially breastfed during that month, and, for ever breastfed infants, how many months since they had last received breast milk (coded as 0 if those currently breastfed, 1 when they had not received breast milk for 1 month, etc). All analyses allowed for the clustered (by ward and infant), stratified sample using the “survey commands” in Stata 9 (Stata Corp, College Station, TX). All SEs presented are adjusted for clustering using Taylor linearization for variance estimation.

The prevalence of cause-specific hospital admissions per month was estimated according to infant feeding practice in the same month. Odds ratios (ORs) were estimated using logistic regression. The ORs were adjusted initially for the following variables: birth weight, gestation, mode of delivery, infant’s age in months, infant’s gender, maternal age in years, whether the infant was first-born, maternal (current) smoking, maternal occupation (coded using the United Kingdom National Statistics Socio-economic Class), maternal education, maternal marital status, and whether the infant lives in rented accommodation. In final models, adjustment was made for variables that were significantly (P < .05) associated with the outcome after adjustment for other variables in the model. Population-attributable fractions (PAFs) for hospitalization that was associated with not breastfeeding were estimated as (proportion of cases exposed) × (OR − 1)/OR, where OR is for not breastfeeding compared with exclusive/partial breastfeeding.

RESULTS
The age at interview of the 15 980 infants ranged between 6 (n = 1) and 12 (n = 5) months (mean and median: 9 months). Forty-two percent of infants were first-born, and 19% were delivered by cesarean section (Table 1). Eighty-nine percent of their mothers described their ethnicity as “white,” and 28% were current smokers. Seventy percent of infants were ever breastfed, with 34% and 24% receiving breast milk for at least 4 and 6 months, respectively (Table 1). Only 1.2% of infants were exclusively breastfed for at least 6 months.

In the first 8 months after birth, 12% of infants had at least 1 hospital admission. The most common causes of hospital admission were LRTI (3.2%), diarrhea (1.1%), asthma/wheezing (0.9%), and other high temperature acute viral infection (not respiratory or meningitis; 0.8%). Approximately 2% of infants had >1 hospital admission. Among those who were hospitalized for diarrhea (n = 185) and LRTI (n = 539), the proportions with at least 1 other hospital admission were 24% and 21%, respectively. Of the 714 infants who were hospitalized for diarrhea or LRTI, 10 (1.4%) were hospitalized for both infections. Those who were hospitalized for diarrhea were more likely to be hospitalized for LRTI than those who not hospitalized for diarrhea, but

<table>
<thead>
<tr>
<th>Table 1: Breastfeeding, Hospital Admissions, and Other Characteristics in the First 8 Months After Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td><strong>Perinatal and infant characteristics</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>First-born</td>
</tr>
<tr>
<td>Delivered by cesarean section</td>
</tr>
<tr>
<td>Gestation, mean, wk</td>
</tr>
<tr>
<td>Birth weight, mean, kg</td>
</tr>
<tr>
<td>Family history of asthma</td>
</tr>
<tr>
<td>Maternal and household characteristics</td>
</tr>
<tr>
<td>Age at delivery, mean, y</td>
</tr>
<tr>
<td>Lone parent</td>
</tr>
<tr>
<td>White ethnicity</td>
</tr>
<tr>
<td>Managerial/professional occupation</td>
</tr>
<tr>
<td>Semi-routine/routine occupation</td>
</tr>
<tr>
<td>More educated (National Vocational Qualification 4/5)</td>
</tr>
<tr>
<td>Annual household income more than £52 000</td>
</tr>
<tr>
<td>Annual household income more than £52 000</td>
</tr>
<tr>
<td>Smoker at interview</td>
</tr>
<tr>
<td>Infant feeding</td>
</tr>
<tr>
<td>Exclusively breastfed</td>
</tr>
<tr>
<td>Any breast milk at 4 mo</td>
</tr>
<tr>
<td>Any breast milk at 6 mo</td>
</tr>
<tr>
<td>Any breast milk at 8 mo</td>
</tr>
<tr>
<td>Exclusively breastfed at 4 mo</td>
</tr>
<tr>
<td>Exclusively breastfed at 6 mo</td>
</tr>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Any hospital admission in the first 8 mo</td>
</tr>
<tr>
<td>Estimated rate for the first 12 mo</td>
</tr>
<tr>
<td>Hospital admission for diarrhea in the first 8 mo</td>
</tr>
<tr>
<td>Estimated rate for the first 12 mo</td>
</tr>
<tr>
<td>Hospital admission for LRTI in the first 8 mo</td>
</tr>
<tr>
<td>Estimated rate for the first 12 mo</td>
</tr>
<tr>
<td>Hospital admission for LRTI/wheeze</td>
</tr>
<tr>
<td>Estimated rate for the first 12 mo</td>
</tr>
</tbody>
</table>

All percentages are weighted to allow for the stratified sample, and CIs allow for clustering. MCS indicates Millennium Cohort Study.

a Annual rate estimated by multiplying rate in first 8 months by 12/8.
the effect was not statistically significant (OR: 1.63; 95% CI: 0.70–3.81; \( P = .26 \)). Therefore, neither infection was considered as a potential confounder for the other infection.

Infant data for the first 8 months were split into 127,798 infant-months. The monthly risk for hospitalization at ages 0 to 8 months was 0.15% for diarrhea and 0.42% for LRTI (Table 2). These risks, when multiplied by 8, are slightly higher than those in Table 1 because they include multiple hospital admissions per infant. Compared with infants who were not breastfed, those who were exclusively breastfed had a large and statistically significant reduction in risk for hospitalization for diarrhea (adjusted OR: 0.37; 95% CI: 0.18–0.78) and LRTI (adjusted OR: 0.66; 95% CI: 0.47–0.92). The effect of partial breastfeeding was weaker and not statistically significant. The PAFs suggest that 53% of diarrhea hospitalizations could have been prevented each month by exclusive breastfeeding and 31% by partial breastfeeding. Similarly, 27% of LRTI hospitalizations could have been prevented each month by exclusive breastfeeding and 25% by partial breastfeeding.

Table 3 shows the association between breastfeeding cessation and hospitalization for diarrhea and LRTI. Here, no distinction was made between exclusive and partial breastfeeding to keep the model relatively simple; otherwise, the effect of breastfeeding cessation would need to be estimated separately according to the months of continued partial breastfeeding, which may range from 0 to 7. Clearly, breastfeeding cessation is strongly correlated with infant’s age; for example, having stopped breastfeeding for 4 months may be assessed only in infants who were aged ≥5 months. However, the ORs in Table 3 are adjusted for infant’s age.

There is a statistically significant increasing linear trend in the effect of breastfeeding cessation for both outcomes in older and younger infants, suggesting that the protective effect of breastfeeding wears off over time. There was evidence of a stronger increasing trend at age 1 to 4 months compared with 5 to 7 months (interaction \( P = .084 \) for diarrhea and \( P = .031 \) for LRTI); therefore, the results are presented stratified by age group. In both age groups, the trend is stronger for diarrhea than for LRTI, although the estimates for diarrhea are adjusted for fewer confounders. For diarrhea, the protective effect of breastfeeding does not seem to persist beyond the first month, after which there is a steady increase in risk over time since cessation; on average, there is a doubling of risk for every month that elapses after breastfeeding cessation (adjusted OR: 1.98; 95% CI: 1.32–2.96) in those aged 1 to 4 months and a 28% increase in risk in those aged 5 to 7 months (adjusted OR: 1.28; 95% CI: 1.01–1.61). For LRTI, the protective effect of breastfeeding weakens as soon as breastfeeding stops.

**DISCUSSION**

Approximately 12% of healthy, singleton, term infants who were born in contemporary United Kingdom have been hospitalized at least once by the time they are 8 months of age; 1.1% of infants have been hospitalized for diarrhea and 3.2% for LRTI. Exclusive breastfeeding protects against hospitalization for diarrhea and LRTI. It is estimated that 53% of diarrhea hospitalizations could have been prevented each month if all infants were exclusively breastfed, and 31% could have been prevented if all were partially breastfed. Similarly, 27% of LRTI hospitalizations could have been prevented each month by exclusive breastfeeding and 25% by partial breastfeeding. However, the protective effect of breastfeeding for both outcomes wears off soon after breastfeeding cessation.

Our study used parental reporting for both hospitalization and breastfeeding. The recall of neither of these variables has been validated in this study population, although maternal recall of mode of delivery and birth weight have been shown to be highly reliable in this

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Association Between Breastfeeding and Hospital Admission per Month in the First 8 Months After Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Feeding</td>
<td>Monthly Prevalence, % (N/N)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Not breastfed</td>
<td>0.18 (158/86 648)</td>
</tr>
<tr>
<td>Partially breastfed</td>
<td>0.08 (17/19 887)</td>
</tr>
<tr>
<td>Exclusively breastfed</td>
<td>0.05 (12/20 352)</td>
</tr>
<tr>
<td>LRTI</td>
<td></td>
</tr>
<tr>
<td>Not breastfed</td>
<td>0.49 (429/86 648)</td>
</tr>
<tr>
<td>Partially breastfed</td>
<td>0.25 (50/19 888)</td>
</tr>
<tr>
<td>Exclusively breastfed</td>
<td>0.30 (60/20 352)</td>
</tr>
</tbody>
</table>

All numbers and percentages are weighted to allow for the stratified sample, and CIs allow for clustering.

* For diarrhea, ORs are adjusted for month (ie, infant’s age), mother’s age at delivery, mode of delivery, and mother’s education. For LRTI, ORs are adjusted for month (ie, infant’s age), infant’s gender, mother’s age at delivery, mode of delivery, household income, whether the infant was first-born, mother’s (current) smoking status, and family history of asthma.

b PAF = [(1358/1186) × 0.59/1.59] = 31%.

c PAF = [(1358/1186) × 1.70/2.70] = 53%.

d PAF = [(429/539) × 0.45/1.45] = 25%.

e PAF = [(429/539) × 0.52/1.52] = 27%.
population. Other studies have shown that maternal reporting of breastfeeding is reliable up to 3 years after the birth of the infant. The breastfeeding rates in our study are slightly higher than those reported in the United Kingdom Infant Feeding Survey for the same time period, perhaps because the infants who were excluded from our study (multiples, preterm infants, and those who were admitted to ICUs) were less likely to be breastfed. Validation studies have found that parental recall of hospitalization in young children is extremely accurate, although we cannot rule out some misreporting of cause of admission. The hospitalization rate for diarrhea in our study (estimated as 1.6% in the first year after birth) is lower than that in a Scottish study (5.7%), but similar to that in a Canadian study (1.1%). We estimate a hospitalization rate for LRTI of 4.8% in the first year after birth, which is similar to rates that were observed in Scotland (4.9%), Australia (5.2%), and the United States (6.0%). Moreover, the effects of breastfeeding in our study were similar when we included admissions for wheezing or asthma in the definition of LRTI (data not shown).

The main strength of our study is the large sample size that is representative of contemporary United Kingdom. Unlike many other studies that have measured the protective effect of breastfeeding, we assessed the effect of both current breastfeeding, using exposure and outcome data from the same month, and past breastfeeding, using outcome data that occurred in the months after breastfeeding cessation. We adjusted for a wide range of confounders. We focused on hospital admissions because they are likely to be reported accurately by parents, and are an important measure of disease severity, and are associated with large and measurable costs.

Our finding of a protective effect of breastfeeding against diarrhea hospitalization is consistent with a study that was conducted in Scotland in the 1980s. In a meta-analysis of 7 studies of hospitalization for respiratory disease, the unadjusted risk ratio for ≥4 months of breastfeeding compared with no breastfeeding was 0.28. However, in the 4 studies that adjusted for socioeconomic status, the adjusted risk ratio was 0.53, which is similar to our adjusted OR of 0.66 for LRTI. It is interesting that our PAF estimates of 53% for diarrhea hospitalizations and 27% for LRTI hospitalizations are consistent with a recent study from Spain that estimated that exclusive breastfeeding for ≥4 months would have prevented 56.4% of nonperinatal, infection-related hospitalizations in children who were younger than 1 year.

There is a large body of data describing how the immunologic properties of breast milk are likely to protect against infection in the infant. In addition, infection may be attributable to contamination of bottles, teats, milk, and food in infants who are not exclusively breastfed. In our developed country setting, where rates of infection and poor hygiene are relatively low, the immune properties of “current” breast milk do not seem to persist after breastfeeding cessation. Alternatively, the immune properties may not persist at sufficient levels to protect against contamination.

**CONCLUSIONS**

Our findings confirm that breastfeeding, particularly when exclusive and prolonged, protects against severe morbidity in contemporary United Kingdom. In our study, only 1.2% of infants were exclusively breastfed for at least 6 months, and the protective effects of breastfeeding were large; a population-level increase in exclusive, prolonged breastfeeding would be of great public health benefit. Our results may be used to estimate the

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**TABLE 3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Months Since Breastfeeding Cessation</th>
<th>Not Breastfed</th>
<th>Linear Trend per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0*</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>LRTI in mo 1–4</td>
<td>0.07 (25810)</td>
<td>0.09 (5757)</td>
<td>0.14 (4758)</td>
</tr>
<tr>
<td>LRTI in mo 5–7</td>
<td>0.07 (14429)</td>
<td>0.26 (2648)</td>
<td>0.11 (3231)</td>
</tr>
<tr>
<td>Diarrhea in mo 1–4</td>
<td>0.32 (25810)</td>
<td>0.59 (5757)</td>
<td>0.64 (4758)</td>
</tr>
<tr>
<td>Diarrhea in mo 5–7</td>
<td>0.19 (14429)</td>
<td>0.30 (2648)</td>
<td>0.24 (3231)</td>
</tr>
</tbody>
</table>

All percentages are weighted to allow for the stratified sample, and CIs allow for clustering. NA indicates not applicable.

* Currently breastfeeding.

* Linear trend assessed excluding the “never breastfed” group.

* For diarrhea, ORs are adjusted for month (ie, infant’s age), mother’s age at delivery, mode of delivery, and mother’s education. For LRTI, ORs are adjusted for month (ie, infant’s age), infant’s gender, household income, whether the infant was first-born, mother’s (current) smoking status, and family history of asthma.
cost-effectiveness of breastfeeding interventions. Better information on the risks and benefits that are associated with infant feeding methods, including prolonged and exclusive breastfeeding, will enable parents to make an informed choice.

ACKNOWLEDGMENTS

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Results of Random Drug Testing in an Adolescent Substance Abuse Program

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. The objective of this study was to estimate from a random urine drug-testing program for adolescents the proportion of drug tests that are susceptible to interpretation errors.

METHODS. This was a secondary analysis of a clinical database and chart review from an adolescent outpatient substance abuse program at a large children’s hospital. We analyzed from 110 adolescent patients (13–21 years of age) all 710 urine drug test results that were collected between December 2002 and July 2005 and 85 original laboratory reports for tests that were collected between December 2002 and May 2006 and were confirmed positive for opioids. We calculated the percentage of tests that were too dilute to interpret (potential false-negatives) and the percentage of confirmed positive tests for oxycodone that did not result in a positive initial screen (potential false-negatives). We also reviewed clinical information to determine whether confirmed positive tests resulted from legitimate use of prescription or over-the-counter medication (potential false-positives).

RESULTS. Of 710 drug tests, 40 negative tests were too dilute to interpret properly, and 45 of 217 positive tests resulted from prescription medication use for a total of 85 tests that were susceptible to error. Of the 85 confirmatory laboratory reports reviewed, 43 were positive for oxycodone, but only 16 of these had produced a positive opiate screen.

CONCLUSIONS. Unless proper procedures are used in collecting, analyzing, and interpreting laboratory testing for drugs, there is a substantial risk for error.
Drug-testing programs have been shown to be a useful therapeutic adjuvant for adults with cocaine disorders when used in combination with other treatments or as a sole therapy within treatment programs. Although few formal assessments have been conducted, many drug court programs for juvenile offenders rely on repeated drug testing to monitor adolescents, and judges have reported sustained improvements when combined with other services and close supervision.

Random urine drug testing has been proposed as a screening and prevention method to reduce substance use by students through school-based drug testing programs. Proponents argue that testing will give students who are not yet drug involved a reason to “say no” and provide an opportunity for drug-involved youth to be identified early and receive a referral to appropriate treatment, although empiric evidence to support these claims is lacking.

Drug testing is a technically complex procedure that must be conducted under rigorously defined procedures for proper collection, screening, and confirmatory testing. The federal government has specified procedures that are known as Mandatory Guidelines for Federal Drug Testing Programs that must be used when federal employees are drug tested, and many workplace programs also have adopted these standards to minimize interpretation error. These guidelines were established for use with adults, and drug use by adolescents varies in important ways. For example, research has demonstrated that adolescents adeptly use information technology such as the Internet to modify their drug use behavior. These same technologies could be used to rapidly disseminate information on methods of defeating drug tests among peers. Many more adolescents than adults are prescribed stimulant medications, and at the same time, abuse of stimulant medications by teenagers is increasing. Adolescents use different drugs than adults. Inhalants are used more commonly by adolescents, and use of prescription medications by adolescents is increasing; these classes of substances are not readily detectable on standard urine screens. These differences suggest that although drug-testing programs for adolescents must be as rigorous as workplace testing programs to avoid tampering with specimens, special adaptations may be required to avoid misinterpretation. Specifically, drug panels that are used for testing adolescents should be designed to detect the drugs that are used most commonly, and physicians or other professionals who are responsible for interpreting these tests must receive enough training in toxicology to interpret them correctly. There is potential for harm from false-negative tests, resulting in delayed diagnoses and reinforcement of behaviors by drug-involved youth who have learned how to defeat drug tests. False-positive tests could cause substantial harm to students who are not using drugs by placing them under a cloud of unjust suspicion that might be very difficult to dispel.

**METHODS**

### Areas for Analysis

On the basis of our experience in working with adolescents, we focused on the following areas in this analysis.

#### Specimen Dilution

A urine drug test may be negative even though an adolescent is using drugs if the specimen is diluted, either in vivo or in vitro, to drive the concentration of the illicit substance below the threshold detection level on an initial screening test. Proper collection technique can minimize in vitro adulteration and dilution, but in vivo dilution (consuming a large volume of fluid and/or a diuretic) will be detected only if each sample is checked for adequate concentration. Creatinine is a byproduct of muscle metabolism, and its concentration in urine is very sensitive to dilution. A urine creatinine level <25 mg/dl suggests a urine sample too dilute for proper interpretation of a negative drug test.

#### Prescription and Over-the-Counter Medications

Laboratory testing for drugs is essentially a 2-stage procedure. The initial stage is a screening immunoassay for multiple drugs of abuse. Immunoassays are reasonably sensitive when the urine is normally concentrated but not very specific. Therefore, all positive screens must be followed by second-stage confirmatory testing with gas chromatography/mass spectrometry (GC/MS), which is highly specific.

Drug tests may be positive in the absence of illicit drug use when a prescription or over-the-counter medication or food substance cross-reacts with a screening immunoassay or contains a substance that is detected by the screening panel. False-positives from cross-reacting substances can be eliminated by confirming each positive screening test by GC/MS, but legitimate use of a prescription medication can be assessed only by a medical history that is supplied by the adolescent and/or a parent.

#### Limitations of Screening Panels

Screening immunoassays test for a limited number of drugs. Certain drugs that commonly are used by adolescents are not reliably detected by multipanel screens. Notably, multipanel tests include an opiate screen but are not designed to detect opioids. The term “opiates” refers to naturally occurring alkaloids that are obtained from the opium poppy (morphine and codeine) and their semisynthetic derivatives (heroin). “Opioids” are synthetic compounds (eg, oxycodone, hydrocodone, fentanyl) that have pharmacologic properties similar to morphine and affinity for the opioid receptor. “Opiate”
assays are designed to detect morphine and codeine and will detect heroin, which is metabolized to morphine. There is variable cross-reactivity for detection of the synthetic opiates, which may be detected if taken in very high dosages. When use is suspected, testing for oxycodone or other opioids via specific immunoassay panel or GC/MS must be ordered separately. If this is not done, then the risk for a false-negative is high. Similarly, 3,4 methylenedioxymethamphetamine (ecstasy) is not detected routinely on amphetamine panels but may be detected by specially designed immunoassays or GC/MS, which must be ordered separately.

Drug-testing Program
The goal of this project was to analyze the drug-testing results from a random drug testing program that was administered by adolescent substance abuse experts using recommended procedures to determine (1) the proportion of tests that were too dilute to interpret; (2) the proportion of positive tests that were determined to result from a cause other than illicit drug use; and (3) the proportion of tests that were confirmed positive for oxycodone and were not detected on a standard drug screening panel that included an opiate assay. The results of this analysis can inform recommendations for adolescent drug-testing programs and may help to assess the feasibility of widespread random drug-testing programs in schools and other settings where access to expertise in medical toxicology may be limited.

We performed a secondary analysis of a clinical database that contained drug test results and of chart review to confirm positive drug tests. The clinical drug testing program that served as the source of the database is described in detail.

Patients
Adolescents and young adults who were 13 to 21 years of age and completed a substance abuse evaluation in a children’s hospital–based substance abuse outpatient program were invited to enter a random drug-testing program when the supervising clinician believed that drug testing was clinically indicated. Generally, drug testing was offered to patients who had a history of illicit drug use other than inhalants or steroids and agreed to a trial of abstinence during the drug-testing period. A total of 110 patients entered the drug-testing program when the supervising clinician believed that drug testing was clinically indicated. Generally, drug testing was offered to patients who had a history of illicit drug use other than inhalants or steroids and agreed to a trial of abstinence during the drug-testing period. A total of 110 patients entered the drug-testing program and completed at least 1 drug test between December 2002 and July 2005. Results from all drug tests were recorded in an administrative database, which formed the data set for this analysis. The team identified 89 GC/MS tests that were done between December 2002 and May 2006 and were recorded in the database as positive for any opiate. Of these, 4 original laboratory initial screening reports were not available (all were recorded as positive for morphine, which can be detected after use of any opiate that is metabolized to morphine, including heroin and codeine but not oxycodone). We reviewed all 85 reports that were available to estimate the false-negative rate.

Random Drug-testing Program
Patients who agreed to participate in the random drug-testing program selected a participating laboratory and presented on the day of entry into the testing program or first random call for a baseline sample and then were called on a random schedule with an average of 1 test per week. Patients were called by 10 AM and required to provide a sample the same day. All test results were reviewed by a certified medical review officer (MRO). The MRO is a physician who has completed special training in proper management of laboratory drug-testing procedures, urine toxicology, and interpretation of test results. Unanticipated results, which include dilute specimens or positive tests, were followed by a patient interview by his or her primary clinician. Patients and their parents were given the results of all confirmed positive or dilute urine tests after the patient–clinician interview. Parents determined consequences for positive drug tests for their children; staff consultation was provided on request. Typical restrictions included suspension of car privileges and grounding. Parents were advised to treat dilute tests as though they had been positive.

Laboratory Procedures
Drug tests were performed at a commercial laboratory using federally specified chain-of-custody procedures.11 After photographic identification, patients removed outer garments and emptied pockets. Specimens were collected in bathrooms with water turned off and toilet water stained blue to prevent adulteration. Specimen temperature was checked immediately, and samples that were below body temperature were not analyzed.

Each test included a standard drug screen immunoassay panel*, urinalysis, and creatinine level. The opiate assay of the urine screen that was used by the commercial laboratory is designed to detect morphine and codeine; oxycodone cross-reacts with the opiate assay when it is present in concentrations >300 ng/mL. Urine specific gravity and creatinine level were used to ensure specimen concentration and integrity. Confirmatory testing via GC/MS was performed on all positive screens, and all tests that were positive for D9-tetrahydrocannabinoid carboxylic acid (THC) were quantified. We added GC/MS tests for synthetic opioids to every order for each patient with a history of opioid use, because oxycodone is not detected reliably by standard screening immunoassays.

*Standard panel includes THC, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, methaqualone, opiates, phencyclidine, and propoxyphene but not synthetic opioids such as oxycodone or hydrocodone.
Analysis

Data were extracted from (1) an administrative database with the results of all drug tests conducted between December 2002 and June 2005 and (2) clinic notes to verify positive drug tests. In a second step, we reviewed the original laboratory reports of 85 drug tests that were confirmed positive for any opioid to determine the proportion of tests that were confirmed positive for oxycodone and were not detected by a routine drug screen. The Committee on Clinical Investigations (institutional review board) at Children’s Hospital Boston approved this protocol.

Negative urine samples with a creatinine level <20 mg/dL were considered too dilute for proper interpretation. For all tests that were positive for opiates, amphetamines, or benzodiazepines, we reviewed the clinic note for the MRO visit immediately after the test date to determine whether the patient was taking a prescription medication that could account for the positive test or gave a history of (legitimate) use of an over-the-counter medication or food that could result in a positive test.

RESULTS

A total of 110 patients completed 710 drug tests (mean: 6.5 tests per patient; range: 1–49). Forty negative tests (6% of total) were too dilute to interpret. Nineteen (17%) participants accounted for all 40 dilute drug tests; 15 participants had 1 or 2 dilute tests, and 4 participants had 4 or more (Table 1).

A total of 480 (68%) of 710 drug tests were negative; 125 (18%) were confirmed positive for THC, 46 (6%) for amphetamines, 10 (1%) for cocaine, 4 (<1%) for benzodiazepines, and 32 (5%) for opiates. In total, 177 (25%) tests were positive for a single substance, and 13 (1.8%) were positive for >1 substance, for a total of 217 positive individual tests.

After chart review, positive tests were categorized further as likely resulting from illicit drug use or legitimate prescription use. Of the 217 positive tests in the initial review, 45 (21%) were attributed to legitimate use of prescription or over-the-counter medications. Of the total 710 completed drug tests, 85 (12.0%) were susceptible to either positive or negative misinterpretation.

We reviewed 85 original laboratory reports for tests that were confirmed positive for opiates, including 43 (51%) for oxycodone. Of these 43, 16 (37%) were detected on a standard drug testing panel (ie, the opiate assay was positive; confirmatory testing was positive for oxycodone but not morphine) and 27 were detected only by GC/MS (ie, the opiate assay was negative, but GC/MS was positive for oxycodone). Of the 27 tests in which the opiate screen was negative and the accompanying GC/MS test was positive for oxycodone, 23 had completely negative drug screens and 4 had a positive screen for another drug (2 for cocaine and 2 for THC).

DISCUSSION

This report demonstrates that a significant proportion of drug tests from a random drug-testing program for adolescents were susceptible to misinterpretation. We found that a small but substantial proportion (6%) of urine samples were negative but too dilute to interpret. This means that up to 6% of specimens, collected under rigorous conditions that are designed to prevent adulteration and dilution, still were too dilute to be interpreted and could have led to false-negative reports. Furthermore, 17% of the adolescents in this sample submitted at least 1 dilute sample, but only 4% submitted >2, suggesting that adolescents who were caught trying to defeat drug testing by dilution once were unlikely to attempt dilution again. Drug-testing programs that use less rigorous collection procedures (eg, staff member outside the bathroom) or no special procedures, as is common practice in most physicians’ offices, likely would have much higher rates of adulterated specimens. We therefore recommend that all adolescent drug-testing programs use the same rigorous urine collection protocol as used with adults in workplace drug-testing programs. Furthermore, clinicians should recognize that even rigorous collection procedures cannot prevent a determined individual from tampering with a urine specimen, and, as in the federal protocol, directly observed specimens should be considered whenever urine tampering is suspected.

Twenty-one percent of all confirmed positive drug tests resulted from licit use of prescription or over-the-counter medications, including a large majority (91%) of amphetamines and a small minority (6%) of opioid-positive tests. We recommend that a clinician conduct a follow-up interview whenever an adolescent has a confirmed positive drug test. However, clinicians must know which medications can account for positive tests to make valid assessments. A recent survey found that few physicians have an adequate knowledge base; 99% misidentified 1 or more substances that can cause positive urine drug tests. Therefore, clinicians who administer adolescent drug-testing programs should obtain additional training and certification, as is required for those who administer workplace drug-testing programs. Furthermore, physicians who order urine drug tests for their

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Positive, n (%)</th>
<th>Legitimate Prescription, n (%)</th>
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<tbody>
<tr>
<td>Amphetamines</td>
<td>46 (6)</td>
<td>42 (91)</td>
</tr>
<tr>
<td>Opioids</td>
<td>32 (5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>4 (&lt;1)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>10 (1)</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>92 (13)</td>
<td>45 (49)</td>
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</table>
adolescent patients should have frequent consultation with expert toxicologists to assist with proper drug test interpretation and to keep informed of changes that may occur in the laboratory, such as adoption of new reagents or new assays. We also recommend that physicians consider toxicology results in the context of all of the clinical information and call the laboratory toxicologist whenever there is a discrepancy, to review the laboratory procedures that were used and to question the results of the test.

Participants in this drug-testing program had a complete history before beginning drug testing, allowing the clinical team to order additional specific tests if the adolescent’s drug of choice was not detected reliably on a routine panel. Had the clinical team relied on routine drug-screening tests only, two thirds of oxycodone use in this sample would have been missed, and more than half (53%) of the tests that were positive for oxycodone were negative for all other substances, suggesting that drug use would have been missed entirely in these teens. This is a significant finding, given that abuse of prescription medications such as OxyContin and benzodiazepines is on the rise, particularly among adolescents. Random school drug-testing programs could test all students with an expansive panel, although such a program likely would be prohibitively expensive. Alternatively, policy makers and program designers who implement programs with more limited testing should be mindful of this significant limitation and monitor the student body for increased use of drugs that are not detected on screening panels.

**Limitations**

The drug-testing program described here was conducted in an adolescent substance abuse program, and participants were identified as having used drugs before enrolling in the program. The percentage of positive drug tests, therefore, is likely to be higher than would be expected in a mandatory school-based program. If this is the case, then we would expect that the percentage of positive tests that result from legitimate use of prescription medication, over-the-counter medication, or food consumption would be higher in a school-based drug-testing program, and expertise in interpretation would be even more important to interpreting test results accurately. Furthermore, the participants from this program are likely to be more knowledgeable about drug use and methods of tampering with drug tests than adolescents in a general population, and the proportion of dilute tests may be higher than would be expected in a general population. However, random drug-testing programs are designed precisely to identify drug-involved teenagers, similar to those in our sample. The overall percentage of teens who try to tamper with specimens may be lower in a mandatory school drug-testing program; however, the same rigorous techniques must be used if the program is to identify successfully teens with drug problems, because a high percentage (up to 17% in this study) of drug-involved adolescents may try to tamper with drug tests by providing dilute specimens.

We extracted data from an administrative database that was not designed for research, and some information, such as urine specific gravity, was missing. It is possible that some of the dilute tests were incidental, and every patient with a dilute urine test should be interviewed to help determine whether intentional dilution was attempted to defeat drug testing. In our experience, many patients with dilute drug tests will acknowledge intentional dilution if asked. It also is possible that patients who are prescribed medications such as amphetamines for attention-deficit/hyperactivity also abuse them. This is an intrinsic limitation to drug testing and may limit its therapeutic or monitoring utility. A future study should address this.

**Implications**

This study demonstrates that drug-testing programs demand rigorous procedures and well-trained personnel to obtain accurate results. This finding has implications for the broad application of drug testing through school-based programs, which is currently advocated by the federal Office of National Drug Control Policy. Although thorough and rigorous drug-testing programs can be designed, they will be expensive to implement, potentially diverting resources away from much needed prevention and treatment programs. “Quick and dirty” drug-testing programs that use procedures of convenience are likely to result in unintended consequences, such as misidentifying some students as using illicit drugs when they are not and enabling others to continue illicit drug use by allowing them to easily evade detection. Adolescents who participate in drug-screening programs that provide little or no clinical interaction may change their drug of choice to a more dangerous substance that is not detected on routine screening panels, such as inhalants or synthetic opioids. Rapid dissemination of information could spread this behavior to an entire group of teens. More study is required to determine the efficacy of rigorous drug-testing programs in reducing drug use by adolescents. Because of the high error rate, we believe that there is no place for the widespread implementation of drug-testing programs that use substandard procedures.

**ACKNOWLEDGMENTS**

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Improving Informed Consent: Suggestions From Parents of Children With Leukemia

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ABSTRACT

OBJECTIVE. The objective of this study was to report suggestions for improving the informed consent process from the perspective of parents of children with leukemia.

METHODS. Recommendations for improving informed consent were elicited from 140 parents of children who had been offered participation in a randomized clinical trial for the treatment of their acute leukemia. Four different methods and data collection time points were used with this group of parents, including open-ended, in-person interviews within 72 hours after the informed consent conference; follow-up telephone interviews 6 months after diagnosis; focus groups during year 3 of the project; and a parent advisory group on informed consent meeting in year 4.

RESULTS. The most frequently cited suggestions for improving informed consent during the interviews and focus groups related to giving parents more time to make their decision, the amount and type of information provided, organization of the consent conference, communication style, and providing additional materials. During the parent advisory group on informed consent meeting, parents developed specific guidelines for organization of the information that is presented during the consent process that include 7 major components: timing, sequence, checklist, checking for understanding, anticipatory guidance, segue into randomized clinical trial discussion with historical perspective, and choice.

CONCLUSIONS. Through the incorporation of parental perspectives that provide an authentic stakeholder voice, our research represents a true partnership approach to improving the consent process. Parents provided practical advice for improving informed consent that can be applied to most adult and pediatric patient populations.
In the United States today, most children with cancer are treated in clinical research trials, and these high participation rates often are linked to significant improvements in treatment. The informed consent of the parents or guardians is an ethical requirement for enrollment of children in these clinical trials. However, communication and decision-making in the context of newly diagnosed pediatric cancer are fraught with difficulties for both physicians and families. Physicians report many obstacles to a good informed consent process, including explanation of extremely complex treatment protocols to parents who are in a state of shock after a recent diagnosis of cancer for their child, as well as time constraints on the informed consent process as a result of clinical urgency to begin treatment. Pediatric oncologists who were surveyed about the quality of informed consent for bone marrow transplantation reported a lack of patient and parent participation in the consent process. In addition, research has shown that many parents do not understand many critical components of clinical trial participation.

These problems with communication and deficits in understanding have prompted a search for ways to improve the informed consent process. Many have called for inclusion of participants’ views of the informed consent process, citing trial participants as an “underutilized resource” whose “voice [is] largely ignored.” In the pediatric context, a number of researchers have gathered information on the parents’ perspective of the informed consent process. These studies include reports of parents’ motives for trial participation, as well as ratings of their satisfaction with their decision regarding participation, the amount of anxiety and feelings of pressure from the consent process, their self-assessed understanding of information, the amount and clarity of information, and whether there was adequate time for decision-making. Some of these authors use parent ratings to then develop suggestions for improving the informed consent process. Unfortunately, the predominant use of closed-ended questions in these studies does not allow parents the opportunity to speak in their own terms and expand on issues that are relevant to them. Therefore, the suggestions that were developed by these researchers may reflect the views and interests of the researchers rather than aspects of the informed consent process that parents consider most important and in need of improvement.

Several researchers have taken the critical next step of asking the parents themselves for suggestions on how to improve the informed consent process, using various methods including focus groups, questionnaires, and interviews. These authors have moved informed consent evaluation research beyond parent ratings of the quality of the consent process to specific recommendations for improving it. These previous studies are limited, however, by their small sample sizes, geographic homogeneity, use of a single method, and cross-sectional design. In addition, only 1 of these studies reported the opinions of parents who decided not to enroll their children in a clinical trial, a group that may have particularly insightful suggestions for improving informed consent.

The data reported here provide crucial information on the parents’ perspective of informed consent from a large, diverse sample of parents, using a longitudinal design and multiple methods. The suggestions that were provided by parents in our study offer honest, useful guidance in our efforts to improve informed consent for future families of children who receive a diagnosis of cancer. Moreover, these recommendations are equally relevant to the informed consent process for clinical trials in numerous other adult and pediatric contexts.

**METHODS**

This article uses data from Informed Consent in the Children’s Cancer Group (CCG-S9901), a large study that was funded by the National Cancer Institute and examined the informed consent process for pediatric leukemia randomized clinical trials (RCTs). We recruited parent-participants from 6 Children’s Cancer Group institutions that routinely treat children with acute leukemia: Rainbow Babies & Children’s Hospital (Cleveland, OH), Children’s Hospital of Philadelphia (Philadelphia, PA), Children’s Hospital Medical Center (Cincinnati, OH), Children’s Hospital of Los Angeles (Los Angeles, CA), MD Anderson Cancer Center (Houston, TX), and Children’s National Medical Center (Washington, DC). The study was approved by the institutional review board at each site.

A thorough description of the methods that were used in the larger study was published previously. We obtained the informed consent of the parents, physicians, and patient (when appropriate) shortly after the patient’s diagnosis with either acute lymphoblastic leukemia or acute myeloid leukemia. Trained researchers observed and tape-recorded the informed consent conference(s) (ICC) that clinicians convened for the purposes of discussing treatment options, including RCT participation. This article uses data from 4 subsequent stages of the research. An overview of the research method is shown in Fig 1.

Parents were interviewed within 72 hours of the ICC with their child’s clinician(s), after they had made a decision about whether to participate in the RCT. Whenever possible, the parent who was most active during the ICC was interviewed. During the interview, parents were asked, “In your opinion, how can we make the process of decision-making better?” During follow-up interviews that were conducted over the telephone 6 to 8 months after diagnosis, these parents were again asked for suggestions with the question, “In your opinion, how
can we improve the process of decision-making about clinical research studies?"

After the observation and interview phase of the study was complete, focus groups were held at each of the participating sites with a sample of 72 parents who had participated in the observation/interview phase of our research. These focus groups were designed to elicit more in-depth parent perspectives on aspects of the informed consent process using a more open-ended, interactive method. A professional facilitator who had a background in education and was unknown to the participants facilitated the discussions, with an observer taking notes. Each session lasted 2 hours and was audiotaped. Participants were purposefully selected to ensure inclusion of the perspectives of both mothers and fathers, ethnic majority and minority parents, and clinical trial participants and those who declined trial participation for their child. The facilitator used a question list to guide the discussions, which included the following questions regarding improving the informed consent process: “What do you think could be done to help parents better understand and make a decision about the research study?” and, “What would you tell doctors to help them help parents to make the most informed or best decision possible about participating in a research study?”

During each focus group, participants were asked to nominate a parent to represent their group in the parent advisory group on informed consent (PAGIC). A 2-day meeting of the 9 PAGIC parents was convened in October 2002. During the meeting, members of PAGIC were asked to provide their interpretations of the data that we had collected during observation of ICCs, parent interviews, and focus groups. They also worked together to develop recommendations for how to improve the informed consent process.

The audiotaped interviews, focus groups, and PAGIC meeting were transcribed, and dialogue in Spanish was translated into English. Responses to the questions in the parent interviews regarding improving the informed consent process were extracted, along with suggestions that were found in the transcripts of the focus groups and PAGIC meeting. A parent’s comment or response was considered a suggestion when he or she (1) directly stated a method for improving the process of informed consent or (2) reported a negative characteristic of their informed consent process that should be improved. All parental suggestions were then reviewed for common
themes by the first author (Dr Eder), using an approach that was based on grounded theory, an inductive process that identifies important themes in data through multiple readings of the transcripts.28 The second author (Ms Yamokoski) verified the themes to ensure that they were mutually exclusive and exhaustive. A set of suggestion categories were developed from the themes. Two coders (Ms Yamokoski and Mr Wittmann) then independently assigned each suggestion to the appropriate category. Dr Eder served as a third independent coder in situations in which there was disagreement. For the parent interview and follow-up telephone interview, the number of suggestions within each category was tallied. Multiple suggestions within the same category that were given by a parent during an interview were counted only once. In addition, suggestions from the parent interview that were repeated by a parent during the follow-up telephone interview were counted only once. Suggestions that were given during the focus groups and PAGIC meeting were categorized but were not counted because of the unstructured discussion format.

RESULTS

Parent Interviews

Demographic characteristics for the sample are shown in Table 1. Eight of the 140 parent-participants were unable to recall discussing a clinical trial with their child’s physician; therefore, these parents were not asked any questions about the informed consent process during the parent interview. Seventy (53%) of the 132 parents who completed the parent interview offered at least 1 suggestion for improving the informed consent process, and these 70 parents gave a total of 103 suggestions. Thirty participants were lost to follow-up in the interval between the parent interview and the follow-up telephone interview. Fifty-eight (53%) of the 110 parents who completed the follow-up telephone interview offered at least 1 suggestion for improving the informed consent process, and these 58 parents gave a total of 74 suggestions. The 177 suggestions that were given during both interviews were grouped into 9 different categories according to the topic of the suggestion. Table 2 shows the 9 suggestion categories in decreasing order of frequency, and examples from each of the categories are in Table 3.

More Time for Decision

The most frequently cited (44 [25%] of 177) suggestion relates to giving parents more time to make a decision about participation in the clinical trial. Parents who offered this suggestion pointed to needing an opportunity to consult with others and cope with their emotions before making the decision. Many of these parents also exhibited knowledge of the trial protocol and wondered why a decision had to be made so far in advance of the randomization portion of the treatment.

Amount of Information

Twenty-nine suggestions relating to the amount of information were given during the 2 interviews. Suggestions in this category were of 3 major types, including

| TABLE 1 | Demographic Characteristics (N = 140) |
|--------------------------------------------------|
| **Characteristic** | **Value** |
| Parent age, mean (range), y | 35.4 (18–51) |
| Patient age, mean (range), y | 7.0 (1–18) |
| **Parent gender, n (%)** | |
| Male | 55 (39.3) |
| Female | 85 (60.7) |
| **Patient gender, n (%)** | |
| Male | 80 (57.1) |
| Female | 60 (42.9) |
| **Patient diagnosis, n (%)** | |
| Standard-risk ALL | 60 (42.9) |
| High-risk ALL | 65 (46.4) |
| AML | 15 (10.7) |
| **Patient trial enrollment status, n (%)** | |
| On RCT | 118 (84) |
| Off RCT | 22 (16) |
| **Parent ethnicity, n (%)** | |
| White | 79 (56.4) |
| Black | 13 (9.3) |
| Hispanic | 36 (25.7) |
| Asian | 6 (4.3) |
| Other | 6 (4.3) |
| **Parent ISP, n (%)** | |
| 1–2 | 34 (24.5) |
| 3 | 48 (34.5) |
| 4–5 | 57 (41.0) |
| **Parent education, n (%)** | |
| Less than high school | 28 (20.1) |
| Completed high school | 32 (23.0) |
| Some college | 79 (56.8) |
| **Parent religion, n (%)** | |
| Protestant | 65 (46.4) |
| Catholic | 59 (42.1) |
| Non-Christian | 5 (3.6) |
| None | 11 (7.9) |

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; ISP, Index of Social Position.

a Socioeconomic status was measured by the Hollingshead ISP, which assigns socioeconomic status using education and occupation. On this scale of 1 to 5, a lower ISP score represents a higher socioeconomic status.
b One missing value.

| TABLE 2 | Suggestion Categories |
|--------------------------------------------------|
| **Suggestion Category** | **Parent Interview** | **Follow-up Interview** | **Total** |
| No suggestion | 62 | 52 | 114 |
| More time for decision | 27 | 17 | 44 |
| Amount of information | 18 | 11 | 29 |
| Details of RCT | 15 | 12 | 27 |
| Organization of ICC | 11 | 11 | 22 |
| Additional materials | 9 | 10 | 19 |
| Communication style | 8 | 5 | 13 |
| Support | 7 | 4 | 11 |
| Translation issues | 4 | 4 | 8 |
| Decision-making preference | 4 | 0 | 4 |
| **Total suggestions** | 103 | 74 | 177 |
TABLE 3  Examples of Interview and Focus Group Suggestions

<table>
<thead>
<tr>
<th>Suggestion Category</th>
<th>Interview Examples</th>
<th>Focus Group Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>More time for decision</td>
<td>“Time! We need more time. We would have wanted to talk with our family and friends. We didn’t even get a chance to talk to our parents because they are in the Philippines.”</td>
<td>“Your body just kind of went on autopilot, and your brain is who knows where. Maybe if they wanted a little longer into the process, I think we would be able to digest it a little more easily and we would retain a little bit more. That first week, you are in shock and you’re just dealing with, ‘What have we got to do now.’ So it’s a little tough for retention purposes.”</td>
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<tr>
<td>Amount of information</td>
<td>“The drugs in the study don’t start for 28 days, so to feel like we should sign and make the decision the first day… after only an hour of finding out your child has leukemia is a little much to be asked to make any decisions, especially when it’s 28 days off. So I think the education process should take place over the course of, as a minimum, a week or 2… You shouldn’t feel like you need to make that decision that day.”</td>
<td>“I think parents need more time to digest the information and more time for the emotions to settle down before they can make those decisions. . . . I think it would be nice, although I don’t know if it’s possible, if you could enroll them in the study after they started the initial treatment. Because I think most kids start initial treatment the same. I think most kids at least that are diagnosed with the same kind of cancer start out with the same kind of treatment, and I think if you could get the parents through the induction phase and then ask them if they want to join the study, I think I probably would have done it.”</td>
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<tr>
<td>Not enough</td>
<td>“It helps if they go over it a couple of times. The first time you don’t finish. I think that might have helped me to stay focused.”</td>
<td>“As opposed to having an intense hour, hour and a half, if you could have a 45-minute period with a little break, even just to give yourself a mental break, and then come back and finish. Or an hour followed by a 15- to 20-minute break and come back and finish. I think that might have helped me to stay focused.”</td>
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<tr>
<td>Too much</td>
<td>“I think they spoon feed families when they first present. It’s too much information, and you are too overwhelmed.”</td>
<td>“I think they spoon feed families when they first present. The more information that I have and the more educated I am, the more comfortable I’ve made the right decision in the end.”</td>
</tr>
<tr>
<td>Tailored</td>
<td>“Just explaining it to the extent that the person needs it explained.”</td>
<td>“Almost, personally, the more information I have, the more I’ve made the right decision in the end.”</td>
</tr>
<tr>
<td>Details of RCT</td>
<td>“As opposed to having an intense hour, hour and a half, if you could have a 45-minute period with a little break, even just to give yourself a mental break, and then come back and finish. Or an hour followed by a 15- to 20-minute break and come back and finish. I think that might have helped me to stay focused.”</td>
<td>“I think the drugs in the study don’t start for 28 days, so to feel like we should sign and make the decision the first day… after only an hour of finding out your child has leukemia is a little much to be asked to make any decisions, especially when it’s 28 days off. So I think the education process should take place over the course of, as a minimum, a week or 2… You shouldn’t feel like you need to make that decision that day.”</td>
</tr>
<tr>
<td>Organization of ICC</td>
<td>“But it was really overwhelming because they would give you a lot of information and then ask you if you want to join the study, I think I probably would have done it.”</td>
<td>“I think that might have helped me to stay focused.”</td>
</tr>
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**TABLE 3**  Continued

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<tr>
<th>Suggestion Category</th>
<th>Interview Examples</th>
<th>Focus Group Examples</th>
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<tr>
<td>Additional materials</td>
<td>“I feel sorry for the people who don’t even understand the terms. So maybe something like a small glossary to look things up . . . and I’m thinking maybe a video.”</td>
<td>“I know 1 thing that helped us was we went out and bought that book by Nancy Keene on childhood leukemia and no one had mentioned that book at all during this, when we first arrived. If someone had given me that book, I would have been happy because I like to read everything and I didn’t have enough to read and I felt just because of how pathetic I was in trying to get him diagnosed, I had to know everything from now on because I was not going to let anything slip. And that book, it was kind of like what to do when you’re pregnant—you know these books that everyone carries around, what to expect in the first years, what to expect in the toddler’s years—they’ve got this childhood leukemia. Okay, prednisone, he’s on that, now you can see that it’s normal and this is how we should behave and they talk about that in that book. That you should tell your child everything, it’s an excellent resource.”</td>
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<tr>
<td>Communication style</td>
<td>“Let the parents ask more questions.”</td>
<td>“Just somebody who you feel like you can sit there and ask questions until you turn blue in the face. You don’t feel like they have to go.”</td>
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<td>Support</td>
<td>“It might help other people to have their pediatrician with them because they have built a relationship so they know the kids and the mother. And then have him involved when the consent forms are given so they can translate for the parent. Normally, they just talk, you know, the parent and the doctor, but in my case I just pulled everybody who I wanted to have support from. But if they suggested it up front for some of the people who don’t know, I think it would be great.”</td>
<td>“Besides the doctors not really answering any questions? You ask them a question and you get 30-word answers that you just don’t understand. I think they should speak in layman’s terms. They should understand that not everybody is a doctor, not everybody is a nurse.”</td>
</tr>
<tr>
<td>Translation issues</td>
<td>“I believe that it is very important for us Hispanic families to have qualified and trained interpreters for this type of work.”</td>
<td>Speaker 1: “Maybe you would suggest to them that they might want to have somebody that they feel very comfortable with coming in to see the doctor with them.”</td>
</tr>
<tr>
<td>Decision-making preference</td>
<td>“I think when parents are in this highly emotional situation, they want a personal recommendation.”</td>
<td>Speaker 2: “Somebody who is a very close friend or something that you are very comfortable with. It helps too if you’ve got somebody sitting there, they might hear something that you really didn’t hear of understand something better. So if you have a relative or a friend, they can say, well this is what I got out of it and you know, you can sit there and kind of talk to each other about it. Or if they are allowed time to ask some questions, too, because that might be helpful.”</td>
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recommendations that (1) more information be given to parents about the trial, (2) less information be given to parents about the trial, and (3) the amount of information given be tailored to each family’s individual needs and preferences for information. The majority (23 [79%] of 29) of suggestions in this category stressed the need for more information. Other parents (5 [17%] of 29) felt overwhelmed by the amount of information that they were given, and 2 of these parents specified that they were given too much information in too short a time. One parent offered a solution to this problem of different parent information preferences by suggesting that the amount of information be tailored to individual parent needs.
Details of RCT
Parents offered 27 suggestions that focused on provision of specific information about the clinical trial, including comparison of standard treatment to the trial, description of the various arms of the trial, the risks and benefits of participation, and results to date.

Organization of ICC
Parents offered 22 suggestions concerning the organization of the informed consent process, including the need for repetition and breaking the process into at least 2 meetings.

Additional Materials
Parents made 19 suggestions regarding the need for additional or better materials about the RCT, including improvement of the consent document as well as provision of videos, books, and other literature.

Communication Style
Thirteen suggestions regarding the doctor’s communication style were given during the interviews. Parents emphasized the importance of doctors communicating in an honest, empathic manner, with limited jargon and plenty of opportunity and encouragement to ask questions.

Support
The 11 suggestions in this category relate to provision of support during the ICC or during decision-making. Many of these suggestions refer specifically to speaking with other parents of children with leukemia who have already been through the clinical trial decision-making process.

Translation Issues
Eight parents whose native language is not English stressed the need for translated materials and qualified interpreters during the informed consent process.

Decision-Making Preference
Parents offered 4 suggestions regarding their preferences for decision-making responsibility. Three parents advocated for a recommendation from the physician, whereas 1 parent advised leaving the choice regarding participation in the RCT completely up to the parents.

Focus Groups
During the focus groups, parent participants introduced and discussed suggestions that revolved around the same themes that were found in the parent interview responses. Although these focus group discussions took place months or years after the ICC, parents still recalled problems with the process and continued to stress the need for improvements related to the 9 suggestion categories listed. Examples of each are shown in Table 3.

PAGIC Meeting
During the meeting, PAGIC parents divided into small groups to listen to segments of audiotaped ICCs from the direct observation phase of the research and evaluate the positive and problematic aspects of the consent communication. Parents then regrouped to share their perspectives with the others. The ICC segments were selected by the research team to be representative of the range of ICC contextual variables in our study, such as institution, protocol, and type of leukemia. There was no a priori discussion agenda, and the parents were allowed to drive the discussion of the audiotape segments.

The conversation among parents during the PAGIC meeting touched on all of the themes outlined above, but the vast majority of suggestions focused on organization of the information that is presented during the ICC. The discussion culminated in the development of the PAGIC Model of Informed Consent (Fig 2), the 7 major components are (1) timing, (2) sequence, (3) checklist, (4) checking for understanding, (5) anticipatory guidance, (6) segue into RCT discussion with historical perspective, and (7) choice. Descriptions of each component in the words of the PAGIC members are given in Table 4.

Timing
Members of PAGIC suggested that the ICCs be scheduled in a way to give parents as much time as possible to make their decision. They also stressed the need for the informed consent process to be broken into at least 2 distinct meetings with a break in between for absorbing the information that they had been given and coping with their emotions. The PAGIC participants argued that because parents go through stages in responding to their emotions and the complex information that they are receiving, physicians should gauge how parents are doing, both emotionally and cognitively, and break up the discussion accordingly. Therefore, the timing of discussion of current treatment should depend on parents’ ability to absorb more information after hearing the information about leukemia (see Fig 2).

Sequence
Figure 2 shows the order in which the major topics of the informed consent process should be covered. PAGIC parents clearly articulated the need for presenting information in a logical sequence to aid comprehension.

Checklist
The PAGIC members developed a checklist of major topics that should be covered consistently in all ICCs. The topics and the meeting in which they should be addressed are shown in Fig 2. Parents also suggested that it might be helpful if another member of the health care team is present to assist in managing the checklist to
allow the physician to be engaged fully with the family during the discussion.

**Checking for Understanding**

Parents emphasized the importance of checking for understanding of the information just presented before moving on to the next topic. The arrows in Fig. 2 demonstrate that physicians should be prepared to explain a subject in various ways until parents understand it clearly and are ready to progress to the next concept. Open-ended questions such as, “What do you understand about X?” are better at eliciting parental understanding than easily dismissed, closed-ended questions such as, “Do you understand?”

**Anticipatory Guidance**

PAGIC parents stressed the importance of the doctor clearly laying out at the end of each discussion what is to come next, including when the next discussion will be, what the next discussion will cover, and when a decision will need to be made.

**Segue Into RCT Discussion With Historical Perspective**

PAGIC parents recommended transitioning into discussion of the RCT by presenting the improvement of the cure rate through time. They suggested that this historical perspective puts the current cure rate in a positive light, which helps parents accept the diagnosis and prognosis. Explaining the role that RCTs have played in the improvement of the cure rate provides an opportunity for physicians to introduce the RCT by explaining the need for additional research to improve the cure rate for future children.

**Choice**

PAGIC parents highlighted how critical understanding of the voluntary nature of the trial is to the informed consent process. They advised using the word “choice” at least 3 times during the ICC to ensure that parents have a full appreciation of the concept.

**DISCUSSION**

At 4 different points during their child’s treatment for leukemia, the parents in our study shared many practical suggestions for improving the informed consent process. Unlike previous work in this area, our research design allowed parents to go beyond simple ratings of aspects of the consent process to provision of explicit recommendations for change on the basis of their own experiences with informed consent.

Parents continually reiterated the need for more time to make the trial decision, which is consistent with the results of many other studies of parental perspectives on the consent process. The time allowed for decision-making about trial participation varies according to the trial offered for a particular child. In this study, 74%...
of patients were offered participation in a trial that required a decision within 72 hours of the child receiving his or her first chemotherapy. The CCG-1991 study that was offered to 26% of the families incorporated a staged consent process that allowed parents to consent up front to the first 28 days of therapy, which is the same on or off the trial, and then make a decision about the randomized portion of the trial by the 28th day. We have

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Timing</td>
<td>Parent 1: &quot;If we need to make a decision in half an hour, once you’re told, let the person digest what he’s being told. Back away. Make sure the parent’s okay to a certain extent, but then let them go for half an hour, or whatever the time frame is for the study, so that it’s not a 1-2 punch.” Parent 2: “So even if it’s only a half hour, that’s better than nothing. That you’re actually getting out of there and then going back in—that’s very important.” Parent 3: “And the parents need some time to digest that the child has leukemia. So I think … even if it’s only half an hour, some parents can just hold their child and cry, and then we’re going to give you some, a little bit, of time, the most time that we can give, and we’re going to come back and give you some options. Even that will help.” Parent 4: “And then it goes back with the basic teaching strategy that you have to monitor and adjust to go with whatever population you’re speaking to. And that can be a little tough and tricky. You have to get a sense, and the right sense, as to who you’re talking to and how much they’re getting. And it’s just monitor and adjust, monitor and adjust as you move along.”</td>
</tr>
<tr>
<td>Sequence</td>
<td>Parent 3: “That’s the first thing to make the parents understand: what is leukemia? And the second thing is, now that you know what leukemia is, now explain to them about the study.” Parent 2: “What I hear is that people are saying I found out that my child has leukemia, and the next step is the study, well, no. The next step is treatment. And then this is the treatment for leukemia. Explain that. And then, as an option, you can participate in the study.” Parent 1: “The concepts build upon each other. I can’t understand a study until I understand the basics of the treatment…. And you can’t understand what treatment for leukemia is until you understand what leukemia is.”</td>
</tr>
<tr>
<td>Checklist</td>
<td>Parent 3: “Maybe a checklist, did I tell them about this, and this. Because it’s not consistent.” Parent 6: “Any plan. Maybe somebody actually during the discussion checking that person. It shouldn’t be the presenter actually doing the checklist, it should be another observer.”</td>
</tr>
<tr>
<td>Checking for understanding</td>
<td>Parent 1: “We’re all saying the parent should understand what’s being presented … if they need to ask questions, whatever they need, if they don’t understand, you go back there and do it again.” Parent 2: “We have built in questions, and they say, “We’ve finished 1 thing. We’ve finished talking about standard treatment. I’m going to go on into something else, but before I do that, do you have any questions on what we just talked about? Is there anything that’s not clear that I can go over again?” And if they’re clear with it, then these are the study and the treatment options with the study, and then you go into that. And somewhere in there, you check on them again. “What can I help you with here?”</td>
</tr>
<tr>
<td>Anticipatory guidance</td>
<td>Parent 3: “And then something I think should be in the checklist is, at the end, what’s next?” Parent 1: “At the end of each session, whether it’s 1 session or 50, set the expectation for the next time. This is how did we get there? Because the parents are asking, how did we get from here to here?” Parent 6: “They need to lay the groundwork for when the follow-up is going to be so that you have time to adjust yourself to hearing about whatever.”</td>
</tr>
<tr>
<td>Segue into RCT discussion with historical perspective</td>
<td>Parent 7: “Like where we were 30 years ago, as far as success rate, and where we are today, and where do we hope to be in the future. And by doing this, it will give us more information to try and improve those chances.” Parent 1: “Unless somebody disagrees, I think it’s only once a parent comes to accept the diagnosis, and anything that’s going to help them feel more comfortable with the decision is to know the cure rate…. So when they say he has an 85% cure rate, I want to see how it’s actually grown because of people who participate in these studies.” Parent 6: “I think we should provide the numbers, this is where we were many years ago, this is where we’re at today, and we hope to get to here.” Parent 1: “Well that of course leads you to say, well how did we get there? Because the parents are thinking, well how did we get from here to here?”</td>
</tr>
<tr>
<td>Choice</td>
<td>Parent 1: “Choice or control—you want to make sure that those concepts are drilled into the parents. That they have a choice.” Parent 7: “I think that choice should be used throughout, but 3 times.” Parent 5: “You don’t have to overkill. Just 3 times: beginning, middle, and end.” Parent 4: “Maybe there can be a general rule that you have to clearly hear the word ‘choice’ 3 times, then they’re going to get it.”</td>
</tr>
</tbody>
</table>
reported elsewhere on the improved understanding and trust levels that were found in the group of parents who were involved in the staged consent process. These data, as well as the parental opinions reported here, suggest the need for additional efforts that aim to increase the number of protocols that allow more time for decision-making. In addition, physicians should plan the consent process in such a way as to allow for as much time for decision-making as possible within the limits of the child’s medical condition and the particular trial protocol being offered.

A common recommendation made by parents was that more information about the clinical trial be provided. Time constraints that are imposed by busy clinical schedules and requirements of the protocol make it a challenge for physicians to spend more time discussing the trial with parents. Greater attention to the quality and organization of the information provided, rather than strictly quantity, may mitigate the additional time burdens that would result from simply providing more information. Parental suggestions on how to organize the informed consent process culminated in the development of the PAGIC Model of Informed Consent during the PAGIC meeting. The PAGIC Model of Informed Consent closely parallels many features of the communication sequence that was proposed by Brown et al to increase patient understanding of information, including presentation of standard treatment before discussion of the clinical trial, some type of segue into the clinical trial discussion, and regular opportunities for patients to respond to the information that they have been provided. PAGIC parents in our study provided additional information on the form that the segue should take and focused more on opportunities for asking questions and ensuring understanding of information after each section. Parents who were interviewed by Kupst et al also recommended explaining information 1 step at a time and checking parents’ understanding before moving on to the next topic. Better organization of the ICC through use of the PAGIC model may ultimately save time for physicians by making backtracking unnecessary and reducing parents’ confusion. In addition, parents may be less likely to feel overwhelmed by the volume and the content of the information if it is presented in a logical order during the course of multiple meetings, rather than jumbled together in 1 long conference. The regular feedback loops that are built into the PAGIC model also serve to increase parental participation in the ICC, which in turn can lead to better understanding.

Many parents in our study made specific requests for greater disclosure of details of the clinical trial, but the particular information desired varied from parent to parent. The finding by Tait et al of differences in priorities for disclosure of elements of informed consent between parents and investigators underscores the importance of eliciting parent information preferences to ensure that they obtain the information they want and need. The variability in parental preferences for decision-making responsibility that was found in our study and others adds emphasis to the need for open communication about individual parent preferences during the ICC.

Parents’ suggestions for limiting the use of jargon and simplifying information have been reported in other studies and are likely to contribute to an improved informed consent process. Implementation of parental recommendations for strategic use of the consent document and other materials as educational tools could further enhance the communication process and lead to more informed decision-making. Likewise, provision of skilled interpreters and translated documents is a basic necessity for communication with non–English-speaking parents. Finally, our results reinforce previous research that stressed the importance of ensuring that parents have access to various social supports, both during the ICC and throughout the decision-making process.

Some might argue that many of the suggestions made by these parents should be intuitive to physicians already. However, these suggestions come from 140 parents who reported on their actual experience of ICCs that were led by 65 different physicians at 6 hospitals that routinely treat children with acute leukemia. Therefore, these recommendations generally are not being put into practice during the informed consent process. Physicians may find it challenging to implement some of these parental suggestions, especially those that require more discussion and decision-making time. The parents developed the PAGIC Model of Informed Consent to alleviate these challenges by providing an organizational structure that enhances the quality and efficiency of the communication process.

A possible limitation of the study is that the PAGIC parents who developed the PAGIC Model of Informed Consent were both vocal and articulate, and their views may not be representative of the majority of parents. However, these parents were asked to review the transcript of the focus group in which they participated and summarize the perspectives of their group during the meeting, and these summaries served as a foundation on which the PAGIC model was built. In addition, the suggestions that were discussed during all 4 stages of the research were fairly consistent; therefore, it is likely that the recommendations developed in the later stages represent the views of the larger group of parents. Furthermore, the suggestions presented here are generalizable to most other adult and pediatric patient populations with minimal adaptation.

CONCLUSION
By using several methods and data collection time points, this study presents a robust plan for improving informed consent. Through the incorporation of paren-
tal perspectives that provide an authentic stakeholder voice, our research represents a true partnership approach to improving the process. Our findings show that parents have valuable advice to offer and therefore are appropriate consultants in our research endeavors. The communication process in which the parents in our study were involved is not fundamentally different from other adult and pediatric contexts that involve a new diagnosis; therefore, there is potential for broad application of the parental recommendations reported here, which could lead to greater patient and parent satisfaction, enhanced understanding, and more informed decision-making in many situations.

ACKNOWLEDGMENTS
This study was supported by the National Cancer Institute (RO1 CA83267).

These data were collected via a limited-institution study in the Children’s Cancer Group (CCG-S9901). We thank Omar Jadue for his valuable assistance throughout the project, the Children’s Oncology Group (formerly Children’s Cancer Group) for their leadership and support, and our research staff for their dedication and excellent work. We appreciate the clinicians, parents, and children who participated in this research and especially acknowledge the tremendous efforts of the members of the PAGIC.

REFERENCES
Neuromotor Outcome at 2 Years of Very Preterm Infants Who Were Treated With High-Frequency Oscillatory Ventilation or Conventional Ventilation for Neonatal Respiratory Distress Syndrome

Patrick Truffert, MD, PhD, Josefa Paris-Llado, PhD, Benoît Escande, MD, Jean-François Magny, MD, Gilles Cambonie, MD, Elie Saliba, MD, Gérard Thiriez, MD, Véronique Zupan-Simunek, Thierry Blanc, MD, Jean-Christophe Rozé, MD, Gérard Bréart, MD, MSC, Guy Moriette, MD

OBJECTIVE. In a previous multicenter, randomized trial, elective use of high-frequency oscillatory ventilation was compared with the use of conventional ventilation in the management of respiratory distress syndrome in preterm infants <30 weeks. No difference in terms of respiratory outcome was observed, but concerns were raised about an increased rate of severe intraventricular hemorrhage in the high-frequency ventilation group. To evaluate outcome, a follow-up study was conducted until a corrected age of 2 years. We report the results concerning neuromotor outcome.

METHODS. Outcome was able to be evaluated in 192 of the 212 infants who survived until discharge from the neonatal unit: 97 of 105 infants of the high-frequency group and 95 of 104 infants of the conventional ventilation group.

RESULTS. In the infants reviewed, mean birth weight and gestational age were similar in the 2 ventilation groups. As in the overall study population, the following differences were observed between the high-frequency ventilation group and the conventional ventilation group: lower 5-minute Apgar score, fewer surfactant instillations, and a higher incidence of severe intraventricular hemorrhage. At a corrected age of 2 years, 93 of the 97 infants of the high-frequency group and 79 of the 95 infants of the conventional ventilation group did not present any neuromotor disability, whereas 4 infants of the high-frequency group and 16 infants of the conventional ventilation group had cerebral palsy.

CONCLUSIONS. Contrary to our initial concern about the increased rate of severe intraventricular hemorrhage in the high-frequency ventilation group, these data suggest that early use of high-frequency ventilation, compared with conventional ventilation, may be associated with a better neuromotor outcome. Because of the small number of patients studied and the absence of any explanation for this finding, we can conclude only that high-frequency oscillatory ventilation is not associated with a poorer neuromotor outcome.
METHODS

Initial Study

The study protocol and results were reported previously in detail. Briefly, infants were eligible when their postmenstrual age at birth was between 24 and 29 weeks and when they required mechanical ventilation as a result of respiratory distress syndrome. Eligible patients were randomly assigned to HFOV with lung volume recruitment strategy or conventional ventilation. A first dose of surfactant was given in both groups after randomization. A total of 273 patients were analyzed: 139 in the HFOV group and 134 in the conventional ventilation group. In the HFOV group, compared with the conventional group, a nonsignificantly smaller proportion of infants developed chronic lung disease at 36 weeks (adjusted odds ratio [OR]: 0.53; 95% confidence interval [CI]: 0.24–1.14]), and a nonsignificantly greater proportion of infants developed grade 3 or 4 IVH after randomization (24% vs 14%; adjusted OR: 1.50; 95% CI: 0.68–1.30). Because previous studies reported increased rates of severe IVH in infants who were randomly assigned to HFOV, accurate grading was ascertained by review of all ultrasound examinations indicating the presence of grades 2 to 4 IVH at the coordinating center, by a radiologist who was not informed about the group assignment. Cystic periventricular leukomalacia (PVL) rates were similar in the HFOV group (10%) and the conventional group (13%).

Follow-up Study

Data on outcome at a corrected age of 2 years were collected by the questionnaires that were used in the EPIPAGE study, as previously reported. Briefly, physicians (pediatric neurologists, pediatricians, neonatologists, or general practitioners) who followed the infants and examined them at 2 years of corrected age were asked to complete a standardized precoded questionnaire. Completing the standardized questionnaire, which was designed to minimize the risk for ambiguous answers, required a detailed physical and neurologic examination that assessed tone, reflexes, posture, and movements. Cerebral palsy (CP) was defined according to the definitions of the European Collaborative study group. The diagnosis of spastic CP was based on the observation of at least 2 of the following 3 findings: abnormal posture and/or movement, increased tone, and abnormal reflexes. Correct classification of our CP cases was checked by an investigator of the EPIPAGE study who was not informed about the ventilation group allocation.

Data were analyzed by SAS software (SAS Institute, Cary, NC). Rate comparisons and crude and adjusted ORs are presented with corresponding 95% CIs. The adjusted ORs were computed by multiple logistic regression.

RESULTS

Of the 273 infants analyzed in the initial trial, 212 survived to discharge from the neonatal unit. A total of 192 infants (90% of discharged infants) were included in the present study: 97 from the HFOV group and 95 from the conventional ventilation group (Fig 1).

Data on the follow-up of these 192 infants were derived from specialized institutions in 69% of cases (follow-up at the initial neonatal center, a hospital pediatric clinic, or an institution that specializes in the detection and care of developmental abnormalities). The remaining infants were followed in less specialized institutions or by private pediatricians or general practitioners. The proportions of infants who were followed in specialized institutions and of infants who were followed according to the latter description were not different between the HFOV and conventional ventilation groups. Forty-two percent of the infants followed belonged to the EPIPAGE cohort.

In the 192 infants assessed at 2 years of age, compared with the 20 infants who died after discharge or who were lost to follow-up, the mean birth weight was lower
(999 ± 242 vs 1109 ± 165 g; \( P = .05 \)) and the proportion of infants with birth weight ≤1000 g was higher (49.5% vs 25%; \( P = .04 \)). There also was a trend for a higher rate of chronic lung disease (supplemental oxygen required at 36 weeks; 26% vs 10%; \( P = .11 \)).

Perinatal and neonatal data by treatment group for the infants evaluated are summarized in Table 1. Similar significant differences were observed as in the total population of the initial trial. In the HFOV group, compared with the conventional ventilation group, lower incidences of preeclampsia and high blood pressure were observed during pregnancy, and fewer infants had a 5-minute Apgar score ≥7 or required >1 surfactant instillation. Other perinatal characteristics were comparable between the 2 treatment groups, and the hospital mortality rate was comparable between the 2 treatment groups (23% vs 22%).

Neonatal mortality related to ultrasound detection of major cerebral complications (severe IVH or cystic PVL) in infants of the 2 treatment groups is described in Table 2. No significant difference was demonstrated.

The neuromotor outcome at a corrected age of 2 years is shown in Table 3. The corrected age at examination was comparable in the 2 groups (median [interquartile]: 25 months [5] in both groups). Spastic CP was diagnosed in 4 (4%) infants of the HFOV group and 16 (17%) infants of the conventional ventilation group; this difference was significant (OR: 0.87; 95% CI: 0.79–0.96). Survival without CP also was more frequent in the HFOV group (OR: 1.89; 95% CI: 1.04–3.44). Most perinatal characteristics of the infants were similar, regardless of whether they developed CP, including severe IVH.

Only the presence of cystic PVL during the neonatal period was significantly associated with the development of CP at the age of 2 years. Cystic PVL was detected in 11 (6%) infants without CP compared with 7 (35%) infants with CP (\( P < .001 \)).

The occurrence of CP in infants with neonatal cerebral complications is assessed in Table 4. Among the infants who were assessed at 2 years, there were significantly more cases of severe IVH in the HFOV group than in the conventional ventilation group (13 [13%] vs 3 [3%] cases; OR: 4.7; 95% CI: 1.2–21.8), in agreement with the results that were observed for the total population included in the initial trial. The proportion of infants who were followed at 2 years and developed cystic PVL during the neonatal period was similar in the 2 groups.

The relationship between CP at 2 years and the use of HFOV or conventional ventilation during the neonatal period was similar in the 2 groups.
Lung immaturity continues to be a major cause of mortality and morbidity in very preterm infants. The objective of HFOV is to reduce acute lung injury. Pulmonary benefits have been demonstrated in animal experiments when HFOV rather than conventional ventilation was used\textsuperscript{17–21} but often were not confirmed in newborn infants.\textsuperscript{3,4,22} In 1 large-scale trial, a beneficial effect was shown, but, despite the inclusion of 500 infants, it was too small to result in a significant reduction of the chronic lung disease rate in survivors.\textsuperscript{3} Our initial observation of a nonsignificantly increased severe IVH rate in infants who received HFOV and the limited follow-up data\textsuperscript{2} justified the present follow-up study.

The follow-up rate was satisfactory. Infants who were followed at 3 years presented higher rates of extremely low birth weight and chronic lung disease than infants who died before 2 years of age or who were lost to follow-up. The rate of infants who were lost to follow-up was similar in the 2 treatment groups. The HFOV group required fewer surfactant instillations. Among the infants reviewed, severe IVH rates remained higher in the HFOV group, whereas cystic leukomalacia rates were similar in the 2 treatment groups.

Severe IVH has been reported to be predictive of the subsequent development of CP.\textsuperscript{5,6,23} However, this predictive value may be only limited; Schmidt et al\textsuperscript{7} reported identical CP rates in 2 groups of infants despite different neonatal IVH rates (9% and 13%). Only 4 of our 13 infants in the HFOV group with severe IVH developed CP, a proportion almost identical to that observed in the EPICOM study in infants with grade 3 IVH.\textsuperscript{15} In the conventional group, only 3 cases of severe IVH were observed, in contrast with 16 cases of CP, a highly unexpected finding. Because all head ultrasounds that showed cerebral bleeding were reviewed centrally, incorrect classification of IVH is very unlikely. A higher hospital mortality of infants with severe cerebral lesions, which could have improved the outcome in the HFOV group, was not observed.

Of the other factors that contribute to CP, the most important probably is PVL,\textsuperscript{23,24} as confirmed by our observation of a significant correlation between cystic PVL and CP. However, the presence of cystic PVL allowed identification of only 7 (35%) of our 20 cases of CP, the same prediction rate was reported in the EPICOM study, when unilateral lesions were considered.\textsuperscript{15} The sensitivity of cerebral ultrasound for the detection of white matter injury is considered to be relatively low.\textsuperscript{24} CP prediction rates that are based on ultrasound could be increased by performing a greater number of ultrasound examinations, which should not be limited to the first 4 weeks after birth, and by using high-quality techniques, as suggested by De Vries et al.\textsuperscript{25} The design of our initial trial focused on ventilatory aspects, and cerebral ultrasound examinations were designed only to detect IVH accurately. These examinations therefore were included

### TABLE 1 Characteristics of Infants Who Were Reviewed According to the Initial Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HFOV Group (N = 97)</th>
<th>Conventional Group (N = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>10 (10)</td>
<td>25 (26)\textsuperscript{*}</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>20 (21)</td>
<td>36 (37)\textsuperscript{*}</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>33 (34)</td>
<td>25 (26)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>58 (60)</td>
<td>62 (65)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>52 (54)</td>
<td>59 (62)</td>
</tr>
<tr>
<td>Neonatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>995 (234)</td>
<td>1004 (252)</td>
</tr>
<tr>
<td>Gestational age, mean (SD), wk</td>
<td>27.6 (1.4)</td>
<td>27.8 (1.5)</td>
</tr>
<tr>
<td>Birth weight ≥1000 g, n (%)</td>
<td>51 (53)</td>
<td>44 (46)</td>
</tr>
<tr>
<td>Gestational age 24–27 wk, n (%)</td>
<td>50 (51)</td>
<td>48 (50)</td>
</tr>
<tr>
<td>Inborn, n (%)</td>
<td>71 (73)</td>
<td>70 (73)</td>
</tr>
<tr>
<td>S-min Apgar score ≥7, n (%)</td>
<td>63 (75)</td>
<td>73 (87)\textsuperscript{*}</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>55 (57)</td>
<td>54 (57)</td>
</tr>
<tr>
<td>Timing, median (interquartile), min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at randomization</td>
<td>144 (100)</td>
<td>130 (102)</td>
</tr>
<tr>
<td>Age at first surfactant instillation</td>
<td>180 (115)</td>
<td>163 (108)</td>
</tr>
<tr>
<td>Respiratory data before randomization, median (interquartile)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{O_2}$:$F_{O_2}$</td>
<td>94 (80)</td>
<td>87 (58)</td>
</tr>
<tr>
<td>$P_{O_2}$:$F_{O_2}$ before second surfactant instillation, median (interquartile)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reservoir outcomes, n (%)</td>
<td>137 (74)</td>
<td>132 (65)</td>
</tr>
<tr>
<td>Need for &gt;1 surfactant instillation</td>
<td>24 (25)\textsuperscript{*}</td>
<td>55 (38)</td>
</tr>
<tr>
<td>Supplemental oxygen at 36 wk</td>
<td>23 (24)</td>
<td>27 (28)</td>
</tr>
</tbody>
</table>

$F_{O_2}$ indicates fraction of inspired oxygen.

\textsuperscript{*}P < .01.

\textsuperscript{b}P < .05.

Period was assessed by multiple logistic regression with adjustment for gestational age, birth weight, antenatal steroids, preeclampsia, high blood pressure during pregnancy, IVH grades 3 to 4, leukomalacia, and 5-minute Apgar score <7. After adjustment, CP was significantly less frequent in the HFOV group than in the conventional ventilation group (adjusted OR: 0.3; 95% CI: 0.1–0.6).

### DISCUSSION

The neurologic outcome of infants who were included in a randomized trial that compared HFOV and conventional ventilation in the treatment of neonatal respiratory distress syndrome was evaluated at a corrected age of 2 years. Data that were collected on the sensorial and cognitive outcome were not sufficiently accurate or comprehensive to allow adequate evaluation. We therefore limited our analysis to neuromotor outcome.

Despite a nonsignificant increase in the severe IVH rate in the HFOV group compared with the conventional ventilation group, the neuromotor outcome actually seemed better in the HFOV group, because CP rates and the combined rates of mortality or CP were lower in the HFOV group compared with the conventional ventilation group. CP and mortality or CP rates remained lower in the HFOV group after adjustment for multiple factors.
in our protocol before randomization, during the first week, between days 7 and 10 and at day 28. No other guidelines concerning the number of examinations or technical issues were given, and the diagnosis of cystic PVL was established at each participating center using local protocols. No evaluation was required at term equivalent. Detection of PVL in our trial therefore was far from optimal.

A total of 34 infants experienced severe IVH or cystic PVL. Twenty-six (76%) of them did not develop CP. Using an optimal ultrasound protocol, De Vries et al. reported that 52% of infants with major ultrasound abnormalities did not develop CP.

Neurologic assessment was similar in the 2 treatment groups. More than two thirds of assessments, distributed equally between the 2 groups, were performed in specialized institutions. All questionnaires were reviewed carefully, as previously described, suggesting the reliability of the information collected. The definition of CP was based on the EPIPAGE study criteria and examination modalities. Infants were evaluated blindly as to treatment groups.

Very few data are available concerning the neurologic outcome of infants who were randomly assigned to receive HFOV or conventional ventilation in the age of surfactant. Two studies reported similar IVH rates and similar neurologic outcomes with either technique. Both of these studies concerned more mature infants, and 1 study reported data from only 1 of 3 centers. The difference in CP rates, although significant, was based on small numbers of patients (4 and 16) and therefore should be interpreted cautiously. The explanation for the higher CP rate in the conventional ventilation group remains highly speculative. Infants may have been more effectively stabilized in the HFOV group, with more limited variations of Pco₂ and blood pressure, but this was not detected in our initial study. However, more infants switched from conventional ventilation to HFOV, thereby identifying a subset of patients who were randomly assigned to conventional ventilation and who had a particularly severe respiratory outcome, possibly increasing the risk for CP.

**CONCLUSIONS**

Our trial raised concerns about the safety of HFOV compared with conventional ventilation, on the basis of an increased severe IVH rate in the group of infants who were randomly assigned to HFOV. Surprisingly, neurologic assessment at a corrected age of 2 years showed a higher CP rate among infants who were randomly assigned to receive conventional ventilation. Cerebral ultrasound examinations during the neonatal period had a low predictive value for CP, highlighting the importance of follow-up. Because of the various limitations of our study, these findings must be interpreted cautiously. Nevertheless, the neuromotor prognosis of infants who are treated early after birth by HFOV seems to be at least as good as that of infants who are treated by conventional ventilation.

**ACKNOWLEDGMENTS**

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REFERENCES


Preterm Birth–Associated Cost of Early Intervention Services: An Analysis by Gestational Age

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ABSTRACT

OBJECTIVES. Characterizing the cost of preterm birth is important in assessing the impact of increasing prematurity rates and evaluating the cost-effectiveness of therapies to prevent preterm delivery. To assess early intervention costs that are associated with preterm births, we estimated the program cost of early intervention services for children who were born in Massachusetts, by gestational age at birth.

METHODS. Using the Pregnancy to Early Life Longitudinal Data Set, birth certificates for infants who were born in Massachusetts between July 1999 and June 2000 were linked to early intervention claims through 2003. We determined total program costs, in 2003 dollars, of early intervention and mean cost per surviving infant by gestational age. Costs by plurality, eligibility criteria, provider discipline, and annual costs for children’s first 3 years also were examined.

RESULTS. Overall, 14,033 of 76,901 surviving infants received early intervention services. Program costs totaled almost $66 million, with mean cost per surviving infant of $857. Mean cost per infant was highest for children who were 24 to 31 weeks’ gestational age ($5393) and higher for infants who were 32 to 36 weeks’ gestational age ($1578) compared with those who were born at term ($725). Cost per surviving infant generally decreased with increasing gestational age. Among children in early intervention, mean cost per child was higher for preterm infants than for term infants. At each gestational age, mean cost per surviving infant was higher for multiples than for singletons, and annual early intervention costs were higher for toddlers than for infants.

CONCLUSIONS. Compared with their term counterparts, preterm infants incurred higher early intervention costs. This information along with data on birth trends will inform budget forecasting for early intervention programs. Costs that are associated with early childhood developmental services must be included when considering the long-term costs of prematurity.
INFANTS WHO ARE born preterm are at increased risk for medical and developmental morbidity.\textsuperscript{1–10} Associated costs impose a significant burden on multiple sectors of the US economy and include long-term hospital, outpatient medical, developmental, and educational expenses. As highlighted in a recent Institute of Medicine report, neonatal and postneonatal medical costs that are associated with low birth weight and preterm birth have been described, but data pertaining to developmental and educational costs that are associated with preterm birth are sparse, especially for the child’s first 3 years.\textsuperscript{11} A full characterization of all costs is necessary when evaluating the cost-effectiveness of preterm delivery prevention therapies and when estimating the impact that increasing preterm birth rates and extreme preterm survivorship will have on future expenditures. This study provides the first population-based estimates of the costs of infant and toddler developmental services for preterm children.

Neonatal and postneonatal hospital and outpatient costs that are associated with preterm birth and, related, low birth weight have been well characterized. Estimates of neonatal inpatient costs for children who are born preterm range from approximately $11,000 to $18,000 (2003 dollars) per birth, compared with $1300 to $1900 (2003 dollars) per term birth.\textsuperscript{12–14} Rogowski et al\textsuperscript{15} estimated the cost of rehospitalizations and outpatient care during the first year for preterm infants who are born <1500 g to be approximately $8000 (1987 dollars) per child. Lewett et al\textsuperscript{16} estimated that each low birth weight child costs an average of approximately $290 in 1998 dollars more than a higher birth weight child for inpatient medical care during the preschool years.

Over the long term, preterm children are more likely than their term counterparts to have neurodevelopmental impairment in multiple domains, including cognitive,\textsuperscript{4,6,17} sensory,\textsuperscript{7–9} and motor impairment,\textsuperscript{10} thereby accruing excess expenses related to developmental and educational services. Children who are 3 years and older and have disabilities are ensured public education that emphasizes special education and related services through part B of the Individuals With Disabilities Education Act of 1997. Two studies examined special education costs as a result of preterm birth for children who were 3 years and older, with the incremental cost estimated to be $1240 (1989–1990 dollars) to $2237 (2005 dollars) per child.\textsuperscript{11,18}

To date, developmental and educational costs for former preterm infants during the first 3 years of life have not been described. Infants and toddlers who have developmental delay or an established disability or, in some states, are at risk for a delay are eligible for early intervention (EI) services as mandated under part C of the Individuals With Disabilities Education Act of 1997. State-coordinated EI programs provide services that enhance physical, cognitive, communication, social/emo-

tional, and/or adaptive development.\textsuperscript{19} The aim of this study was to estimate the cost of EI services in a population-based cohort, by gestational age (GA) at birth.

METHODS

Data Source

Data for these analyses were derived from the Pregnancy to Early Life Longitudinal (PELL) data system. PELL is a public–private partnership among the Boston University School of Public Health, Massachusetts Department of Public Health, and the Centers for Disease Control and Prevention, the funding agency. The core PELL database consists of linked Massachusetts birth certificate, death certificate, and birth-related hospital discharge data from 1998–2003 births for both mothers and infants. Details of PELL linkage methods are presented elsewhere.\textsuperscript{20}

Core PELL records for the 80,177 in-state, resident births that occurred during fiscal year 2000, July 1, 1999, through June 30, 2000, were linked to EI program and claims data from 16,949 children who were born during this period and received EI services. Overall, 15,157 (89.4%) EI program records linked back to a record in the core PELL data set. Of these, 14,446 (95.3%) had ≥1 claim in the data set. For analysis, records were stripped of name, address, and other identifying information, and a data use and confidentiality agreement was completed with the Massachusetts Department of Public Health to perform the current analyses.*

Variables

Birth Characteristics

The date of last menstrual period and clinical estimate of GA were recorded on the birth certificate. We defined GA as the number of weeks from last menstrual period when this value was valid according to Alexander’s criteria.\textsuperscript{21} Otherwise, GA was defined as the clinical estimate of weeks’ gestation. Valid GA between 24 and 42 weeks were available for 77,034 (96.1%) of the 80,177 Massachusetts births and for 14,033 (97.1%) of the 14,446 with ≥1 claim. GA was categorized further as very preterm (24–31 weeks), moderately preterm (32–36 weeks), and term (37–42 weeks). Plurality was calculated using methods that were developed by Lazar et al\textsuperscript{22} and was categorized as singleton or multiple birth.

*The authors linked birth, death, and hospital discharge data with EI program data to conduct this study on behalf of the Massachusetts Department of Public Health’s Early Intervention Program. Personally identifiable information that is received by the EI program is protected under the provisions of the Individuals with Disabilities Education Act, which adopts the privacy protections of the Family Educational Rights and Privacy Act (20 USC §1232g and 34 CFR Part 99). Under these laws, parental consent is not required to disclose identifiable data to an organization that is conducting a study for or on behalf of the EI program. The use of EI program data for this study was permissible under these laws because the authors conducted the study on behalf of the EI program and destroyed direct identifiers from the analytic file once the linkage was completed.
Time to death was calculated from date of death as recorded on the death certificate and date of birth from the birth certificate. Neonatal death was defined as death that occurred 0 to 28 days from birth.

**EI**

A child was classified as receiving EI services when he or she had ≥1 EI claim in the data set. In most cases, there was a separate claim in the data set for each service encounter. The claim record included the date of the encounter, service type, discipline of the service provider, length of the encounter, and charge. Types of services that were included in the data set were screenings (an initial visit during which EI staff obtain preliminary information from the family of the child who is referred to the program to determine whether the child is likely to be eligible for services), intake assessments (an evaluation to determine whether the child is eligible for services), ongoing assessments (periodic reevaluations to determine developmental progress and continued need for services), and provision of developmental services. A proportion of the children who were classified as receiving services received only a screening (7%) or a screening and intake assessment (22%) but did not go on to receive developmental services. Disciplines of the service providers included developmental specialists, social workers, physical therapists, occupational therapists, speech/language pathologists, nurses, psychologists/counselors, and autism service providers. Additional description of assessment and service provision in the Massachusetts EI program is presented elsewhere.20

Hourly rates varied according to the type and the setting of the service, ranging from $21 for a child group to $98 for an intake assessment. Hourly rates did not vary according to the discipline of the provider. Individual claims were not available for autism services, which were used by 2.3% of the children in EI and constituted 7.8% of total costs. For these services, only the total program costs per child for the entire time in EI were available. Charges data were not available for vision or hearing services, used by 0.5% of EI participants. Claims data were examined routinely by the EI fiscal manager for accuracy and completeness and were reviewed periodically by external auditors (Steve McCourt, MHA, written communication, 2006).

EI programs were reimbursed 100% for each charge by private health insurance, Medicaid, or state funds according to rates that were fixed yearly by the state. Charges therefore represent the full cost to the government and third-party insurers but may not reflect the provider’s true cost of providing services. Nevertheless, charges are used to estimate costs in this analysis, and the costs reported are expenditures of the Massachusetts EI program. Costs were converted to 2003 constant dollars using the Medical Care component of the Consumer Price Index. Dates of service were not available for autism services. We assumed that autism services were split evenly among the years in which the child was enrolled in EI. We then converted those costs that were assumed to have occurred before 2003 into 2003 constant dollars.

Claims data did not include reimbursements that totaled approximately $2.5 million per year and were paid to EI programs from state and federal funds to cover travel expenses that were incurred by parents. Claims also did not include a total of approximately $800 000 in state and federal funds that were awarded yearly to assist programs with administrative expenses (Robert Seymour, BS, written communication, 2006).

Additional EI program data were available in the data set. For these analyses, we included results from the intake assessment that was conducted to determine eligibility. Massachusetts EI defines eligibility as meeting 1 of 4 broad eligibility criteria as documented on the evaluation record corresponding to the first referral: (1) diagnosis with a disabling physical or mental condition referenced by 1 of 197 International Classification of Diseases, Ninth Revision codes, (2) a 25% delay behind chronological age in 1 of 7 areas of functioning (gross motor, fine motor, cognitive, receptive language, expressive language, social/emotional, or adaptive functioning) as determined by a standardized developmental assessment, (3) presence of 4 or more of 18 defined biological and environmental risk factors that are associated with delay, and (4) determination by a multidisciplinary team that the child has questionable quality of developmental skills and functioning.

To characterize type and severity of participants’ conditions, we categorized children into 6 eligibility groups:

1. Clinical judgment: having no developmental delay or medical condition, 0 to 3 risk factors, but clinical judgment of need for services
2. At risk: having 4 or more risk factors for delay but no developmental delay or medical condition
3. Mild/moderate developmental delay: having a developmental delay in ≥1 domain, none of which exceed 50% of chronological age; no medical condition; and 0 to 3 risk factors
4. Severe developmental delay: having a developmental delay of 50% or more behind chronological age in ≥1 domain, no medical condition, and 0 to 3 risk factors
5. Established condition: having a medical condition, no developmental delay, and 0 to 3 risk factors
6. Multiple criteria: meeting 2 or more of the criteria.

Because of the small number of preterm EI participants in the clinical judgment and established conditions groups, the 2 groups were combined for analysis.
Analysis
For analysis, we included live in-state births of infants who were born at 24 to 42 weeks’ GA to Massachusetts resident women. Costs were calculated for the infants who survived to 28 days of age. We present total program costs, mean cost per surviving infant, and mean and median cost per participant, by GA. Total program cost, mean cost per surviving infant, and mean cost per participant for each GA category are presented by plurality, and total program cost and cost per surviving birth also are presented for each GA category by discipline of service provider, eligibility category, and year of life.

RESULTS
Overall, 77,034 children were born in Massachusetts to resident women from July 1, 1999, through June 30, 2000, with a GA of 24 to 42 weeks; 76,901 survived to 28 days. Of births, 14,033 (18.2%) received EI services. Selected infant and maternal characteristics of Massachusetts births and children who received EI services are presented in Table 1. Table 2 presents the number of live births at each GA, along with the number of infants who survived to 28 days and the number and percentage who received EI services, by GA. Overall, 1.2% of births were very preterm, 8.7% were moderately preterm, and 90.1% were term. The percentage of infants who received services was highest among infants who were born at <32 weeks’ GA and also was elevated among moderately preterm infants compared with term infants.

The total program cost of EI services for children who were born during the study period was almost $66 million. Table 3 presents program costs, mean cost per surviving infant by GA, and mean and median EI cost per participant, by GA. Term births comprised the large majority of births and incurred >75% of total EI program costs. Sixteen percent of costs were incurred by moderately preterm births, and 8% of costs were incurred by very preterm births. The mean cost per surviving infant for EI services for an infant who was born very preterm was >7 times that of a term infant; the mean cost per moderately preterm birth was more than twice the cost per term birth. From 27 to 40 weeks’ GA, cost per surviving infant decreased with increasing GA. Among those who received EI services, the mean and median costs per child were highest for those who were born very preterm and lowest for those who were born at term, although the difference in cost per participant between the 2 groups was not as large as the difference in cost per birth between the 2 groups.

Overall, EI program cost for singleton births was more than $59 million and for multiple births was almost $7 million. Term infants comprised >80% of the program cost of singleton births. In contrast, only 28% of costs of multiples were for term births and 72% were for preterm births. Among both singletons and multiples, the mean cost per surviving infant was highest among very preterm infants and also higher among the moderately preterm infants compared with term infants. In all GA categories, the mean cost per multiple birth was higher than the mean cost per singleton birth. Among participants, overall mean cost per multiple infant was >10% higher than mean cost per singleton. For very preterm and term births, the mean cost per multiple birth was higher than the mean cost per singleton birth, whereas for moderately preterm births, the mean cost per singleton birth was 15% higher than the mean cost per multiple birth (Table 4).

EI participants qualified for services in the following eligibility criteria: 4% were at risk for delay, 46% had mild/moderate developmental delay, 26% had severe developmental delay, 16% had multiple criteria, 5% were eligible by clinical judgment, and 2% had an established condition. Total program costs were as follows: $1,984,543 for the at-risk group, $23,118,297 for the mild delay group, $20,109,100 for the severe delay group, $14,824,667 for the multiple criteria group, and

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Infant and Maternal Characteristics of all Massachusetts Births and Those Who Received EI Services: Massachusetts Children Born July 1999 to June 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Massachusetts Births, n (%)</td>
</tr>
<tr>
<td>Infant characteristics</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39,418 (51.2)</td>
</tr>
<tr>
<td>Female</td>
<td>37,616 (48.8)</td>
</tr>
<tr>
<td>Plurality</td>
<td></td>
</tr>
<tr>
<td>Singleton</td>
<td>73,812 (95.8)</td>
</tr>
<tr>
<td>Twin</td>
<td>3007 (3.9)</td>
</tr>
<tr>
<td>Triplet or more</td>
<td>215 (0.3)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td></td>
</tr>
<tr>
<td>&lt;1500</td>
<td>844 (1.0)</td>
</tr>
<tr>
<td>1500–2499</td>
<td>4468 (5.8)</td>
</tr>
<tr>
<td>≥2500</td>
<td>71,714 (93.1)</td>
</tr>
<tr>
<td>Medical diagnosis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5656 (7.3)</td>
</tr>
<tr>
<td>No</td>
<td>71,378 (92.7)</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>5181 (6.7)</td>
</tr>
<tr>
<td>20–34</td>
<td>55,521 (72.1)</td>
</tr>
<tr>
<td>≥35</td>
<td>16,331 (21.2)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>28,896 (37.6)</td>
</tr>
<tr>
<td>≥1 y of college</td>
<td>48,023 (62.4)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57,140 (74.2)</td>
</tr>
<tr>
<td>Black</td>
<td>5564 (7.2)</td>
</tr>
<tr>
<td>Other</td>
<td>14,270 (18.5)</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>54,712 (72.6)</td>
</tr>
<tr>
<td>Government</td>
<td>19,418 (25.8)</td>
</tr>
<tr>
<td>None/other</td>
<td>1210 (1.6)</td>
</tr>
</tbody>
</table>

* With valid gestational age 24 to 32 weeks.
* Having ≥1 record in the EI claims data set.
* Diagnosis at hospital discharge after birth of 1 of 197 diagnoses that qualifies a child for EI services.
DISCUSSION

Whereas medical costs that are associated with preterm infants have been well described, data concerning long-term developmental and educational costs are more sparse, with available estimates limited to those that are derived from survey data and to costs that are incurred after age 3. Moreover, the available data concerning special education costs are described by birth weight rather than GA. This study used claims data to describe the cost of EI services from birth to age 3 in a cohort of infants who were born in Massachusetts. The large sample size allowed detailed examination of the costs by GA.

Overall, more than $15 million was spent on EI services in Massachusetts for children who were born during a 1-year period at <37 weeks’ GA. For EI services that were provided during 3 years, each preterm infant cost almost $2000, approximately $1200 higher than the cost per term infant. The incremental cost of EI services for each preterm infant was approximately one seventh that of neonatal hospital care and less than one half the incremental cost of special education costs for school-aged children.12–16,18

As expected given the considerable morbidity that is associated with extremely preterm birth,23 the EI cost per infant who survived the neonatal period was highest among those who were born at the lowest GAs. We also found elevated costs per surviving infant for moderately preterm infants (those born at 34 to 36 weeks’ GA). These data are consistent with those of others who have found increased morbidity and costs associated with moderately preterm birth.13,14 From 27 to 40 weeks’ GA, EI costs per surviving infant continually decreased as GA increased. These results suggest that interventions that successfully delay preterm delivery for even 1 week should result in future EI savings.

Although a higher percentage of children who were born preterm received EI services and the EI cost per surviving infant was higher for preterm births than for term births, preterm infants accounted for only 17% of

Table 5 presents EI program costs for each of the first 3 years of life. EI program costs ranged from approximately $7 million in the first year of life to more than $40 million in the third year of life. Third-year costs were substantially higher than first- and second-year costs for both preterm and term infants. During each of the first 3 years of life, children who were born at term accrued higher program costs than children who were born preterm. In each of the first 3 years of life, mean cost per surviving preterm infant was higher than the mean cost per surviving term infant. In the first year, the mean cost per birth for very preterm infants was >22 times the mean cost per birth for term infants, whereas during the third year, the mean cost per surviving preterm infant was <5 times the mean cost per surviving term infant.

Table 2 Receipt of EI Services by GA, July 1999 to June 2000: Massachusetts Children Born July 1999 to June 2000

<table>
<thead>
<tr>
<th>GA, wk</th>
<th>Births, n</th>
<th>Neonatal Survivors, n</th>
<th>EI, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>60</td>
<td>37</td>
<td>30 (81.1)</td>
</tr>
<tr>
<td>25</td>
<td>58</td>
<td>50</td>
<td>48 (96.0)</td>
</tr>
<tr>
<td>26</td>
<td>83</td>
<td>71</td>
<td>64 (90.1)</td>
</tr>
<tr>
<td>27</td>
<td>107</td>
<td>95</td>
<td>86 (90.5)</td>
</tr>
<tr>
<td>28</td>
<td>120</td>
<td>112</td>
<td>98 (87.5)</td>
</tr>
<tr>
<td>29</td>
<td>146</td>
<td>145</td>
<td>122 (84.1)</td>
</tr>
<tr>
<td>30</td>
<td>198</td>
<td>197</td>
<td>156 (79.2)</td>
</tr>
<tr>
<td>31</td>
<td>243</td>
<td>241</td>
<td>169 (70.1)</td>
</tr>
<tr>
<td>32</td>
<td>395</td>
<td>393</td>
<td>263 (66.9)</td>
</tr>
<tr>
<td>33</td>
<td>606</td>
<td>604</td>
<td>297 (49.2)</td>
</tr>
<tr>
<td>34</td>
<td>1021</td>
<td>1017</td>
<td>364 (37.8)</td>
</tr>
<tr>
<td>35</td>
<td>1639</td>
<td>1635</td>
<td>493 (30.2)</td>
</tr>
<tr>
<td>36</td>
<td>3034</td>
<td>3030</td>
<td>722 (23.8)</td>
</tr>
<tr>
<td>37</td>
<td>5604</td>
<td>5596</td>
<td>1086 (19.4)</td>
</tr>
<tr>
<td>38</td>
<td>12 391</td>
<td>12 377</td>
<td>2174 (17.6)</td>
</tr>
<tr>
<td>39</td>
<td>19 820</td>
<td>19 805</td>
<td>3140 (15.9)</td>
</tr>
<tr>
<td>40</td>
<td>18 626</td>
<td>18 618</td>
<td>2724 (14.6)</td>
</tr>
<tr>
<td>41</td>
<td>10 065</td>
<td>10 061</td>
<td>1503 (14.9)</td>
</tr>
<tr>
<td>42</td>
<td>2818</td>
<td>2817</td>
<td>474 (16.8)</td>
</tr>
<tr>
<td>24–31</td>
<td>1015</td>
<td>948</td>
<td>773 (81.5)</td>
</tr>
<tr>
<td>32–36</td>
<td>6695</td>
<td>6679</td>
<td>2159 (32.3)</td>
</tr>
<tr>
<td>37–42</td>
<td>69 324</td>
<td>69 274</td>
<td>11 101 (16.0)</td>
</tr>
<tr>
<td>Total</td>
<td>77 034</td>
<td>76 901</td>
<td>14 033 (18.2)</td>
</tr>
</tbody>
</table>

* In-state births to Massachusetts resident mothers.
* Infants who survived 28 days and were born in state to resident mothers.
* Having ≥1 record in the EI claims data set.

$4 142 600 for the other group. Costs that were incurred by preterm births comprised 32% of total program costs in the at-risk group, 17% in the mild/moderate delay group, 20% in the severe delay group, 40% in the multiple criteria group, and 16% in the other criteria group. Overall, mean cost per surviving birth ranged from $26 for the at-risk group to $301 for the mild/moderate developmental delay group. Figure 1 presents mean program costs per surviving infant by eligibility group.

Total program costs varied according to the discipline of the service provider: $17 224 175 was spent on services that were provided by developmental specialist/educators, $4 638 012 by autism providers, $5 456 834 by social workers, $8 538 900 by physical therapists, $10 247 007 by occupational therapists, $13 348 414 by speech language pathologists, $3 636 593 by nurses, and $2 671 908 by psychologist/counselors. Services for preterm infants ranged from 11% of total program costs for services from autism providers to 35% for services from physical therapists. Cost of services from each provider per surviving infant was highest for children who were born very preterm, although the differential between preterm and term differed by the discipline of the service provider. For services that were provided by a physical therapist, cost per very preterm infant was almost 14 times the cost per term infant. In contrast, the cost per very preterm infant for services that were provided by specialty services providers was less than twice the cost per term infant (Fig 2).
EI participants. Therefore, the majority of children in EI and the majority of EI program costs were incurred by children who were born at term, with EI costs for these children 3 times the costs for preterm infants. To our knowledge, EI costs for term infants have not been reported previously and are worthy of additional study. In Massachusetts, that the largest costs are for term infants likely reflects that a large proportion of children who receive EI services are enrolled after age 1 because of a language delay but have no risks identified earlier. Nevertheless, in the past decade, the percentage of preterm births has increased 20% in Massachusetts and nationwide.23,24 If this trend continues, then the distribution of program costs by GA may change such that costs that are incurred by preterm infants will constitute a greater proportion of program costs.

In addition to filling a gap in the published data regarding the long-term cost of preterm birth, these cost estimates are useful to the state and to individual EI programs. Our study provides estimates by GA both of EI costs per surviving infant and per program participant. Costs per birth are useful to the state in anticipating future EI budgets given the percentage of the population that is born preterm. EI costs per participant are useful to individual programs for budgeting as well as for quality assurance purposes, because individual programs can compare resources that are spent on each participant who is born preterm to expenditures per preterm par-

### Table 3: EI Program Costs by GA, July 1999 to June 2003: Massachusetts Children Born July 1999 to June 2000

<table>
<thead>
<tr>
<th>GA, wk</th>
<th>Neoreonal Survivors, n</th>
<th>EI Costs, $</th>
<th>Per Survivor, Mean</th>
<th>Per Child in EI, Median (Range)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>37</td>
<td>266,917</td>
<td>7214</td>
<td>7179 (94–34,641)</td>
<td>8897</td>
</tr>
<tr>
<td>25</td>
<td>37</td>
<td>266,917</td>
<td>7214</td>
<td>7179 (94–36,641)</td>
<td>8897</td>
</tr>
<tr>
<td>26</td>
<td>50</td>
<td>434,499</td>
<td>8690</td>
<td>8458 (318–22,937)</td>
<td>9052</td>
</tr>
<tr>
<td>27</td>
<td>71</td>
<td>495,718</td>
<td>6982</td>
<td>5703 (92–65,893)</td>
<td>7746</td>
</tr>
<tr>
<td>28</td>
<td>685,002</td>
<td>7211</td>
<td>5713 (188–39,357)</td>
<td>7965</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>112</td>
<td>733,417</td>
<td>6548</td>
<td>5382 (47–44,939)</td>
<td>7484</td>
</tr>
<tr>
<td>30</td>
<td>145</td>
<td>756,468</td>
<td>5217</td>
<td>3383 (94–58,942)</td>
<td>6201</td>
</tr>
<tr>
<td>31</td>
<td>197</td>
<td>958,345</td>
<td>4865</td>
<td>3072 (46–53,383)</td>
<td>6143</td>
</tr>
<tr>
<td>32</td>
<td>241</td>
<td>782,020</td>
<td>3245</td>
<td>2689 (92–74,276)</td>
<td>4627</td>
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<tr>
<td>33</td>
<td>393</td>
<td>1,176,821</td>
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<td>2528 (47–46,807)</td>
<td>4475</td>
</tr>
<tr>
<td>34</td>
<td>604</td>
<td>1,570,931</td>
<td>2601</td>
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<td>1,017</td>
<td>1,802,243</td>
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<tr>
<td>36</td>
<td>1,635</td>
<td>2,385,547</td>
<td>1459</td>
<td>2917 (45–43,088)</td>
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<td>37</td>
<td>3,607,239</td>
<td>1,116,726</td>
<td>898</td>
<td>2640 (18–73,625)</td>
<td>5113</td>
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<tr>
<td>38</td>
<td>12,377</td>
<td>13,843,547</td>
<td>699</td>
<td>2372 (21–85,037)</td>
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<tr>
<td>39</td>
<td>19,805</td>
<td>11,166,726</td>
<td>616</td>
<td>2326 (22–84,435)</td>
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<tr>
<td>40</td>
<td>10,061</td>
<td>7,002,187</td>
<td>696</td>
<td>2489 (21–58,766)</td>
<td>4659</td>
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<tr>
<td>41</td>
<td>2817</td>
<td>1,758,993</td>
<td>624</td>
<td>1924 (45–57,428)</td>
<td>3711</td>
</tr>
<tr>
<td>42</td>
<td>9,112,386</td>
<td>5,112,386</td>
<td>5393</td>
<td>4191 (46–74,276)</td>
<td>6614</td>
</tr>
<tr>
<td>24–31</td>
<td>1477</td>
<td>10,542,781</td>
<td>1578</td>
<td>2735 (45–51,012)</td>
<td>4883</td>
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<tr>
<td>32–36</td>
<td>6679</td>
<td>50,255,212</td>
<td>725</td>
<td>2416 (18–85,037)</td>
<td>4527</td>
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<tr>
<td>37–42</td>
<td>69,274</td>
<td>65,910,379</td>
<td>857</td>
<td>2,350 (18–89,914)</td>
<td>4696</td>
</tr>
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</table>

*Infants who survived 28 days and were born in state to resident mothers.

### Table 4: EI Program Costs by Plurality and GA, July 1999 to June 2003: Massachusetts Children Born July 1999 to June 2000

<table>
<thead>
<tr>
<th>GA, wk</th>
<th>Neonatal Survivors, n</th>
<th>EI, n</th>
<th>EI Costs, $</th>
<th>Per Survivor, Mean</th>
<th>Per Child in EI, Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>24–31</td>
<td>665</td>
<td>524</td>
<td>3,204,409</td>
<td>4819</td>
<td>6115</td>
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<tr>
<td>32–36</td>
<td>5,237</td>
<td>1,477</td>
<td>7,524,777</td>
<td>1,457</td>
<td>5,095</td>
</tr>
<tr>
<td>37–42</td>
<td>67,804</td>
<td>10,707</td>
<td>48,383,728</td>
<td>714</td>
<td>45,119</td>
</tr>
<tr>
<td>Total</td>
<td>73,706</td>
<td>12,708</td>
<td>59,112,914</td>
<td>802</td>
<td>46,52</td>
</tr>
</tbody>
</table>

*Infants who survived 28 days and were born in state to resident mothers.

**Having ≥1 record in the EI claims data set.**
Participant in the state overall. Ongoing analysis, using population-based data, of trends in birth rates and EI participation by GA will assist further with more long-term budget planning. These data also will provide cost estimates for future cost-avoidance analyses.

In each GA category, twins and higher order multiples were more likely to receive EI services and incurred higher costs per infant than did singletons. Multiples also had higher costs than singletons when data were stratified by birth weight instead of GA (data not shown). Overall, infants from multiple births constituted nearly one quarter of all preterm infants. That at each GA each infant from a multiple birth incurred higher costs than his or her singleton peer has implications for planning future EI expenditures, because the rate of multiple births has increased almost 50% in the past decade in Massachusetts and ~30% nationwide. If this trend continues, then the preterm birth–associated cost of EI will increase at a faster rate than would be expected given the increasing rates of preterm birth in general.

Not only did overall costs differ for preterm and term infants, but also the types of developmental morbidity, services provided, and associated costs differed by GA. More than one half of all very preterm infants in EI were eligible by multiple criteria and another 20% with a severe delay, reflecting the considerable morbidity that is associated with preterm birth. The morbidity that is associated with moderately preterm birth was somewhat less severe, with >40% of EI participants eligible with a mild to moderate delay. Term EI participants demonstrated the least severe morbidity, with almost one half eligible with a mild to moderate delay and only 13% eligible with multiple criteria.

The difference in mean cost per surviving birth between preterm and term infants was greatest for services that were provided by physical therapists, occupational therapists, and nurses, reflecting the increased physical disabilities and medical complications that are associated with preterm birth. For all services, however, the mean cost per birth was higher for preterm versus term infants, demonstrating the wide range of morbidity that is associated with preterm birth. It should be noted that the distribution of costs across service providers depends in part on the reimbursement rates set for each service.

In our population, the yearly cost of EI was highest for children who were aged 2 to 3 years, followed by children who were aged 1 to 2 years. This may be attributable largely to the fact that many toddlers were enrolled during their second and third years of life. Nevertheless, even among very preterm children, virtually all of whom were enrolled before 1 year of age, the highest costs were incurred during the third year of life. Most likely new delays emerged during the second and third years of life, particularly language delays. These data demonstrate that costs that are associated with preterm birth increase and continue long term.

Our results are subject to several limitations. We obtained GA from the birth certificate. Although the validity of GA as recorded on the birth certificate has been demonstrated in other states, Massachusetts has not validated birth certificate data against medical charts. To examine the robustness of our findings, we reanalyzed the data by birth weight and found the same patterns as when data were categorized by GA.

Claims data could be linked to GA data only for in-state births to resident mothers. Because the true cost of EI includes costs that are incurred by children who are born out of state and/or to mothers who were living out of state at the time of birth, these estimates underestimate total EI program costs. Furthermore, if GA-specific EI costs of children who were born out of state or to nonresident mothers were different from in our cohort,
then our results may under- or overestimate the mean cost of EI per child. The error that results from unlinked EI claims records likely is minimal, however, because almost 90% of EI participants were members of the study population. Although in our data the charges are reimbursed in full and therefore represent costs that are incurred by government and third-party insurers, our estimates may underestimate the true cost of EI from the providers’ perspective, because reimbursement rates for EI are fixed, and some providers claim that they do not reflect the true cost of providing services.

These estimates only included costs for developmental services that were provided by the state-coordinated EI program and did not include supplemental services that were received outside the program. The percentage of children who receive additional developmental intervention is not known, although it is presumed to be low, because services that are provided within the program are comprehensive. Estimates did not include indirect costs to parents, such as time taken off from work. Most services were provided in naturalistic settings such as at home or a child care facility, minimizing parents’ time away from work. Nevertheless, parents may have incurred some costs related to time spent with program staff.

Massachusetts EI serves a higher percentage of the population than most other states, in part because of the state’s relatively inclusive eligibility criteria. Unlike some states, Massachusetts enrolls children who are at risk for delay in addition to children with established delays or disabilities. Moreover, the state’s definition of developmental delay, 25% behind chronological age, is more liberal than many other states’ requirement of 30% to 50% delay. The estimate of cost per surviving infant presented here therefore may be higher than costs that are incurred by other states. We presented costs for children who were eligible with differing eligibility criteria. Costs of EI in states with more restrictive eligibility criteria may resemble more closely the costs that are incurred by the severe delay, established condition, and multiple criteria groups. In addition to the state’s inclusive eligibility criteria, Massachusetts has a relatively high percentage of families with health insurance, which may lead to greater EI program awareness through improved health care access and subsequently higher EI program costs compared with other states. Massachusetts’s child find activities have been shown to be very effective in identifying high-risk infants, which also may contribute to higher EI service use and costs in Massachusetts than in other states. Costs presented here also may differ from those of other states because of differences in third-party reimbursement. Massachusetts has extensive third-party reimbursement for EI services. In other states, some services may be provided outside the auspices of the program to ensure third-party reimbursement. Furthermore, cost of developmental services may vary by geographic region. Health care and educational costs in the Northeast typically are higher than in other regions of the United States.

The results presented here are limited to descriptive analysis. It cannot be determined, therefore, to what extent preterm birth per se, as opposed to a higher prevalence of certain medical conditions among preterm infants, is responsible for elevated EI costs among preterm infants. Use of multivariate models to examine birth characteristics that predict future EI expenditures will help to answer that question and will be the focus of future research.

CONCLUSIONS
Despite technologic advances, preterm birth continues to be associated with considerable medical, developmental, and educational costs. Our findings fill a previous gap in the description of preterm birth–associated costs that are incurred during early childhood. Understanding the full spectrum of costs that are associated with preterm birth will provide valuable information on the societal savings to be gained in the prevention of preterm births.

ACKNOWLEDGMENTS
The PELL data system is supported by the Centers for Disease Control and Prevention grants S1887-21/23 and S3485-23/23. Additional funding for EI program evaluation was provided by US Department of Education Early Intervention grant 45139021.

We thank Jean Shimer, Cynthia Wisniewski, Stephen

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**TABLE 5**

<table>
<thead>
<tr>
<th>GA, wk</th>
<th>Neonatal Survivor, n</th>
<th>EI Program Costs by Year of Life and GA, July 1999 to June 2003: Massachusetts Children Born July 1999 to June 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cost, $</td>
<td>Mean per Survivor, $</td>
</tr>
<tr>
<td></td>
<td>Year 1 (age 0–1 y)</td>
<td>Year 2 (age 1–2 y)</td>
</tr>
<tr>
<td>24–31</td>
<td>948</td>
<td>1,229,212</td>
</tr>
<tr>
<td>32–36</td>
<td>679</td>
<td>1,957,126</td>
</tr>
<tr>
<td>37–44</td>
<td>69,274</td>
<td>4,048,511</td>
</tr>
<tr>
<td>Total</td>
<td>76,901</td>
<td>7,214,849</td>
</tr>
</tbody>
</table>

*Infants who survived 28 days and were born in state to resident mothers.*
REFERENCES


24. Massachusetts Births 2003. Boston, MA: Division of Research and Epidemiology, Center for Health Information, Statistics, Research, and Evaluation, Massachusetts Department of Public Health; April 2005


ARTICLE

Twenty-Year Trends in Fatal Injuries to Very Young Children: The Persistence of Racial Disparities

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Departments of \textsuperscript{a}Health Policy and Management and \textsuperscript{b}Epidemiology and \textsuperscript{c}Injury Free Coalition for Kids, Mailman School of Public Health, and \textsuperscript{d}Columbia University Center for the Health of Urban Minorities, Columbia University, New York, New York; \textsuperscript{e}Department of Surgery, Columbia University at Harlem Hospital, New York, New York

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Mortality trends across modifiable injury mechanisms may reflect how well effective injury prevention efforts are penetrating high-risk populations. This study examined all-cause, unintentional, and intentional injury–related mortality in children who were aged 0 to 4 years for evidence of and to quantify racial disparities by injury mechanism.

METHODS. Injury analyses used national vital statistics data from January 1, 1981, to December 31, 2003, that were available from the Centers for Disease Control and Prevention. Rate calculations and $\chi^2$ test for trends (Mantel extension) used data that were collapsed into 3-year intervals to produce cell sizes with stable estimates. Percentage change for mortality rate ratios used the earliest (1981–1983) and the latest (2001–2003) study period for black, American Indian/Alaskan Native, and Asian/Pacific Islander children, with white children as the comparison group.

RESULTS. All-cause injury rates declined during the study period, but current mortality ratios for all-cause injury remained higher in black and American Indian/Alaskan Native children and lower in Asian/Pacific Islander children compared with white children. Trend analyses within racial groups demonstrate significant improvements in all groups for unintentional but not intentional injury. Black and American Indian/Alaskan Native children had higher injury risk as a result of residential fire, suffocation, poisoning, falls, motor vehicle traffic, and firearms. Disparities narrowed for residential fire, pedestrian, and poisoning and widened for motor vehicle occupant, unspecified motor vehicle, and suffocation for black and American Indian/Alaskan Native children.

CONCLUSIONS. These findings identify injury areas in which disparities narrowed, improvement occurred with maintenance or widening of disparities, and little or no progress was evident. This study further suggests specific mechanisms whereby new strategies and approaches to address areas that are recalcitrant to improvement in absolute rates and/or narrowing of disparities are needed and where increased dissemination of proven efficacious injury prevention efforts to high-risk populations are indicated.
Both intentional and unintentional injuries have a modifiable component when well-focused interventions are implemented.\textsuperscript{1–6} Injury prevention efforts of varying scope and intensity have targeted an array of potentially fatal injury mechanisms in the past 50 years, some directly aimed at reducing historically existing racial and ethnic disparities in residential fire, poisonings, pedestrian injury, motor vehicle traffic, suffocation, homicide, and others.\textsuperscript{7} When legislative or regulatory efforts have been combined with access to safety devices and parental education programs, notable successes have been reported in resource-limited neighborhoods.\textsuperscript{1–6,8–16} Although increasingly more effective methods have evolved to address excess mortality and serious morbidity that are associated with injury, application of this knowledge, access to safety devices, changes in behavior, and achieved rates of safety practices may be lower in resource-limited communities. To the extent that newly engineered products and modifications to behavior, the home, community, and environment are effective at preventing death from injury, lack of access or delayed implementation may be reflected in higher injury mortality and lowered life expectancy.\textsuperscript{17,18}

Although examination of individual communities is important for assessment of how well interventions work, examination of national injury mortality trends is essential for assessment of the impact of how fully and effectively injury prevention efforts are penetrating at-risk populations. The value in conducting such analyses is that the findings may provide clues to population subgroups and/or injury mechanisms for which additional or redirected national efforts are indicated. This study examined >20 years of injury-related mortality for infants and young children by race for all-cause, unintentional, and intentional injury across specific injury mechanisms for which local and/or national interventions of varying intensities have been attempted.

\textbf{METHODS}

\textbf{Data Sources}

Injury-related mortality was examined by race for infants and children who were aged 0 to 4 years from January 1, 1981, to December 31, 2003, using data from the National Vital Statistics registration system with mandatory reporting in all 50 states and the District of Columbia.\textsuperscript{19} Death certificates from which the mortality data originate contain physician- or medical examiner-reported information on age, race/ethnicity, date, and cause and place of death. Decennial enumeration of the US population is conducted by the Bureau of the Census with intercensus population estimation. The Office of Statistics and Programming, National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention provided data access and categorizations that were based on the \textit{International Classification of Diseases, Ninth Revision} (ICD-9) and ICD-10 coding for specific conditions and injury mechanisms.\textsuperscript{20–22}

\textbf{Classification of Intent and Mechanism of Death}

Classification of ICD-9 and ICD-10 coding for unintentional, intentional, undetermined intent, and specific mechanisms of death used standard definitions from the Centers for Disease Control and Prevention.\textsuperscript{19} Death as a result of undetermined intent accounted for a small number of deaths and is included in all-cause injury analyses only.

Unintentional motor vehicle traffic deaths were analyzed for the following categories: all motor vehicle traffic, occupant, pedestrian, and unspecified. Classifications of death that were attributable to other unintentional injury mechanisms in this study include drowning, residential fire/flame, suffocation, poisoning, and falls. Fire-arm injury includes all intents.

\textbf{Transition From ICD-9 to ICD-10}

Injuries were classified using ICD-9 for deaths that occurred between 1981 and 1998 and ICD-10 coding for 1999 to 2003.\textsuperscript{19,20} Homogeneous ICD classifications were maintained within groups by collapsing only years of the same ICD classification scheme.

\textbf{Classification of Race and Ethnicity}

Race classification was analyzed similarly throughout the study period for white, black, American Indian/Alaskan Native, and Asian/Pacific Islander children. Data on Hispanic origin were not available before 1990. Sensitivity analyses, performed after Hispanic origin became available, examined the robustness of rates that were calculated with the inclusion and exclusion of Hispanic ethnicity from each racial group and found small or negligible effects across most injury mechanisms. $\chi^2$ test for trend is presented for Hispanic ethnicity with the data on which trend analyses are based beginning in 1990 rather than 1981. For consistency in graphic illustration of trends, Hispanic ethnicity is included as an addition to the graphs without adjustment of racial categories established in 1981.

\textbf{Statistical Analyses}

Mortality rates (per 100 000 persons) used 3-year time intervals to create larger cell sizes and provide more stable numerical estimates. Linear trend in proportions used the $\chi^2$ test for trends Mantel extension, available in Epi Info 3.2.2,\textsuperscript{23} to analyze trends in mortality rates within race and ethnicity with adjustment for the last uneven interval. Mortality rate ratios, used to examine the relative change in minority groups, compared the earliest (1981–1983) and the latest (2001–2003) study period for black, American Indian/Alaskan Native, and Asian/Pacific Islander children, with white children as the comparison group. All rates and rate ratios are for
homogeneous ICD versions (ICD-9 or ICD-10, but not mixed within time periods) with 95% confidence intervals. The \( \chi^2 \) test was used in univariate analyses of categorical variables. Statistical significance is defined as having a \( P \leq .05 \).

RESULTS

Study Population

The study population was comprised of US infants and children who were aged 0 to 4 years during the study time frame (1981–2003). The racial and ethnic composition for 2003 is shown in Table 1. Within Hispanic ethnicity, race was white (94.1%), black (3.7%), American Indian/Alaskan Native (1.1%), and Asian/Pacific Islander (1.1%).

All-Cause Injury Rates in 2003

The total population all-cause injury rate (per 100 000) for the latest year (2003) for which mortality data were available was 17.8 for children aged 0 to 4 years, but this varied significantly by race ranging from 7.9 in Asian/Pacific Islander children to 37.2 for American Indian/Alaskan Native children. Non-Hispanic white and Hispanic children had more similar all-cause injury mortality rates (16.0 vs 14.8).

Unintentional and Intentional Injury Rates in 2003

Although the unintentional injury rate (per 100 000) was 13.7 for the total population, rates varied widely by race, from a low of 5.9 in Asian/Pacific Islander children to a high of 28.0 in American Indian/Alaskan Native children and 20.6 in black children. Injury rates among Hispanic and white children were intermediate (11.1 and 13.0). Similarly, the intentional injury rate (per 100 000) for the total population was 3.6 but was lowest in Asian/Pacific Islander children (1.9), highest in black (8.5) and American Indian/Alaskan Native children (8.1), and again intermediate in white (2.4) and Hispanic children (3.4).

Relative Rank of Injury Among All Causes of Death in 2003

The relative rank of injury among all causes of death differed significantly between those who were aged 0 to 1 year and 1 to 4 years. Injury was the leading cause of death in children who were aged 1 to 4 years across all race/ethnic groups, with all-cause injury (intentional and unintentional) accounting for >40% of all deaths in 2003, except among Asian/Pacific Islander children, for whom injury comprised 27.9% of all deaths. Among infants who were aged 0 to 12 months, unintentional injury ranked sixth among overall causes of death behind congenital anomalies, short gestation, sudden infant death syndrome, pregnancy complications, and placental conditions. Although there was considerable variation in the distribution of injury mechanisms across racial groups in infants who were aged 0 to 12 months, ~90% of all injury-related mortality was accounted for by 4 injury mechanisms.

<table>
<thead>
<tr>
<th>Mechanism of Injury, n (%)</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>American Indian/Alaskan Native</th>
<th>Asian/Pacific Islander</th>
<th>Total (Includes Other Races)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population*</td>
<td>11 500 485 (58.2)</td>
<td>3 066 198 (15.5)</td>
<td>4 157 920 (21.0)</td>
<td>185 669 (0.9)</td>
<td>859 007 (4.3)</td>
<td>19 769 279 (100.0)</td>
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<td>All injury deaths</td>
<td>1835 (16.0)</td>
<td>921 (30.0)</td>
<td>617 (14.8)</td>
<td>69 (37.2)</td>
<td>68 (7.9)</td>
<td>3524 (17.8)</td>
</tr>
<tr>
<td>Unintentional</td>
<td>1496 (81.5)</td>
<td>630 (68.4)</td>
<td>463 (75.0)</td>
<td>52 (75.4)</td>
<td>51 (75.0)</td>
<td>2701 (76.6)</td>
</tr>
<tr>
<td>Intentional</td>
<td>1507 (15.2)</td>
<td>261 (28.3)</td>
<td>142 (23.0)</td>
<td>15 (21.7)</td>
<td>16 (23.5)</td>
<td>717 (20.3)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>60 (3.3)</td>
<td>30 (3.3)</td>
<td>12 (1.9)</td>
<td>2 (2.9)</td>
<td>1 (1.5)</td>
<td>106 (3.0)</td>
</tr>
</tbody>
</table>


** Race does not include individuals of Hispanic origin.

† Row percentages; all other percentages are column percentages.

© Includes occupant, pedestrian, unspecified, and other categories.
mechanisms: suffocation, motor vehicle traffic, drowning, and residential fire/burn.


**Trends in All-Cause Injury Mortality**

All-cause injury rates declined significantly for all racial and ethnic groups examined ($\chi^2$ trend in white children: 1393.2 [$P < .000001$]; black children: 572.6 [$P < .000001$]; American Indian/Alaskan Native children: 66.4 [$P < .000001$]; Asian/Pacific Islander children: 50.0 [$P < .000001$]; and Hispanic children: 127.9 [$P < .0000001$]). Most of the observed improvement was attributed to declines in unintentional (Fig 1A) rather than intentional injury (Fig 1B). Despite declines in all-cause injury for all minority groups (data not shown), declines also occurred in the white comparison group, leaving mortality rate ratios for black and American Indian/Alaskan Native children relatively unchanged and nearly twice that of white children (Table 2).

**Trends in Unintentional Injury Mortality**

Despite significant improvements in unintentional injury among all racial groups (Fig 1A), rate ratios for unintentional injury in black and American Indian/Alaskan Native children remained 1.6 to 1.8 times higher than those for white children (Table 2). Percentage improvement in unintentional injury during the study time frame was ~80%. Asian/Pacific Islander children were notable for consistently having the lowest unintentional injury rates during the study time frame (Fig 1A).

**Trends in Intentional Injury Mortality**

Little progress was made in net improvement of intentional injury rates in 2003 compared with 1981. Small declines were observed for mortality rates among Asian/Pacific Islander and black children, with American Indian/Alaskan Native children showing wide fluctuations without improvement (Fig 1B). Black children showed steadily rising intentional mortality rates in the 1980s, with rates peaking in the early 1990s. Both Hispanic and black children showed improvement after 1990 (Fig 1B). Paradoxically, although mortality rate ratios declined slightly (Table 2), this was partially attributable to worsening rates in the white comparison group. When 20-year trends are examined, white children showed significant worsening, whereas black, American Indian/Alaskan Native, and Asian/Pacific Islander children.

**FIGURE 1**

A, Unintentional injury–related mortality trends. Mortality rates (deaths per 100 000) and $\chi^2$ test for trends are shown for American Indian/Alaskan Native children ($\chi^2$ trend 87.0, $P < .000001$), black children ($\chi^2$ trend 662.4, $P < .000001$), Hispanic children ($\chi^2$ trend 139.3, $P < .000001$), white children ($\chi^2$ trend 1859.0, $P < .000001$), and Asian/Pacific Islander children ($\chi^2$ trend 66.4, $P < .000001$). B, Intentional injury–related mortality trends. Mortality rates (deaths per 100 000) and $\chi^2$ test for trends are shown for American Indian/Alaskan Native children ($\chi^2$ trend 0.98, $P = .32$), black children ($\chi^2$ trend 1.1, $P = .29$), Hispanic children ($\chi^2$ trend 5.3, $P = .02$), white children ($\chi^2$ trend 31.6, $P < .000001$), and Asian/Pacific Islander children ($\chi^2$ trend 0.11, $P = .74$). Am Indian/AK indicates American Indian/Alaskan Native; Asians/PI, Asian/Pacific Islander.
showed insignificant 20-year trends in violence-related deaths (Fig 1B).

**Trends in Motor Vehicle Traffic and Pedestrian Mortality**

Motor vehicle traffic–related mortality rates were highest in black and American Indian/Alaskan Native children, lowest in Asian/Pacific Islander children, and intermediate for Hispanic and white children (Fig 2). Trend analyses demonstrated significantly declining 20-year injury rates for total motor vehicle traffic, occupant, and pedestrian injury deaths among all race and ethnic groups examined (Fig 2). Improvements in motor vehicle pedestrian traffic deaths continued for all race and ethnic groups during the latest study time frame (Fig 2C), whereas a leveling off/worsening occurred in the category of motor vehicle occupant mortality (Fig 2B) for all groups except Asian/Pacific Islander children. Additional examination of trends during the last 2 study periods for occupant deaths in infants (aged 0 to <12 months) reveal that non-Hispanic white, Hispanic, Asian/Pacific Islander, and Indian/Alaskan Native children showed a tendency toward continued improvement, whereas improvement in black children slowed. Occupant mortality among young children aged 1 to 4 years showed a tendency toward increased mortality in black, Hispanic, and American Indian/Alaskan Native children.

Black and American Indian/Alaskan Native children have mortality ratios that are significantly higher than those of white children for total motor vehicle traffic, motor vehicle occupant, and motor vehicle pedestrian (Table 2). Although there were significant declines in total motor vehicle mortality across all racial groups, improvement in occupant injury was greater for white children, and disparities actually widened for both black and American Indian/Alaskan Native children compared with white children (Table 2). Black and American Indian/Alaskan Native children experienced a narrowing of disparities in motor vehicle pedestrian injury. Relative to white children, disparities in unspecified motor vehicle mortality among both black and American Indian/Alaskan Native children showed a trend of significant widening during the study time frame (Table 2).

**Drowning Mortality**

Drowning rates improved significantly during the study period in all racial and ethnic groups examined, with the largest absolute improvement observed among American Indian/Alaskan Native children (Fig 3A). Although American Indian/Alaskan Native children continued to have the highest drowning rates among the racial groups examined, disparities in mortality rate ratios narrowed during the study time frame (Table 2). Despite improvements in white children outpacing those of black and Asian/Pacific Islander children, white children maintained their position as having the second highest mortality from drowning (Fig 3A).

**Residential Fire/Flame Mortality**

Mortality as a result of residential fire declined significantly across all racial/ethnic groups (Fig 3B), with racial disparities for black and American Indian/Alaskan Native children narrowing during the study time frame (Table 2). Black children exhibited the highest mortality rates as a result of residential fire/flame throughout the study, with rates that were nearly fourfold higher than those of white children during the earliest time frame. Despite steady declines in mortality as a result of residential fire/flame among black children, white children also exhibited declines during the last decade, resulting in maintenance of a nearly threefold disparity (Table 2).

**Table 2**

<table>
<thead>
<tr>
<th>Injury Mechanism</th>
<th>Black</th>
<th>American Indian/Alaskan Native</th>
<th>Asian/Pacific Islander</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate Ratio (95% CI)</td>
<td>% Change</td>
<td>Rate Ratio (95% CI)</td>
</tr>
<tr>
<td>All causes</td>
<td>1.93 (1.85–2.02)</td>
<td>−0.03</td>
<td>2.00 (1.76–2.29)</td>
</tr>
<tr>
<td>Unintentional</td>
<td>1.64 (1.56–1.73)</td>
<td>−0.04</td>
<td>1.81 (1.55–2.12)</td>
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<tr>
<td>Intentional</td>
<td>3.18 (2.91–3.47)</td>
<td>−0.19</td>
<td>2.86 (2.19–3.73)</td>
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<tr>
<td>Motor vehicle traffic</td>
<td>1.38 (1.24–1.54)</td>
<td>0.07</td>
<td>2.76 (2.15–3.55)</td>
</tr>
<tr>
<td>Occupant</td>
<td>1.31 (1.11–1.54)</td>
<td>0.39</td>
<td>2.85 (1.99–4.08)</td>
</tr>
<tr>
<td>Pedestrian</td>
<td>1.63 (1.33–2.00)</td>
<td>−0.19</td>
<td>1.39 (0.69–2.81)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1.32 (1.07–1.63)</td>
<td>0.52</td>
<td>3.91 (2.61–5.85)</td>
</tr>
<tr>
<td>Drowning</td>
<td>0.74 (0.64–0.86)</td>
<td>0.10</td>
<td>1.12 (0.74–1.69)</td>
</tr>
<tr>
<td>Residential fires</td>
<td>2.84 (2.44–3.30)</td>
<td>−0.28</td>
<td>1.38 (0.74–2.58)</td>
</tr>
<tr>
<td>Suffocation</td>
<td>2.49 (2.28–2.72)</td>
<td>0.28</td>
<td>1.89 (1.40–2.56)</td>
</tr>
<tr>
<td>Poisoning</td>
<td>2.74 (1.99–3.76)</td>
<td>−0.10</td>
<td>1.22 (0.30–4.93)</td>
</tr>
<tr>
<td>Falls</td>
<td>1.32 (0.91–1.92)</td>
<td>−0.55</td>
<td>0.50 (0.07–3.58)</td>
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<tr>
<td>Firearms, all intents</td>
<td>3.00 (2.26–3.59)</td>
<td>0.25</td>
<td>3.07 (1.35–6.98)</td>
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</tbody>
</table>


* All specific injury mechanisms are unintentional except firearms.

* Unstable estimate because of small numbers.
FIGURE 2
A. All motor vehicle traffic injury mortality trends. Mortality rates (deaths per 100,000) and $\chi^2$ test for trends are shown for American Indian/Alaskan Native children ($\chi^2$ trend 13.0, $P = .0003$), black children ($\chi^2$ trend 7.6, $P < .00001$), Hispanic children ($\chi^2$ trend 60.9, $P < .00001$), white children ($\chi^2$ trend 547.7, $P < .00001$), and Asian/Pacific Islander children ($\chi^2$ trend 46.2, $P < .000001$). B. Motor vehicle occupant injury mortality trends. Mortality rates (deaths per 100,000) and $\chi^2$ test for trends are shown for American Indian/Alaskan Native children ($\chi^2$ trend 8.2, $P = .0044$), black children ($\chi^2$ trend 19.8, $P = .0001$), Hispanic children ($\chi^2$ trend 62.0, $P < .00001$), white children ($\chi^2$ trend 398.3, $P < .00001$), and Asian/Pacific Islander children ($\chi^2$ trend 27.2, $P < .000001$). C. Motor vehicle pedestrian injury mortality trends. Mortality rates (deaths per 100,000) and $\chi^2$ test for trends are shown for American Indian/Alaskan Native children ($\chi^2$ trend 21.0, $P < .00001$), black children ($\chi^2$ trend 182.4, $P < .000001$), Hispanic children ($\chi^2$ trend 65.0, $P < .000001$), white children ($\chi^2$ trend 434.7, $P < .000001$), and Asian/Pacific Islander children ($\chi^2$ trend 24.0, $P < .000001$). Am Indian/AK indicates American Indian/Alaskan Native; Asians/PI, Asian/Pacific Islander.
Suffocation Mortality

Among children who were aged 0 to 4 in 2003, unintentional suffocation ranged between 13.9% of all injury-related mortality in Hispanic children to 26.0% in black children (Table 1). The relative racial disparities that were observed during the early study periods were maintained during the last study period, with American Indian/Alaskan Native and black children exhibiting higher rates than white children and Asian/Pacific Islander and Hispanic children having lower rates than white children (Fig 3C; Table 2). Mortality as a result of suffocation showed no significant trend toward improvement in any race or ethnic group and actually demonstrated a trend toward worsening in later study years (Fig 3C).

The majority of unintentional suffocation deaths...
were in the group aged 0 to 12 months, in which unintentional suffocation accounted for nearly two thirds of all injury-related deaths. In this group, suffocation as a proportion of injury-related deaths was lowest in Asian/Pacific Islander children (33.3%); highest in black children (75.1%); and intermediate in non-Hispanic white children (63.4%), Hispanic children (45.5%), and American Indian/Alaskan Native children (50.0%).

Poisoning Mortality
Deaths as a result of unintentional poisoning accounted for a relatively small proportion of all injury-related mortality (Table 1) and showed improvements in all race and ethnic groups during the study (Fig 3D). Poisoning mortality decreased from the 1980s until the late 1990s, when improvements leveled off, and by 2003, small increases in poisoning death rates were observed among white, black, Hispanic, and Asian/Pacific Islander children (Fig 3D). Despite a slight narrowing of disparities between white and black children, black children maintained a 2.7-fold higher rate of mortality as a result of poisoning at the last study period (Table 2).

Firearm-Related Injury Mortality, All Intent
Although firearm injury deaths declined during the study period, accounting for only 1.6% of all injury-related deaths in children who were aged 0 to 4 in 2003, 83.4% of these occurred in minority children, with black children accounting for more than half of all firearm injury deaths (Table 1). During the study period, 2167 deaths in children aged 0 to 4 years were attributable to firearms, with disparities during the study time frame widening in both black and American Indian/Alaskan Native children relative to white children. χ² for trend demonstrated significant lowering of firearm injuries during the study for white, black, and Hispanic children (Fig 3E). Despite this, black and American Indian/Alaskan Native children continued to have mortality rate ratios triple those of white children (Table 2).

DISCUSSION
The findings of this study seem conceptually paradoxical because we report the coexistence of improving injury rates and widening racial disparities across many injury mechanisms, a situation that occurred when declines in white rates exceeded those of minority populations. The trend of decreasing all-cause injury mortality during the past 22 years is attributed primarily to significant improvements in unintentional injury. Compared with white children, black children continue to exhibit significant racial disparities in all-cause, unintentional injury, and intentional injury despite declining rates among black children in all mechanisms examined except unintentional suffocation. Disparities narrowed between black and white children for residential fires, poisoning, and pedestrian deaths but widened for unintentional suffocation, firearms, motor vehicle occupant, and unspecified motor vehicle mortality.

A wide array of injury prevention efforts preceded or occurred concomitantly during this study.1,2,5–17,24–34 There are reports of declining injury rates with injury prevention efforts such as smoke detectors/smoke alarms, child restraint systems, speed limit and driver licensing laws, helmets, child safety caps, and window guards to protect against falls.1,2,6,8,9,25–34 Much of the historical decline in injury deaths is credited to a combination of passive and active injury prevention measures, including legislative and regulatory enforcement, educational efforts, and increased access to safety products1,2,6,9,16,24 as well as economic conditions and advances in trauma care.

Although there were significant trends toward improvement within racial groups, disparities in motor vehicle occupant mortality widened among black and American Indian/Alaskan Native children compared with white children. Mortality improvements were most notable for infants who were younger than 12 months, suggesting that additional work to increase use of booster seats in vulnerable populations is warranted. Pedestrian traffic-related mortality showed consistent downward trends in this study. Reports of efficacious prevention initiatives include “Safety Cities,” rerouting traffic, improved traffic signs, speed controls, and building of playgrounds to provide alternative play spaces to the sidewalk and street.3,4,35–36 Despite improving rates in black children, significant disparities in pedestrian mortality remain.

Although the level of improvement of residential fire mortality in black children is impressive, a nearly threefold disparity in burn mortality continues for black compared with white children despite legislation/regulations, improved building codes, safety education, and promotion of smoke detectors/alarms. Some studies have questioned the effectiveness of smoke alarm give-away programs,34 and updated building codes may have less benefit in urban black neighborhoods with infrequent new construction. Cigarette smoking, a reported contributor to house fires, is increasing in black individuals of childbearing age.37–38 Smoking seems to be a risk factor for residential fires through adults’ smoking in bed and increased accessibility of matches and lighters by children.12–14,39–40 Effective smoking cessation programs for adults may prove an efficacious injury prevention tool for residential fire prevention for very young children.

Mortality as a result of poisoning, once a leading cause of death in children aged 0 to 4 years, declined by >90% since the introduction of legislation that requires child safety caps on medicines, vitamins, and household products.9 Although racial/ethnic disparities remained, poisoning mortality declined during the study and was no longer a major source of mortality in 2003. However,
we observed evidence of a troubling trend showing increases in recent poisoning deaths in Hispanic and black children, suggesting that injury surveillance systems should continue to monitor unintentional poisonings in this age group. In comparison, drowning accounts for more than twice as many fatalities in very young children but is reported to be an underrecognized source of injury, leading clinicians to omit this mechanism from their counseling sessions.41

Rates of unintentional suffocation mortality actually increased and disparities widened during the last 5 years of this study. Among black children, deaths from this cause began to increase in the late 1990s and rose to higher levels than that observed at the baseline, an increase that was accompanied by a significant widening of disparities between black and white children for this injury mechanism. The relative disparities that were observed during the early study periods were maintained during the last study period, with American Indian/Alaskan Native children also exhibiting higher mortality. Most of the increase in deaths occurred in infants who were aged <1 year, suggesting the need for additional study to assess whether this trend of increasing suffocation represents a data anomaly possibly associated with shifts in diagnostic classifications or a real increase in injury indicating a need for intensified culturally appropriate efforts directed toward known risk factors that are associated with an unsettling trend.42

All-intent firearm deaths declined in young children despite lack of significant improvement in intentional injury in most racial groups during the study period. Despite declines, disparities showed a trend toward widening in both black and American Indian/Alaskan Native children compared with white children. Previous studies noted disparities43 as well as effective preventions for lowering of firearm injury.43–46

This study has limitations. We did not have data that allowed investigation of contributing factors, such as socioeconomic status, social and environmental conditions, or ethnicity data necessary to produce 20-year trends for Hispanic children. Hispanic ethnicity was comprised of >90% white children, and, with few noted exceptions, Hispanic rates were similar to those of non-Hispanic white children. The composition of the study population changed during the study period to include increasing numbers of minority infants and children. This should have had minimal effect on our findings because we calculated race-specific mortality rates with denominators that had been established using standard means for intercensus estimates of population change calculated by the Census Bureau for use in national health statistics. Injury coding changed from ICD-9 to ICD-10 near the end of the study period. Because each period of analysis used the same ICD coding system for all race and ethnic groups, we believe that any effect of ICD coding on rates and thus rate ratios likely would have been similar across race.

CONCLUSIONS
Black and American Indian/Alaskan Native children had significantly higher injury mortality for all-cause, intentional, and unintentional injury than white, Hispanic, or Asian/Pacific Islander infants and children. Compared with white children, black children exhibited significantly lower mortality in only 1 injury mechanism: unintentional drowning. Progress in narrowing disparities between black and white children and between American Indian/Alaskan Native and white children was variable across injury mechanisms. The most notable improvements were observed for residential fire, pedestrian, and poisoning deaths, whereas disparities widened for motor vehicle occupant, unspecified motor vehicle, and suffocation for both black and American Indian/Alaskan Native children. The maintenance or widening of injury-related disparities across several mechanisms suggests that historical prevention efforts, particularly related to unintentional suffocation and intentional injury in very young children, are not sufficient to eliminate observed racial disparity gaps. This study further suggests the need to (1) continue injury surveillance, particularly in areas where disparities remain and improvement in injury rates slowed or worsened; (2) expand the proportion of high-risk populations reached with targeted, well-focused, efficacious injury prevention approaches for which some progress has been accomplished but disparities remain; and (3) develop new strategies and approaches to address areas that seem recalcitrant to improvement in absolute rates and/or to narrowing of disparities.

ACKNOWLEDGMENTS
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Impact of the State Children’s Health Insurance Program on Adolescents in New York

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ABSTRACT

OBJECTIVES. Adolescents face financial and nonfinancial barriers to health care. Little is known about the impact of health insurance on health care for adolescents. We assessed the impact of New York’s State Children’s Health Insurance Program on access, use, and quality of care for adolescents.

METHODS. Adolescents and their parents from a stratified random sample of new enrollees in New York’s State Children’s Health Insurance Program were interviewed by telephone shortly after enrollment (baseline, \(n = 1118\) adolescents and their parents) and 1 year later (follow-up, \(n = 970\)). Outcome measures included access (having a usual source of care and reported unmet health needs), use (preventive care and other types of visits), and quality (satisfaction with care, receipt of confidential care and preventive counseling). Outcomes were assessed at baseline (year before the State Children’s Health Insurance Program) versus follow-up (year during the State Children’s Health Insurance Program).

RESULTS. The proportion of adolescents who reported having a usual source of care increased during State Children’s Health Insurance Program compared with before (69.9\% to 87.1\%). The proportion with any unmet health care need (54.3\% to 42.1\%) or with unmet need for preventive care (53.8\% to 40.6\%) decreased, with elimination of racial disparities that existed before the State Children’s Health Insurance Program. After enrollment in the State Children’s Health Insurance Program, more adolescents reported having had a preventive care visit (65.9\% to 74.2\%); emergency department use did not change. No differences in satisfaction were noted, although significant increases were noted in both parent- and adolescent-reported rates of having received confidential care and preventive counseling.

CONCLUSIONS. Adolescents who enrolled in New York’s State Children’s Health Insurance Program experienced improved access, use, and quality of care. These findings suggest that the provision of health insurance can help to improve health care for adolescents.
Since 1997, the State Children’s Health Insurance Program (SCHIP) has provided publicly supported health insurance expansions for low-income children and youth who are not eligible for Medicaid or covered by private insurance. In New York State, we previously reported that enrollment in SCHIP for children aged 0 to 18 was associated with improved access, continuity, and quality of care and with a greater proportion of care being delivered within a usual source of primary care.1 Between 1995 and 2002, the proportion of adolescents without insurance coverage in poor and near-poor families declined by >25%.2 In addition, the quality of care that was received by children and adolescents before enrollment in SCHIP reflects high levels of unmet health care needs and suboptimal receipt of recommended preventive services.3,4 Although these findings suggest that SCHIP might improve care for adolescents, relatively little is known about the impact of health insurance on health care for adolescents.

Adolescents and young adults face unique financial and nonfinancial barriers to health care.5 Adolescents have poorer access to care than younger groups, yet they are at substantial risk for morbidity and mortality related to their behaviors.6-7 Although many young people report having a source of primary health care and use health care services, relatively few receive recommended preventive services, and many forgo needed care.6-9

In the first 5 years of SCHIP, >1.5 million adolescents had enrolled nationally,10 and almost one third of 2001 SCHIP enrollees were adolescents.11,12 We have reported that the population of adolescents who enrolled in SCHIP in both New York and Florida had high rates of health care use before SCHIP enrollment yet still had high levels of health care needs and unmet needs on enrollment in SCHIP.11 In addition, a significant number had fair or poor health status. These findings were more pronounced among black and Hispanic youth, demonstrating the presence of racial disparities in access to care among adolescent SCHIP enrollees in these 2 states. The majority of enrollees were from families who were living in poverty, and most were uninsured before their enrollment in SCHIP.8 Clearly, one measure of the success of SCHIP will be the degree to which programs effectively serve these adolescents.

New York’s SCHIP Program, Child Health Plus, was modeled on commercial managed care insurance and first was established as a state-specific program in 1991. New York’s SCHIP served as one of the prototypes for the separate-model program option when SCHIP was created nationally in 1997. At the time of this study, New York’s SCHIP was administered by 32 managed care plans. Children were eligible for coverage if they were 0 to 18 years, at or below 230% of the federal poverty level (FPL), residing in New York, not covered by other insurance, and not eligible for Medicaid. Monthly premiums ranged from no premium (for families <160% of FPL) to $9 to $15 per child per month for other income levels. A percentage of all families above 230% of FPL purchased New York’s SCHIP for the full premium; approximately two thirds of all enrollees received full state subsidy. Cost-sharing levels and benefit packages were uniform statewide and included ambulatory, emergency, inpatient, pharmacy, dental, and mental health services. These benefits were similar to those offered by commercial plans but were less comprehensive than Medicaid benefits.1

This article uses data from a study of New York State’s SCHIP program to assess the impact of SCHIP on adolescents’ health and health care. We describe the characteristics and needs of adolescents who entered SCHIP (baseline) and the impact of SCHIP on access to care, use, and parent-reported quality of services among adolescent SCHIP enrollees. In addition, we describe the impact of SCHIP on access to care and use from adolescents’ self-report.

METHODS

Study Design
We used a time 1/time 2 (T1/T2) cohort design. Detailed methods have been reported elsewhere.1 Briefly, we selected adolescents who were newly enrolled in New York’s SCHIP and interviewed these youth and their parents roughly 4 to 6 months after enrollment (T1) and again 13 months after enrollment (T2). The T1 interview reflected the teen’s experience during the year before SCHIP enrollment, and the T2 interview reflected experience during the first year after SCHIP enrollment. We also conducted a baseline interview with a comparison group who enrolled in SCHIP 1 year after the study group enrolled to account for possible secular trends in characteristics and experiences of new SCHIP enrollees. Parents and adolescents in the comparison group completed an identical interview about their experiences in the year before SCHIP enrollment.1 The University of Rochester Research Subjects Review Board approved this study.

Sample
New York State administrative files were used to identify new enrollees. A stratified random sample (1 unique adolescent per family) of new SCHIP enrollees was selected from 4 geographic regions (New York City, the urban environs of New York City, upstate urban areas, and upstate rural regions) and 3 race/ethnicity groups (white non-Hispanic, black non-Hispanic, and Hispanic); other racial/ethnic groups were excluded. The comparison group consisted of randomly selected parents of children throughout New York State who were newly enrolled in SCHIP during the appropriate time period. Data were weighted to account for the sampling design.
and reported estimates represent adolescent SCHIP enrollees statewide.

**Telephone Interviews**
The National Opinion Research Center conducted T₁ interviews via telephone between March 15, 2001, and September 15, 2001, and follow-up T₂ interviews between December 1, 2001, and May 4, 2002, using Computer Aided Technology, Inc. Interviews were conducted in English and Spanish, day and evening, 7 days per week. Adolescent interviews were designed to ensure confidentiality of responses.

**Measures**
Key questions were obtained from standard instruments and were developed collaboratively with other SCHIP evaluation projects that were supported by the Child Health Insurance Research Initiative. Demographics included age, gender, race/ethnicity, geographic region, family structure (number of parents), family income, and parent education. Race and Hispanic ethnicity were measured separately. Adolescents’ place of residence was categorized as rural or urban on the basis of Rural Urban Commuting Areas codes. Previous health insurance was assessed as the number of months the adolescent was insured during the year before SCHIP enrollment and the type of insurance before SCHIP (private, public, or none). Health status was assessed by a standard self-report question (parent report of child’s health as excellent, good, fair, or poor), by parent report of special health care needs, and by adolescent report of risk behaviors. Presence of special health care needs was determined by parent report using the Child and Adolescent Health Measurement Initiative (CAHMI) 5-question screener. Youth-reported risk behavior items for tobacco use, depression risk (feeling sad or depressed in the past year), and having had sexual intercourse came from the CAHMI Young Adult Health Care Survey (YAHCS). Access measures that were reported by questions to parents and teens included the presence of a usual source of care (USC), accessibility of the USC (using 4 measures from the Consumer Assessment of Healthcare Providers and Systems), and assessment of unmet health care needs. Use measures (parent and teen report) assessed preventive care and other types of visits, including any use of emergency department (ED), outpatient, or hospital-based services and prescription medication use during the periods before and during SCHIP. Quality measures included parent and adolescent ratings of specific aspects of care during the year before and then the year after SCHIP enrollment; ratings of the health care provider at 3 months after enrollment and 1 year later using Consumer Assessment of Healthcare Providers and Systems items; and assessment of the quality of specific preventive services, including provider counseling and private/confidential care using YAHCS measures. Assessment of quality using the YAHCS was pertinent only for youth who had received preventive care in the previous 12 months.

**Statistical Analyses**
Bivariate analyses of health care access, use, and quality were conducted for the year before New York’s SCHIP to describe baseline characteristics and health care experiences. We then estimated multivariate models to generate adjusted rates to assess the change in key outcome measures before versus during SCHIP. All models controlled for the effects of before–after differences in analyses of the entire sample and in analyses of subgroups. Multivariate analyses controlled for demographic and socioeconomic measures, including age, gender, race/ethnicity, single-parent household, household size, family income, maximum parent education, parental employment status, and urban residence. All analyses were weighted to be representative of the population of white, black, and Hispanic adolescents who were newly enrolled in New York’s SCHIP.

In all analyses, we used sample weights to obtain estimated means and odds ratios. Stata 8.2 was used to account for the complex weighting and stratification strategy. We first summarized baseline demographics, health characteristics, and insurance measures (baseline survey) for adolescents in the SCHIP population. Subsequent analyses compared baseline (before SCHIP) versus follow-up (during SCHIP) using survey design–based F tests and t tests.

To assess whether bivariate results of key outcomes were affected by confounding demographic and previous insurance variables, we estimated multivariate logistic regression models for having a USC, unmet needs, preventive and other types of visits, and confidential care measures each as dependent variables, controlling for demographic characteristics and previous insurance status. We calculated adjusted proportions and confidence intervals for follow-up versus baseline separately for each subgroup. We then compared these adjusted results with the unadjusted bivariate results. Generalized estimating equations were used to estimate logistic population-averaged models with exchangeable correlation structure to account for the correlation between baseline and follow-up responses for the same subject.

**RESULTS**

**Response Rates and Comparison Group Analyses**
Baseline interviews were completed with 1118 adolescents and their parents shortly after enrollment, and 970 (87%) of these individuals completed follow-up interviews 1 year later. A total of 401 parents and/or adolescents in the comparison group completed interviews. Previously described analyses of the comparison group
suggest that there were no major secular trends during the 1-year period studied.1

**Demographics of Adolescents Enrolled in SCHIP**

Demographics, health status, and health/risk behaviors of the 970 adolescents who were interviewed at both T1 and T2 are reported in Table 1. The mean age at SCHIP enrollment was 14.8 years, and 75% of adolescent enrollees were black or Hispanic. The majority of parents had completed high school or more, and 82.5% reported that their family income was <160% of the FPL. More than two thirds (71%) of adolescents were uninsured for the entire year before their enrollment in SCHIP.

**Health Status and Health Behaviors**

More than 1 (13.6%) in 8 adolescents reported fair to poor health status at SCHIP enrollment (Table 1). On the basis of the CAHMI 5-item screener that was asked of parents, 19.4% of adolescents had special health care needs. One in 4 adolescents reported feeling sad or hopeless every day for 2 weeks or more in the past 12 months. Approximately 14% reported smoking cigarettes, and one fifth reported having had sexual intercourse.

**Health Care Access and Use**

The proportion of parents who reported that their adolescent had a USC increased from 79% before SCHIP to 95% during SCHIP (P < .0001; Table 2). Financial reasons for not having a USC decreased during SCHIP enrollment: 31% of parents reported not having a USC because they did not have health insurance before SCHIP, compared with only 4% during SCHIP (P < .0001). Parent-reported rates of using a clinic at a hospital as the USC increased from 15% to 26% (P = .001), whereas the proportion who reported that the USC was a doctor’s office outside a hospital decreased slightly, from 42% to 37% (P = .072).

Parents were more likely to report that their adoles-

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**TABLE 1** Demographics, Health Status, and Health Behaviors of Adolescents Who Were Newly Enrolled in SCHIP

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
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<tr>
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<tr>
<td>Middle adolescent (14–16)</td>
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<tr>
<td>Late adolescent (17–18)</td>
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<td>Income &lt;160% FPL</td>
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<td>Single-parent household</td>
<td>58.1</td>
</tr>
<tr>
<td>Health insurancea</td>
<td></td>
</tr>
<tr>
<td>No. of months insured during year before SCHIP</td>
<td></td>
</tr>
<tr>
<td>None (uninsured all year)</td>
<td>70.8</td>
</tr>
<tr>
<td>1–11</td>
<td>11.1</td>
</tr>
<tr>
<td>All 12</td>
<td>18.2</td>
</tr>
<tr>
<td>Type of last insurance (for those with previous insurance)</td>
<td></td>
</tr>
<tr>
<td>Any private</td>
<td>67.6</td>
</tr>
<tr>
<td>Medicaid</td>
<td>23.8</td>
</tr>
<tr>
<td>Other</td>
<td>11.6</td>
</tr>
<tr>
<td>Health status and behaviorsb</td>
<td></td>
</tr>
<tr>
<td>Fair to poor health status</td>
<td>13.6</td>
</tr>
<tr>
<td>Sad in past 12 mo</td>
<td>25.8</td>
</tr>
<tr>
<td>Smoked cigarettes</td>
<td>13.9</td>
</tr>
<tr>
<td>Had sexual intercourse</td>
<td>20.3</td>
</tr>
</tbody>
</table>

**TABLE 2** Parental Report of Adolescent’s USC, Use, and Receipt of Confidential Care, Before and During SCHIP Enrollment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before SCHIP, %</th>
<th>During SCHIP, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>USC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had a USC</td>
<td>78.6</td>
<td>94.8</td>
<td>≤.0001</td>
</tr>
<tr>
<td>Top reasons for not having a USC</td>
<td>(n = 161)</td>
<td>(n = 42)</td>
<td></td>
</tr>
<tr>
<td>Seldom gets sick</td>
<td>23.9</td>
<td>54.3</td>
<td>.002</td>
</tr>
<tr>
<td>Recently moved</td>
<td>18.9</td>
<td>2.9</td>
<td>.009</td>
</tr>
<tr>
<td>Do not know where to go for care</td>
<td>2.6</td>
<td>6.8</td>
<td>.161</td>
</tr>
<tr>
<td>Did not have health insurance</td>
<td>30.8</td>
<td>4.1</td>
<td>≤.0001</td>
</tr>
<tr>
<td>Place closed or moved</td>
<td>2.6</td>
<td>0.0</td>
<td>.330</td>
</tr>
<tr>
<td>Cannot afford it</td>
<td>10.9</td>
<td>5.8</td>
<td>.410</td>
</tr>
<tr>
<td>Other reason no USC</td>
<td>10.2</td>
<td>26.1</td>
<td>.030</td>
</tr>
<tr>
<td>Type of USC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor’s office outside hospital</td>
<td>42.2</td>
<td>36.8</td>
<td>.072</td>
</tr>
<tr>
<td>Doctor’s office in hospital</td>
<td>6.2</td>
<td>3.6</td>
<td>.142</td>
</tr>
<tr>
<td>HMO-run clinic</td>
<td>2.7</td>
<td>0.8</td>
<td>.016</td>
</tr>
<tr>
<td>Community health center</td>
<td>20.8</td>
<td>21.4</td>
<td>.816</td>
</tr>
<tr>
<td>ED</td>
<td>3.5</td>
<td>5.6</td>
<td>.224</td>
</tr>
<tr>
<td>Clinic at hospital</td>
<td>15.4</td>
<td>26.4</td>
<td>.001</td>
</tr>
<tr>
<td>School clinic</td>
<td>0.2</td>
<td>0.4</td>
<td>.314</td>
</tr>
<tr>
<td>Health department</td>
<td>4.5</td>
<td>3.4</td>
<td>.373</td>
</tr>
<tr>
<td>Other</td>
<td>4.3</td>
<td>1.6</td>
<td>.018</td>
</tr>
<tr>
<td>Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive or routine visit</td>
<td>65.9</td>
<td>74.2</td>
<td>.003</td>
</tr>
<tr>
<td>Mean no. of routine visits</td>
<td>1.31</td>
<td>1.74</td>
<td>≤.0001</td>
</tr>
<tr>
<td>ED use</td>
<td>18.0</td>
<td>18.3</td>
<td>.898</td>
</tr>
<tr>
<td>Illness or injury visit</td>
<td>23.5</td>
<td>22.9</td>
<td>.780</td>
</tr>
<tr>
<td>Specialist visit</td>
<td>12.9</td>
<td>24.0</td>
<td>≤.0001</td>
</tr>
<tr>
<td>Mental health care</td>
<td>4.8</td>
<td>6.4</td>
<td>.287</td>
</tr>
<tr>
<td>Dental care</td>
<td>57.8</td>
<td>62.4</td>
<td>.111</td>
</tr>
<tr>
<td>Vision care</td>
<td>28.2</td>
<td>27.1</td>
<td>.646</td>
</tr>
<tr>
<td>Prescription medication use</td>
<td>38.9</td>
<td>46.7</td>
<td>.003</td>
</tr>
<tr>
<td>Receipt of confidential care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescent had an opportunity to speak privately with a provider</td>
<td>36.6</td>
<td>59.0</td>
<td>≤.0001</td>
</tr>
</tbody>
</table>

HMO indicates health maintenance organization.
cent had a preventive visit during SCHIP (74%) compared with before SCHIP (66%;  P = .003). Parents also were more likely to report that their adolescent had a visit to a specialist (P ≤ .0001) or used prescription medications (P = .003) during the year when they were enrolled in SCHIP compared with the year before. ED use and other specialty services use (eg, mental health, dental, vision) remained the same during SCHIP enrollment compared with before SCHIP.

On the basis of parent report, SCHIP enrollment improved access to care and eliminated disparities in USC that were present before SCHIP: parents of 92% of white adolescents, 75% of black adolescents, and 74% of Hispanic adolescents reported that their teenager had a USC before SCHIP enrollment (P = .002 for racial/ethnic difference before SCHIP). During the year after enrollment, parents reported that 96% of white, 94% of black, and 95% of Hispanic adolescents had a USC (P = .745 for racial/ethnic difference during SCHIP; all P < .01 for T1 to T2 changes).

Gender and age differences in preventive care use also were found. Adolescent boys were significantly more likely to have had a preventive visit during SCHIP (80%) compared with before (68%;  P ≤ .0001). More than 60% of girls had preventive visits, with no significant differences before versus after SCHIP enrollment. Older teens (aged 17–18) had the largest increase in use of preventive visits during SCHIP (from 50% to 72%;  P = .001) compared with early (aged 12–13) and middle (aged 14–16) adolescents, whose preventive care use increased from 72% to 82% (P = .096) and 66% to 73% (P = .099), respectively.

Adolescents’ reports of improved access and use during SCHIP confirmed parents’ reported changes (Table 3). Adolescents were more likely to report that they had a USC in the year after they were enrolled (87%) compared with the year before (70%;  P ≤ .0001). Adolescents also were significantly less likely to report that they had any unmet health care need (P ≤ .0001) or an unmet need for preventive care (P ≤ .0001) during the year when they were enrolled in SCHIP compared with the previous year. Reported needs for mental health or reproductive health remained unchanged; however, relatively few adolescents identified needs for these services in either baseline or follow-up surveys.

**Receipt of Confidential Care**
The proportion of parents who reported that their child had an opportunity to speak privately with the provider increased substantially, from 37% before SCHIP to 59% during SCHIP (P ≤ .0001; Table 2). Adolescents’ reports were similar to parents’ reports on this item: nearly 40% reported that they had an opportunity to speak privately with their provider before compared with 54% during SCHIP (P ≤ .0001; Table 3). Baseline gender differences were noted: the proportion of girls who reported that they received confidential care increased from 35% to 56% (P ≤ .0001); increases for boys were not statistically significant (from 45% before to 53% during SCHIP;  P = .106).

**Multivariate Analyses**
Multivariate models were used to adjust the associations between baseline and follow-up reports for access, use, unmet need, and receipt of confidential care (Table 4). When adjusted for demographics and previous insurance status, SCHIP resulted in increased rates of reporting a USC, more preventive care, specialty care, prescription medication use, fewer unmet needs, and more confidential care delivery. In fact, on multivariate analyses, all measures improved except for having an ED visit.

**Perceived Health, Worry, and Satisfaction With SCHIP**
Neither parents nor adolescents reported that their health was better during SCHIP than it was before SCHIP. However, parents reported significantly less worry about their child’s health 1 year after enrollment

<table>
<thead>
<tr>
<th><strong>TABLE 3</strong></th>
<th>Adolescent Report of USC, Unmet Needs, and Confidential Care, Before and During SCHIP Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td><strong>Before SCHIP, %</strong></td>
</tr>
<tr>
<td>Had a USC</td>
<td>69.9</td>
</tr>
<tr>
<td>Had any unmet need</td>
<td>54.3</td>
</tr>
<tr>
<td>Unmet need for preventive care</td>
<td>53.8</td>
</tr>
<tr>
<td>Unmet need for mental health care</td>
<td>6.5</td>
</tr>
<tr>
<td>Unmet need for reproductive health care</td>
<td>4.9</td>
</tr>
<tr>
<td>Had an opportunity to speak privately with a provider</td>
<td>39.9</td>
</tr>
</tbody>
</table>

* Asked of girls only.

<table>
<thead>
<tr>
<th><strong>TABLE 4</strong></th>
<th>Adjusted Rates for Key Access, Use, and Quality Measures (Parent and Adolescent Report), Before and During SCHIP Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td><strong>Adjusted Rates</strong></td>
</tr>
<tr>
<td></td>
<td>Before SCHIP (Time 1)</td>
</tr>
<tr>
<td>Parent report</td>
<td>Had a USC</td>
</tr>
<tr>
<td></td>
<td>Had a preventive/routine visit</td>
</tr>
<tr>
<td></td>
<td>Had an ED visit</td>
</tr>
<tr>
<td></td>
<td>Had a specialist visit</td>
</tr>
<tr>
<td></td>
<td>Used prescription medications</td>
</tr>
<tr>
<td></td>
<td>Adolescent had an opportunity to speak privately with the provider</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, race/ethnicity, geographic region, and previous insurance status.
compared with the baseline (51% vs 45%; \( P = .028 \)). The proportion of parents who reported that they were more satisfied with the benefits in SCHIP compared with their adolescent’s last health insurance increased from 67% to 73% (\( P = .028 \)). A high proportion of both parents and adolescents reported that they were more satisfied with their providers (62% and 76%, respectively) and with their care (74% and 84%, respectively) than before they had enrolled in SCHIP.

**Receipt of Preventive Counseling**

More parents reported that their teen’s provider had counseled on a variety of health issues during the year when they were enrolled in SCHIP compared with the year before enrollment, including guns/weapons, smoking, drugs, alcohol and sexuality, and behaviors to expect from their child (Table 5). The proportion of teens who reported that their provider discussed various health issues with them also increased significantly for condom use and healthy eating, and a trend was noted for several other counseling items. For example, 38% of adolescents reported that their provider counseled them about condoms before SCHIP compared with 45% during SCHIP enrollment (\( P = .014 \)), and 58% reported discussing healthy eating before compared with 67% during SCHIP (\( P = .01 \)).

**DISCUSSION**

Our study demonstrates that enrollment in SCHIP increased access to care and improved the quality of care that was received by adolescents in New York. In this analysis of low-income white, black, and Hispanic youth, most of whom were uninsured before enrollment, SCHIP insurance was associated with greater access to a USC; more use of preventive care, specialty care, and prescription medications; and fewer unmet needs. SCHIP also seemed to eliminate preexisting racial disparities in access; differences for black and Hispanic adolescents that were noted in the year before enrollment were no longer present during SCHIP—that is, access to care during SCHIP was equivalent among white, black, and Hispanic adolescents.

Adolescents’ access to health care is among the worst of all age groups, and relatively few interventions have shown to be effective in improving their access to care. Although insurance benefits are not always matched to the needs of adolescents, Medicaid and SCHIP programs often are believed to offer the potential for providing comprehensive insurance coverage to many uninsured adolescents.\(^{22}\) Our findings suggest that New York’s SCHIP does improve adolescents’ access and use of services. Adolescents perceived a difference in their use of and need for preventive care before and during SCHIP enrollment. They also reported fewer unmet needs, likely because preventive care use improved. It is interesting that there were no increases in ED use during the study period, suggesting that SCHIP targets needed access and does not merely increase use of all health care. Despite concerns about availability of reproductive health care under SCHIP,\(^{12,23}\) relatively few adolescents reported unmet needs for reproductive care. However, this may reflect New York’s long-standing history of supporting enhanced access to family planning services for underserved adolescents and adults,\(^{24}\) independent of SCHIP.

Other studies of New York’s SCHIP have demonstrated that SCHIP is effective in improving access to care for specific populations, including children with asthma and those with special health care needs.\(^{1,25}\) We also have shown that SCHIP reduces racial and ethnic disparities in a population of children aged 0 to 18, based on parental reports alone.\(^{26}\) These analyses show that elimination of racial/ethnic disparities in access can be achieved with enrollment of adolescents into New York’s SCHIP.

Early studies of SCHIP in 5 states suggested that there was room for improvement in adolescents’ access to and use of preventive and specialist care and prescription drug coverage.\(^{18}\) This article adds to this evidence for the impact of SCHIP on improved access to care by including

### Table 5 Parent and Adolescent Report of Receipt of Preventive Counseling, Before and During SCHIP Enrollment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parent Report</th>
<th>Adolescent Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before SCHIP, %</td>
<td>During SCHIP, %</td>
</tr>
<tr>
<td>Growth and development</td>
<td>60.7</td>
<td>68.9</td>
</tr>
<tr>
<td>School performance</td>
<td>57.9</td>
<td>64.8</td>
</tr>
<tr>
<td>Healthy eating</td>
<td>51.0</td>
<td>54.4</td>
</tr>
<tr>
<td>Behaviors you can expect</td>
<td>35.6</td>
<td>46.6</td>
</tr>
<tr>
<td>Things you can do to help your child</td>
<td>31.2</td>
<td>41.3</td>
</tr>
<tr>
<td>Smoking, drugs, alcohol, sexuality</td>
<td>28.1</td>
<td>43.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>37.5</td>
<td>45.3</td>
</tr>
<tr>
<td>Condoms</td>
<td>37.5</td>
<td>45.3</td>
</tr>
<tr>
<td>Guns and weapons</td>
<td>28.1</td>
<td>43.7</td>
</tr>
<tr>
<td>Feeling sad</td>
<td>33.1</td>
<td>39.0</td>
</tr>
</tbody>
</table>

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adolescents' own reporting about their care. This is especially important for older adolescents, because the proportion of care that is obtained without parents' knowledge increases during the adolescent years.6 Financial barriers to not having a USC decreased significantly with enrollment in SCHIP, because parents were most likely to cite nonfinancial reasons for not having a USC during SCHIP. Although adolescents' reported rates of having a USC were slightly lower than rates that were reported by parents, a comparable increase was noted by both parents and adolescents during SCHIP enrollment. In addition, enrollment in SCHIP was associated with less parental worry about their child's health, although neither teens nor parents reported actual changes in perceived adolescent health status.

We found some improvement in the quality of care at preventive visits during SCHIP, reported by adolescents and parents alike. Slightly more than half of teens and parents reported that teens had an opportunity to speak privately with their provider. Both parents and adolescents reported significant increases in adolescents' receipt of preventive counseling on several health topics, which may reflect increased preventive care use. Similar improvements in communication also were reported recently by Alabama's SCHIP program.27 However, Florida's SCHIP evaluation studies have not shown comparable changes in the quality of care received by youth.1 Nonetheless, there remains significant room for improvement even in New York's SCHIP, because some parents and adolescents still were not satisfied with SCHIP and unmet health care needs remained relatively high, with >40% of adolescents reporting any unmet need. In addition, although recommended by adolescent preventive care guidelines,28,29 nearly half of adolescents reported that they did not have an opportunity to speak privately with a provider, and fewer than half received preventive health screening/counseling on various health topics.

Seventy percent of adolescents in our study were uninsured during the entire year before SCHIP enrollment, and our findings suggest that SCHIP improved access to care and use of services for new adolescent SCHIP enrollees in general. Millions of US adolescents are uninsured, and many would be eligible for SCHIP if their families applied for coverage;2 as many as 62% of uninsured children and families might qualify for Medicaid or SCHIP if they applied.30 Providers and policy makers have focused appropriately on maintaining SCHIP funding and on enrollment policies that can help to ensure continuous coverage for poor children and families. However, many states do not target adolescents for outreach and enrollment,23 and some states have implemented other policies that create barriers to adolescents' eligibility and enrollment.12 Therefore, substantial work remains to identify and enroll adolescents who are eligible for coverage if all adolescents are to receive the care that they need.

Our study is limited in that our survey data are based on parent and adolescent self-report. We did not compare self-reported access and use of care with provider reports or medical charts and could not verify self-reported data for the content of care received or for unmet needs. However, parent- and adolescent-reported rates increased comparably on several measures, including having a USC, receiving private care, and receiving preventive counseling. This suggests that both parents and adolescents perceived changes in their use of health care and the quality of care received during SCHIP. However, we were unable to examine the reasons that preventive visit quality improved in the current study. In addition, although adolescents were contacted separately after their parents had given consent and were given the opportunity to schedule a time to complete the interview at their convenience, adolescents may not have answered all of the questions honestly. However, our finding that many adolescents disclosed 1 or more risk-taking behaviors is similar to other studies that used the YAHCS survey measures.18 Another limitation is that our findings may not be generalizable to all SCHIP populations. We did not study all racial/ethnic groups beyond white, black, and Hispanic, and we studied only adolescents who were enrolled in New York. Therefore, although 18% of the nation's entire 2001 SCHIP population resided in New York,11 these findings may not generalize to other states or to the entire population.

CONCLUSIONS
Overall, SCHIP has shown improvements in access and quality of care delivered to adolescents in New York. SCHIP had the greatest impact on improving health care access and quality for vulnerable populations, such as those who were previously uninsured, and resulted in a reduction in disparities in access for black and Hispanic youth. The investments in SCHIP programs for low-income adolescents produce significant improvements in health care access and quality, especially for those who are most vulnerable. These findings suggest that SCHIP can help to improve adolescents' access to care and provide strong evidence for continuation and expansion of policies to provide health insurance to all. Youth enroll in SCHIP with significant unmet health care needs. Although these improve during SCHIP, SCHIP benefits and delivery systems need to address a variety of ongoing health care needs to help ensure that the needs of adolescents are met. Focused programmatic efforts and outreach strategies likely will be needed to reduce further the barriers to care for some types of adolescent services.
ACKNOWLEDGMENTS

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Efficacy of a Pill-Swallowing Training Intervention to Improve Antiretroviral Medication Adherence in Pediatric Patients With HIV/AIDS

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. We aimed to retrospectively assess the efficacy of pill-swallowing training provided as a clinical intervention to referred pediatric patients with HIV in relation to improved adherence and subsequent related health outcomes. The primary goal of this study was to demonstrate participation in pill-swallowing training is associated with improved medication adherence as documented by routine pharmacy pill counts. Secondary objectives were to assess corresponding improvements in clinically observed biologic indicators of adherence, specifically, immunologic functioning (CD4+ T-cell%) and viral load, over time.

PATIENTS AND METHODS. A retrospective chart review of 23 pediatric patients with HIV aged 4 to 21 years who were clinically referred for pill-swallowing training by an experienced pediatric psychologist for either noted difficulties with currently prescribed antiretroviral regimens and/or desire to change the child’s regimen/formulary. Patient demographics, reason(s) for pill-swallowing training referral, number of pill-swallowing training sessions required to attain success, adherence, CD4+ T-cell%, and viral load were abstracted at baseline and at ~3 and 6 months posttraining.

RESULTS. Modal number of sessions required to acquire the pill-swallowing skill was 1 session. Younger children (aged 4–5 years) required a median of 2 training sessions, while older children required ≥3 sessions. A significant improvement in adherence from baseline to 6 months post–pill-swallowing training completion was observed, as were significant related improvements in CD4+ T-cell% and viral load.

CONCLUSIONS. Participation in pill-swallowing training related to improved medication adherence at 6 months posttraining. Subsequent improvements in related CD4+ T-cell% and viral load were noted over time, most significantly at 6 months postintervention. These preliminary findings provide justification for additional study via a prospective, randomized, controlled clinical trial. Pill-swallowing train-
Curing potentially is a successful time-limited, cost-effective intervention to improve adherence to antiretroviral therapies, and thus medical status, in children with HIV.

Currently available highly active antiretroviral therapies (HAART) to treat HIV/AIDS require combination therapy with multiple daily dosing, few of which come in pediatric-friendly formulations. During routine clinic visits for medical care, parents of younger perinatally HIV-infected patients frequently report difficulty administering prescribed anti-HIV medications to their children. In addition, youth who acquired HIV behaviorally during adolescence report to practitioners difficulty with taking medications as prescribed, citing “the pills are too big,” and “I’m afraid I’m gonna choke,” as reasons for their own nonadherence. Because of limited available pediatric-friendly antiretroviral formulations, parents are offered alternative methods and techniques by which to administer their children’s required medications (eg, opening gel caps and sprinkling contents into foods or liquids). Consequently, children frequently develop and demonstrate behavioral resistance to taking anti-HIV medications in powder or liquid formulation. Such behavioral resistance often is attributed to the medication’s bad taste or unpalatable texture and/or is compounded by children’s developed aversion to the foods or liquids that are used to mask the taste or conceal the medicine.

Therefore, for young patients, it is ideal to change the formula (eg, switch from powders and/or liquids to pills or gel caps) before the child refuses to take medications without having an alternative method of medication administration or substitute formulary readily available. A goal of pill-swallowing training (PST) with young children is optimally to avoid a period of time when the child does not get his or her required medications as a result of refusing to take his or her current formulary (because of texture, taste, volume, etc) and not yet be able to swallow pills, resulting in a twice-daily difficult power struggle between parent and child around medication administration. Therefore, it is desirable to train young children to swallow pills while still compliant with liquid and/or powder formulary to encourage the acquisition of the new skill that, once acquired, will be experienced and thereby perceived by the child as an “easier” way to take medications. Despite parents’/guardians’ expressed exasperation and requests for help after repeated difficulty with administering their children’s medications in liquid or powder form, when offered, parents/guardians often express reticence to try PST or change their child’s formulary. Reasons given for reservations related to parent/guardian perceptions of their child’s inability to swallow “those big pills” or their own or their child’s previous difficulty with swallowing pills without the benefit of PST, which otherwise would allow for a change in the prescribed regimen.

Children’s inability to take antiretroviral medications as prescribed (nonadherence) has significant potential negative health consequences, including the potential for increased viral replication, immune suppression, and, when not taken consistently as prescribed within the acceptable dosing window, the potential to develop viral resistance to treatment, thereby limiting a young person’s future treatment options for later life. Therefore, PST may provide an efficacious, time-limited, cost-effective, clinical intervention for young children with HIV to improve adherence to antiretroviral medications and thus related subsequent health benefits as reflected by improvements in CD4 T-cell% and viral load (VL) suppression while also preserving future treatment options.

Data presented herein were obtained via an institutional review board–approved, retrospective chart review study to document the efficacy of a PST technique in relation to improved adherence outcomes. PST was provided routinely as a referral-based clinical intervention at a specialty pediatric/adolescent HIV/AIDS clinic in the midsouthern United States. Others have described the PST procedure1-2 and success in acquiring the pill-swallowing skill,2-4 but no reports to date have documented the subsequent related improvements in medication adherence and secondary improvements in health outcomes in relation to provision of PST as a clinical intervention. Although the primary goal of this exploratory study was to assess improvements in adherence after participation in PST, it also was important to assess changes in commonly monitored biological indicators of antiretroviral adherence, specifically, CD4+ T-cell% and VL in relation to improved adherence observed. Therefore, study hypotheses proposed that participation in PST would relate to improved medication adherence as documented by routine pharmacy pill counts, and, secondarily, as a result of improved adherence, it was anticipated that participation in PST would relate to subsequent improved immunologic functioning (CD4+ T-cell%) and decreased HIV VL at ~3 months after training with sustained improvements at ~6 months after completion of PST.

METHODS

Participants

The study cohort was a convenience sample that comprised all participants who were clinically referred for PST within a 2-year period and who were 6 months out from the completion of PST. Twenty-three pediatric and young adult patients with HIV/AIDS had been referred to the clinic pediatric psychologist for PST because of noted difficulties with prescribed antiretroviral regimens and/or in preparation for a desired formulary change. Patient demographics were as follows: male gender, 12
(52.2%); black race, 21 (91.3%); white race, 2 (8.7%); mean age at referral, 7.5 years (SD: 4.6; range: 4.2–21.5 years); perinatally acquired HIV, 21 (91.3%); behaviorally acquired HIV, 2 (8.7%); baseline CD4+ T-cell%, <25%, immunosuppressed, 12 (52.2%).

Procedure
Data were collected in August 2003, and the chart review period covered referrals from June 2001 through May 2003. PST followed a modified version of the shaping protocol documented by Czyzewski et al.1,2 Patients participated in individual training sessions in which the appropriate swallowing technique first was modeled by the trainer (the clinic pediatric psychologist), then practiced by the child by first swallowing pieces of gummy worm candy cut to size to emulate commensurate placebo gel cap sizes before making the transition to lactose-filled placebo gel caps, all of which were swallowed in gradually increasing sizes. Successfully swallowing 2 of each placebo size with ease was required before progressing to the next size. When any swallowing difficulty was apparent on either of the first 2 trials, a third attempt was made before returning to the previous size at which success was achieved or progressing to the next size. The number and length of sessions were determined by the individual patient’s rate of progress and the target gel cap size dictated by their prescribed or desired treatment regimens. Each child participated in as many sessions as needed to achieve success (eg, reach target pill size) or until it was determined the child was not developmentally ready to acquire the skill. In general, following the recommendation of the PST protocol, sessions did not exceed 30 minutes. The length of each session depended on the participant’s level of enthusiasm or hesitation to engage in or continue with the training. For those who eagerly engaged in PST and readily grasped the pill-swallowing concept, individual sessions typically lasted 15 to 30 minutes in length. It is interesting that for the 2 young adults reviewed, sessions lasted ~45 minutes and typically required considerable time to address cognitive interference and/or anticipatory anxiety issues that contributed to hesitation to initiate the actual swallowing training.

Values that were abstracted from medical charts to assess efficacy of the training for each patient included the baseline levels of adherence to their prescribed antiretroviral regimen; CD4+ T-cell% and VL before the onset of training; and repeated assessments of adherence, CD4+ T-cell%, and VL at ~3 months and again at ~6 months after completion of training. Adherence was measured by routine pharmacy pill count, which was reported as a percentage on the basis of the number of pills returned in the prescription vial by the patient, subtracted from the number of pills dispensed in the vial, adjusted for the number of days remaining/past in the refill period, divided by the number of pills that should have been taken in the interim period since the last refill was dispensed. Adherence to liquid medications was assessed in a similar manner; however, volume that was returned in the bottle and measured in milliliters was compared with the calculated expected volume to have been consumed by the date of the adherence check. Adherence checks were assessed routinely by a trained pharmacy technician using standardized methods described, which are appropriate regardless of medication formulary being measured. Adherence reported for each patient was derived as an average across individual adherence percentages calculated for each medication prescribed in the patient’s regimen. At baseline, medications primarily were in liquid or powder form, with the exception of those who were provided pills with instructions to crush them into a powder or capsules with instructions to open and sprinkle the contents in liquid or over food (eg, in cereal, pudding, apple sauce). At the ~3- and 6-month time points, medications primarily were in pill form, with the exception of those few patients who required that a study medication remain in liquid form.

Analyses
The association between age group and number of training sessions was investigated using an exact Mantel-Haenszel χ2 test. Changes from baseline in adherence percent and VL (copies per mL) were analyzed using an exact nonparametric Wilcoxon signed-rank test. CD4+ T-cell% values were categorized into 0% to 14%, 15% to 24%, and >25% corresponding to Centers for Disease Control and Prevention–defined clinical cutoffs for classifying immune suppression1 and analyzed using an exact marginal homogeneity χ2 test for paired categorical data. Spearman’s rank correlation coefficient was used to investigate the relationship between various continuous measurements. The effects of regimen type, pill burden (number of pills per day), and liquid medication volume adjusted for assessment time point were explored in individual repeated measures mixed models.6 These models included a main effect for treatment variable and assessment time point and accounted for the correlation of repeated assessments over time for a given participant. Exact tests were performed using StatXact-5 for Windows.7 For this exploratory, retrospective, study, P < .10 was considered significant.8

RESULTS
Patients were referred for PST primarily because of nonadherence (56.5%) or desired formulary change (43.5%) as a result of difficulty with the prescribed regimen or development of viral resistance. Twenty-two (95.7%) referred patients were successful with training (Table 1). One child, who was 5 years of age and presented with significant developmental delay, was not able to grasp the pill-swallowing concept. Because of
behavioral refusal, training was discontinued during the first attempted session. As per recommendation in the PST protocol used, had this been a prospective trial, PST is not recommended for a child with developmental delay, and, therefore, a child with developmental delay would have been excluded from participation. However, this child also had a gastric tube in place, so this child did not take any medications by mouth (as all other participants did), and supportive community-based health services were placed to ensure medication administration and adherence. As a result of these factors, this child’s data were not included in analyses.

The modal number of PST sessions that were required to obtain success was 1. The number of sessions that were required to complete training increased with age (Spearman’s $r = 0.66, P = .001$). Younger children (age 4–5 years) required fewer training sessions (Table 1) to reach their target pill size and make the transition to their medication regimen than older children (40% of 4- to 5-year-olds required only 1 session; 50.0% of participants aged $\geq 8$ years required $\geq 4$ sessions; $P = .038$; Table 1). Participation in training resulted in a complete formulary change (eg, powder/liquid, opening and sprinkling gel cap contents to swallowing gel caps whole) for 18 (81.8%) patients and a regimen change for 10 (45.5%) patients; most remained on 3 antiviral medications.

Adherence was significantly improved at $\sim 6$ months (T3) from baseline (T1), increasing by a median of 9.8% ($P = .014$; Table 2). An increase in adherence was noted at $\sim 3$ months, when 41.2% (7 of 17) had improved from baseline, and by $\sim 6$ months, when 71.4% (10 of 14) had improved (Fig 1). It should be noted that adherence was not fully assessable because patients/parents presented for their scheduled clinic visit without returning medication bottles to the pharmacy. A significant improvement in CD4$^+$ T-cell% emerged from baseline to $\sim 3$ months (T2; $P = .063$) and from baseline to $\sim 6$ months ($P = .004$; Table 3). The lack of significant difference between T2 and T3 suggests that initial changes in CD4$^+$ T-cell% were sustained over time. The percentage of patients who showed no evidence of immune suppression ($\geq 25\%$ CD4$^+$ T-cells) increased from 50% (11 of 22) at baseline to 81.8% (18 of 22) at $\sim 6$ months. There was a corresponding decrease in VL by 6 months, with a median decrease in VL of 1258 copies per mL ($P = .093$; Table 4). Although trends in improvement over time were noted in CD4$^+$ T-cell% and VL in response to formulary change alone ($n = 12$), these differences were nonsignificant (data not shown). However, there was a noted improvement from T1 to T3 in CD4$^+$ T-cell% for those who changed their medication regimen after PST ($n = 10$; exact marginal homogeneity $\chi^2$ test, $P = .031$). For patients who had only a formulary change, 83.3% showed no evidence of immunosuppression at T3 compared with 66.7% at T1. For patients who had a medication regimen change, 80% showed no evidence of immunosuppression at T3 compared with 30% at T1. Given the degree of immunosuppression for this group at T1, clearly a regimen change was indicated after PST, and clinical response was evidenced at T3. However, for those who had only a formulary change, a greater percentage was not immunosuppressed at T1, indicating that a regimen change was not clinically warranted for this group.

No significant relationships were found between adherence and regimen type or pill burden (number of pills per day). Surprising, however, for those who were prescribed liquid medication, increased liquid volume was related significantly to better adherence ($P = .043$), pos-

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**Table 1. Summary Statistics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary reason for PST referral, n (%)</td>
<td></td>
</tr>
<tr>
<td>Nonadherence</td>
<td>13 (56.5)</td>
</tr>
<tr>
<td>Desired formulary change</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>Secondary reason for PST referral, n (%)</td>
<td></td>
</tr>
<tr>
<td>Gagging/vomiting</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>Success with PST, n (%)</td>
<td>22 (95.7)</td>
</tr>
</tbody>
</table>

**Note:**

- One child presented with significant developmental delay and was not able to acquire the pill-swallowing skill; therefore, training was discontinued. Data for this child were not included in analyses.
- Because of acquiring the pill-swallowing skill, some patients had changes in either or both their regimen and the formulary of their regimen.

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**Table 2. Time-Point Comparisons for Adherence**

<table>
<thead>
<tr>
<th>Pairs</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Median (Range)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1–T2</td>
<td>17</td>
<td>2.4 (11.7)</td>
<td>0.0 (−10.4 to 31.0)</td>
<td>.689</td>
</tr>
<tr>
<td>T2–T3</td>
<td>15</td>
<td>3.8 (14.9)</td>
<td>6.0 (−33.0 to 34.0)</td>
<td>.149</td>
</tr>
<tr>
<td>T1–T3</td>
<td>14</td>
<td>10.9 (14.0)</td>
<td>9.8 (−14.3 to 34.5)</td>
<td>.014</td>
</tr>
</tbody>
</table>

**Note:**

Data are percentages, which are based on number of pills (or liquid/powder volume) returned in the prescription vial, subtracted from the number of pills/volume dispensed in the vial, adjusted for the number of days remaining/past in the refill period, divided by the number of pills/volume that should have been taken in the interim period since the last refill was dispensed. T1 indicates baseline (pre-PST); T2, 3 months after PST; T3, 6 months after PST. Positive mean and median values indicate improved adherence from earlier time point (positive difference, eg, T2–T1).

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$a$ Exact nonparametric Wilcoxon signed-rank test.
sibly because many who retained at least 1 medication in a liquid formulation did so as required by clinical trial research participation. Therefore, those who were reviewed for this study and remained on liquid medication may have been more compliant as a result of their commitment to participate in research in addition to the close follow-up related to study visits and monitoring of study medications. Given the study’s small sample size, the distributional assumption of normality for the repeated measures mixed model was difficult to evaluate. Therefore, it should be noted that nonparametric analyses indicated a significant positive relationship between liquid volume and adherence at baseline (Spearman’s r = 0.64, P = .004); however, no significant correlations were detected at ~3 months and ~6 months. It is important to note that no patients who participated in our PST demonstrated a decline in health status during the study period.

**DISCUSSION**

All but 1 participant (with significant developmental delay) demonstrated success in acquiring the pill-swallowing skill, resulting in desired formulary change and/or regimen change because of having failed a previous regimen or the development of viral resistance. Younger children acquired the skill more readily, most likely because they were naïve to pill swallowing and therefore were not influenced by previous negative experiences. In addition, younger children typically were of an age at which it is expected they had not yet developed size conservation whereby increasing gel cap size did not create a reticence to attempt each new gel cap size as it was presented during the training. Noted success with PST provides support to indicate that children as young as 4 years can readily acquire the ability...
to swallow pills regardless of target size required for their regimen (for some of whom was #00 placebo or the size equivalent of a 1000 IU vitamin E gel cap), contrary to initial caregiver concerns or expectations.

Findings of this retrospective study support the proposed hypotheses. Specifically, success with PST as a clinical intervention related to improved medication adherence as documented by routine pill counts. Secondary to improved adherence, participants demonstrated related improved immunologic functioning (CD4 T-cell%) and decreased VL after the completion of PST, and these improvements emerged at ~3 months and were evident at ~6 months after completion of training. In addition, although participation in PST allowed for a formulary change for all participants for whom a formulary change was available, a more noteworthy effect of participation was demonstrated for those who also were able to change their treatment regimen as a result of participation in PST. Those who experienced only a formulary change showed a trend toward improved VL and immunologic functioning. However, for those who also experienced a regimen change subsequent to PST, a greater, although still nonsignificant, trend was noted in improved VL, whereas a significant improvement in immune status over time was demonstrated by a significant proportion of those who showed no evidence of immunosuppression at T3 in comparison with T1. Although the relationship here would be speculative because of the retrospective nature of this study, successful participation in PST seems to provide a clinical intervention that may permit a regimen change to a potentially more therapeutic regimen, which otherwise previously was not an option for these participants because the more potent regimen is available only in pill form and cannot be opened, crushed, squeezed, or chewed.

Although this was an exploratory retrospective study, findings suggest that PST may be a viable, time-limited (1–4 sessions), cost-effective intervention (psychologist’s time versus monthly cost of medications, repeated laboratory work to monitor CD4+ T-cell% and VL, and patients’ health risk to develop viral resistance associated with nonadherence) to improve adherence to HAART and, secondarily, related to improvements in immunologic and viral status in young children with perinatally acquired HIV. Providing training before a desired formulary change seems to aid in the successful transition from liquid/powder formulations and prepares the child for success with pills, resulting in subsequent improved adherence.

The utility of this training has implications for standard of care in pediatric HIV, especially for children as young as 4 years of age, who readily seem to acquire the skill with successful transfer of training to their prescribed medications. PST has an implication for reducing the cost of HIV patient care through reduced nonadherence (eg, cost of dispensed medications otherwise not taken, thrown away, or having to be redosed because of gagging/vomiting; increased cost because of more frequent medical care visits and monitoring, not to mention additional laboratory work to monitor response via CD4+ T-cell%, VL, and genotyping as a result of viral resistance). These findings provide support for additional investigation via a prospective study of PST as a therapeutic intervention to be provided as a standard of care to young children before size conservation or behavioral refusal that is observed in older children becomes an issue.

Limitations of this study include those related to conducting a retrospective chart review in which prospective data are not gathered uniformly, at predetermined time points, or specifically for each patient included, whereby timing and completeness of data are inexact. Despite that participants typically were scheduled for routine medical care approximately every 3 months, baseline adherence, VL, and CD4+ T-cell% data were not obtained routinely on the date that PST began, and the timing for T2 and T3 data was not exactly at 3 and 6 months after completion of training for desired adherence checks and laboratory values. For the 18 participants with baseline adherence data available for analysis, 72% of assessments were within 30 days of the start of PST; for VL and CD4+ T-cell%, which were assessed in all 22 participants, 73% and 68%, respectively, were obtained within 30 days of the start of PST. Values that subsequently were closest to 3 months (adherence median: 85.0 days; CD4+ T-cell% median: 91.0 days; VL median: 95.5 days) and 6 months (adherence median: 181.0 days; CD4+ T-cell% median: 192.5 days; VL median: 185.5 days) were used. As previously noted, a number of adherence observations were missing, which may be a potential source of bias if those with missing data differed in adherence compared with those whose data were fully assessable. On the basis of clinical experience, those who adhered well were equally as likely not to return medication vials for adherence checks as those who were nonadherent; therefore, no directional bias is expected for these missing data, but this cannot be determined objectively here.

The small sample size should be kept in mind when interpreting these results. The absence of significant findings may be attributable to the limited power to detect important differences. For example, although not significant, the trends for pill burden were in the expected direction. Although corresponding improvements in VL and CD4+ T-cell% were detected, other confounding factors and temporal variations could be at play. PST was provided as a routine clinical intervention on the basis of intention to treat to all eligible patients who demonstrated developmental readiness (as young as 3.5 years). Although it would have been ideal for research purposes, no comparison control group was available for review because all children of similar age in
this clinic subsequently had been provided PST and thus transitioned to pill formulary. Therefore, a larger randomized, controlled study is needed to demonstrate clearly the efficacy of pill-swallowing on adherence and to strengthen the link to clinical outcomes (VL and CD4+ T-cell%).

Aside from other unavoidable logistic constraints related to retrospective chart review data, consistency in PST was obtained because all patients were seen for the clinical intervention by the same pediatric psychologist. It also should be noted that patients with known adherence difficulties receive adherence counseling by their primary care practitioner, pharmacist, and, in many cases, also their social worker as routine standard of care before and in addition to referral to the pediatric psychologist for PST. As a result, it is not possible to assess or account for the role that these supportive services may contribute to the findings.

CONCLUSIONS
Although this preliminary retrospective study is the first to relate the efficacy of PST to improved adherence and subsequent related improvements in health outcomes (CD4+ T-cell% and VL), a larger prospective longitudinal study is needed to strengthen the evidence for PST as a cost-effective brief intervention to improve adherence in young patients who have HIV and are prescribed HAART regimens over both the short and long term. One benefit of such a randomized, clinical trial would be the inclusion of a comparison control group by which the treatment effect of PST could be assessed definitively. Although this particular study explored the efficacy of PST for children with HIV, the findings demonstrate that children who have a chronic health condition and are as young as 4 years readily acquire the pill-swallowing skill. The related improved adherence after participation in PST reduces the risk that viral resistance will develop, and as a result of acquiring the pill-swallowing skill, increased regimen options become available to young children. Therefore, with improved and sustained adherence, those regimens remain available as future treatment options for later life as the child ages up. As a result, the noted subsequent improvements in adherence after participation in PST have much farther reaching implications for improved health outcomes not only for children with HIV but also for those with other pediatric conditions for which medication adherence, whether over the short or long term, is critical for symptom management or infectious disease control.

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Declines in Low Birth Weight and Preterm Birth Among Infants Who Were Born to HIV-Infected Women During an Era of Increased Use of Maternal Antiretroviral Drugs: Pediatric Spectrum of HIV Disease, 1989–2004

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ABSTRACT

OBJECTIVE. Our goal was to determine trends in low birth weight and preterm birth among US infants born to HIV-infected women.

METHODS. We used data from the longitudinal Pediatric Spectrum of HIV Disease, a large HIV cohort, to assess trends in low birth weight and preterm birth from 1989 to 2004 among 11 321 study infants. Among women with prenatal care, we also assessed risk factors, including maternal antiretroviral therapy during pregnancy, that were predictive of low birth weight and preterm birth using univariate and multivariate logistic regression models.

RESULTS. Overall, 11 231 of 14 464 infants who were enrolled in Pediatric Spectrum of HIV Disease were tested during the neonatal period. From 1989 to 2004, testing increased from 32% to 97%. The proportion of HIV-exposed infants who had low birth weight decreased from 35% to 21% and occurred in all racial/ethnic groups. Prevalence of preterm birth decreased from 35% to 22% and occurred in all groups. Any maternal antiretroviral therapy use increased from 2% to 84%. Among 8793 women who had prenatal care, low birth weight was associated with a history of illicit maternal drug use, unknown maternal HIV status before delivery, symptomatic maternal HIV disease, black race, Hispanic ethnicity, and infant HIV infection. Antiretroviral therapy or lack of it was not associated with low birth weight. Among women with prenatal care, preterm birth was associated with a history of illicit maternal drug use, symptomatic maternal HIV disease, no antiretroviral therapy, receipt of a 3-drug highly active antiretroviral therapy regimen with protease inhibitors, black race, and infant HIV infection.

CONCLUSIONS. The proportion of infants who had low birth weight or were born preterm declined during an era of increased maternal antiretroviral therapies. These Pediatric Spectrum of HIV Disease trends differ from the overall increases in both outcomes among the US population.
The United States has one of the highest rates of low birth weight (LBW; <2500 g) and preterm birth (<37 weeks) among industrialized countries. Infants who have LBW or are born preterm have increased rates of morbidity and mortality. Prevalences of LBW and preterm birth, respectively, have risen to 8.1% and 12.5% as of 2004 in the general US population. The proportion of LBW has increased among white infants, as a result of assisted reproductive technology, but black infants still have higher LBW proportions. LBW is higher among certain risk groups, including women who use illicit drugs and/or have sexually transmitted diseases. Among US HIV-infected women, LBW percentages have been reported between 12% and 48%. Among US infants of HIV-infected women, reported prevalences of preterm birth are 13% to 38.3%.

It is not known whether the prevalences of LBW and preterm birth among infants who are born to HIV-infected women have changed as drug therapy have evolved into regimens of highly active antiretroviral therapy (HAART). Some studies in Europe, in the United States, and Latin America have suggested that protease inhibitors (Pis) are associated with an increased risk for preterm birth, but this finding has not been reported consistently. Recent evidence suggests that HAART has led to increased pregnancy rates among HIV-infected women who are enrolled in the Adult/Adolescent Spectrum of HIV Disease. HAART availability has reduced perinatal HIV transmission, but HAART's impact on LBW and preterm birth is less clear. Recent recommendations for scheduled cesarean sections, which can reduce risks that are associated with vertical HIV transmission to <2%, could increase prevalence of preterm birth if done earlier than the recommended 38 weeks. This analysis assesses LBW and preterm birth trends among infants who were born to HIV-infected women between 1989 and 2004. All infants were enrolled in the Pediatric Spectrum of Disease (PSD) study, a large, longitudinal HIV study in the United States.

Methods

PSD Project

Conducted from 1989 to 2004, the PSD study was 1 of the largest perinatal and pediatric HIV studies of HIV-infected and HIV-exposed children in the world. The PSD study reviewed newborn and pediatric medical charts of live-born, HIV-exposed/infected infants and HIV-infected children and adolescents and was performed under a protocol that was reviewed and approved by the institutional review board of the Centers for Disease Control and Prevention. PSD chart abstractions were conducted at 8 US geographic sites. PSD enrollees were identified through contact with key practitioners, review of HIV laboratory logs, and review of medical charts at the participating hospitals. Data that were collected from the pediatric medical charts included mode of delivery, birth weight, and gestational age of the infant. Additional information that was collected included maternal race/ethnicity, history of maternal prenatal care (recorded as any prenatal care, no prenatal care, or unknown prenatal care), month and year of infant testing, maternal antiretroviral therapy (ARV; beginning in 1995), the presence of maternal HIV symptoms at delivery, prenatal maternal HIV status, self-reported history of maternal drug use, and the child’s most severe HIV status based on the 1994 Centers for Disease Control and Prevention Pediatric HIV Classification.

Data on the maternal CD4 counts and viral loads are not included consistently in newborn/pediatric charts and were not collected in PSD. Data on type of delivery were collected throughout the study, but supplemental information on why cesarean sections were done was not collected until 2003, but such deliveries have increased.

Definitions

The primary outcomes of this study were LBW, defined as <2500 g, and preterm birth, occurring at <37 weeks' gestational age. Gestational age in PSD was abstracted from either pediatric or obstetric assessment in the medical charts; such assessments were not uniform throughout the PSD sites. Maternal HIV status was categorized by whether the mother's HIV was diagnosed before the child's birth (before pregnancy or during pregnancy) or at/after delivery. Symptomatic maternal HIV disease was defined as clinical HIV symptoms at delivery. A history of maternal drug abuse is defined as self-report any previous use of crack/cocaine or other street drugs and/or exchange of sex for drugs or money or urine drug screening. Prenatal care is defined only as maternal receipt of such care; PSD chart reviews did not assess the visit numbers or the trimester when care began. The age at first testing was calculated by subtracting the child’s birthday from month and year of initial testing.

Use of maternal ARV during pregnancy was recoded into a single categorical variable on the basis of receipt of any ARV during pregnancy and the maximum number of ARV drugs. Monotherapy was receipt of a single drug, dual therapy was use of 2 drugs, and triple therapy was HAART (receipt of 3 drugs, including either a PI or other non-PI triple ARV therapy).

Inclusion Criteria

The PSD analysis was limited to white non-Hispanic, black non-Hispanic, and Hispanic infants who were born in 1989 through 2004, for whom available data included both birth weight and gestational age, and whose HIV testing first was conducted during the first 30 days of life (neonatal period). Only infants who were tested during the neonatal period were included so that the ascertainment was consistent across birth years. Those criteria...
were met by 11,231 infants and included both HIV-infected and -exposed infants.

Statistical Analysis
We used SAS 8.0 to characterize PSD trends in LBW and preterm birth and also assessed risk factors for both LBW and preterm birth among women who had prenatal care. Because preterm birth and LBW are highly correlated, we excluded preterm birth from the multivariate assessment of LBW and did not include LBW in the assessment of preterm birth. In addition, we did not include cesarean section as a variable in the models for preterm birth because no statistically significant changes in gestational age were found after HAART became routinely available to pregnant women. Performance of elective cesarean sections could have decreased the mean gestational age if performed at an earlier age (see “Results”).

Results of the univariate and multivariate analyses for LBW and preterm birth are presented as odds ratios with 95% confidence intervals. All variables in the univariate analyses were entered in the logistic regression models. Risks that were significant at an α level of .10 remained in the model using a stepwise method. Perinatal exposure to 2 ARV drugs was used as the referent group because some European studies have suggested that PI-based HAART regimens during pregnancy can be associated with LBW and/or preterm birth.

RESULTS
Characteristics of Infants and Mothers
The majority of the 11,231 infants were black (6916 [62%]) and male (5776 [51%]). The mean birth weight was 2890 g (range: 415–5360 g); the mean gestational age was 37.3 weeks (range: 26–42 weeks). The mean gestational age of infants who were delivered by cesarean section was 37.5 weeks in 1999, the year in which cesarean delivery was shown to reduce vertical transmission, and declined to 37.3 weeks in 2004. The change in gestational age was not statistically significant. The mean gestational age of infants who were delivered vaginally was 38 weeks in 1999 and 37.8 weeks in 2004, a change that was not statistically significant. Almost one quarter (2485 [22%]) of PSD infants were born before 1994, when the Pediatric AIDS Clinical Trial 076 results demonstrated that a regimen of prenatal, intrapartum, and postpartum zidovudine could reduce the risk for perinatal HIV transmission by two thirds. The percentage of HIV-infected women who received any prenatal care increased from 48% in 1989 to 78% in 1995 (the year that HIV testing recommendations and policies were adapted for pregnant women) to a peak of 90% in 2001 and declined to 84% in 2004. More than half of the PSD mothers (6665 [59%]) had not received any ARV. The proportion of women who had cesarean sections increased from 19% in 1989 to 57% in 2004. A minority of mothers (1720 [15%]) had an unknown HIV status before pregnancy or delivery, a figure that declined from 43% in 1989 to 8% in 2004. Overall, one third of mothers reported illicit drug use, but reported use declined from 67% in 1989 to 12% in 2004. A minority of mothers had symptomatic HIV disease at delivery (755 [7%]).

Changes in LBW, Preterm Birth, and HIV Infection and Antiretroviral Medication
Between 1989 and 2004, the proportion of LBW infants declined from 35% (1989) to 21% (2004) with a nadir of 19% (2003). During the same period, preterm births declined from 35% (1989) to 22% (2005) with a low of 18% (2001). During the 15-year period, given both HAART and obstetric interventions including elective cesarean section before onset of labor, the proportion of HIV-infected infants declined from 28% in 1989 to 1% in 2004.

The declining trends of LBW in PSD were observed for all 3 study groups (black non-Hispanic, white non-Hispanic, and Hispanic); proportions of LBW were highest for black infants throughout the study. Averaged across the 1989–2004 period, LBW proportions were 25% for non-Hispanic black infants, 18% for non-Hispanic white infants, and 20% for Hispanic infants. The respective LBW declines between 1989 and 2004 were 36% to 22% among black non-Hispanic infants, 21% to 0% among white non-Hispanic infants, and 38% to 21% among Hispanic infants.

In the same period, preterm birth among PSD infants declined among all 3 racial/ethnic groups. Overall, preterm birth was 23% for non-Hispanic black infants, 17% for non-Hispanic white infants, and 18% for Hispanic infants. Between 1989 and 2004, preterm birth among non-Hispanic black infants declined from 39% to 22% (2004), among non-Hispanic white infants from 17% to 0%, and among Hispanic infants from 33% to 27%.

Trends in Maternal ARV Use
Documented maternal receipt of any ARV increased from 2% in 1991 to 82% in 2004 in PSD. Triple ARV therapy including either a PI or a non-PI regimen increased from 2% in 1996 to 72% in 2004. Among all women, triple ARV therapy with a PI increased from 1% in 1996 to 55% in 2004; triple therapy with a non-PI regimen increased from 1% in 1996 to 14% in 2004.

Factors Associated With LBW and Preterm Birth Among Women With Prenatal Care, 1989–2004
Factors that were associated with LBW in univariate analysis and multivariate logistic regression are shown in Table 1. In the logistic model, LBW was associated with history of maternal drug use, unknown maternal HIV
status before delivery, symptomatic maternal HIV disease, black race, Hispanic ethnicity, and infant HIV infection. Male gender was predictive of normal birth weight.

Factors that were associated with preterm birth in univariate analysis and multivariate logistic regression are shown in Table 2. In the logistic model, preterm birth was associated with history of maternal drug use, symptomatic maternal HIV disease, no ARV therapy, 3-drug HAART therapy including a PI, black race, and infant HIV infection.

**DISCUSSION**

This study presents encouraging evidence that LBW and preterm birth both have declined among PSD infants during a period (1989–2004) when therapy for maternal treatment and perinatal HIV prevention evolved into highly potent HAART regimens. \(^{17}\) Simultaneously, vertical HIV transmission from mother to child declined from 26% to 2% or less in the United States. \(^{34}\) The declines occurred during a period, beginning in 1995, of increased emphasis on routine HIV testing of all pregnant women \(^{16–18}\) and close follow-up and comprehensive pregnancy management.

Compared with the general US population, LBW and preterm birth still are markedly higher among infants who are born to HIV-infected women. \(^{6–10}\) LBW and preterm prevalences as high as 48% and 38%, respectively, \(^{11}\) have been reported. Although this study focuses on the PSD cohort, \(^{12}\) it is likely that the declines in LBW and preterm birth can be observed in other US perinatal HIV cohorts. The prevalences of LBW and preterm birth in the PSD cohort remain higher than the almost 8% and 12% reported for the general US population in 2004, \(^{2}\) but the declining trends of LBW and preterm births in all 3 ethnic groups represent significant health gains for infants who are born to HIV-infected mothers.

This PSD study did find consistent risks for LBW and preterm birth among infants who were born to HIV-infected women. A history of maternal drug abuse, symptomatic maternal HIV disease, black race, and infant HIV infection were associated with both LBW and preterm birth. All of these risks are well-documented associations with LBW and preterm birth in other studies \(^{3,6–14,39–43}\) that focused on other high-risk groups of pregnant women, including those with HIV.

Importantly, this study did not find any consistent association with HAART or lack of ARV with LBW. We did find an association between preterm birth and both no ARV and triple ARV therapy with a PI. Studies from Europe, the United States, and Latin America have found inconsistent associations between LBW and preterm birth. \(^{10,16–27}\) This study found such an association, but PSD data are insufficient to answer the question about associations between ARV and adverse maternal

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight &lt;2500 g (n = 1744, n (%))</th>
<th>Weight ≥2500 g (n = 7049, n (%))</th>
<th>Crude OR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal factors</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug use</td>
<td>661 (27)</td>
<td>1771 (73)</td>
<td>1.82 (1.63–2.04)</td>
<td>1.80 (1.61–2.02)</td>
</tr>
<tr>
<td>No drug use history</td>
<td>1083 (17)</td>
<td>5278 (83)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Unknown HIV/AIDS before delivery</td>
<td>208 (23)</td>
<td>690 (77)</td>
<td>1.25 (1.05–1.48)</td>
<td>1.26 (1.07–1.50)</td>
</tr>
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<td>Known HIV/AIDS before delivery</td>
<td>1536 (19)</td>
<td>6359 (81)</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Symptomatic HIV</td>
<td>174 (27)</td>
<td>472 (73)</td>
<td>1.54 (1.28–1.86)</td>
<td>1.43 (1.18–1.72)</td>
</tr>
<tr>
<td>Not symptomatic HIV</td>
<td>1570 (19)</td>
<td>6577 (81)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>ARV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>585 (23)</td>
<td>1980 (77)</td>
<td>1.46 (1.20–1.76)</td>
<td>1.46 (1.20–1.76)</td>
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<td>1 drug</td>
<td>520 (20)</td>
<td>2101 (80)</td>
<td>1.22 (1.01–1.48)</td>
<td>1.22 (1.01–1.48)</td>
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<tr>
<td>2 drugs</td>
<td>176 (17)</td>
<td>866 (83)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>3 drugs: HAART, non-PI</td>
<td>330 (19)</td>
<td>1451 (81)</td>
<td>1.12 (0.91–1.38)</td>
<td>1.12 (0.91–1.38)</td>
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<tr>
<td>3 drugs: HAART, PI</td>
<td>133 (17)</td>
<td>649 (83)</td>
<td>1.01 (0.78–1.30)</td>
<td>1.01 (0.78–1.30)</td>
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<tr>
<td><strong>Infant factors</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1135 (22)</td>
<td>4092 (78)</td>
<td>1.41 (1.15–1.73)</td>
<td>1.63 (1.33–1.99)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>479 (17)</td>
<td>2295 (83)</td>
<td>1.06 (0.86–1.30)</td>
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<tr>
<td>White</td>
<td>130 (16)</td>
<td>662 (84)</td>
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<td>Reference</td>
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<tr>
<td>Male</td>
<td>806 (18)</td>
<td>3693 (82)</td>
<td>0.78 (0.70–0.87)</td>
<td>0.78 (0.70–0.87)</td>
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<tr>
<td>Female</td>
<td>938 (22)</td>
<td>3356 (78)</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Gestational age</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 wk</td>
<td>1092 (68)</td>
<td>522 (32)</td>
<td>20.94 (18.32–23.67)</td>
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</tr>
<tr>
<td>≥37 wk</td>
<td>652 (9)</td>
<td>6527 (91)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected</td>
<td>188 (26)</td>
<td>543 (74)</td>
<td>1.45 (1.21–1.73)</td>
<td>1.34 (1.12–1.60)</td>
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<tr>
<td>Negative/indeterminate</td>
<td>1556 (19)</td>
<td>6506 (81)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; aOR, adjusted odds ratio.
outcomes, in part because maternal CD4 counts, viral load, and details of drug therapy were not collected.

The increased emphasis on HIV testing for pregnant women opened the door to improve both access to prenatal care and pregnancy outcome. Despite the reduction of perinatal HIV transmission in the United States, ongoing surveillance is needed to monitor pregnancy outcomes as more HIV-infected women choose to bear children. This study found that the PSD cohort experienced better access to prenatal care, and ARV improved during the same period when vertical HIV transmission declined. However, the study cannot determine whether access to ARV and prenatal care are causal events in the declines of LBW and preterm delivery.

The PSD cohort is 1 of the largest pediatric/perinatal cohorts assembled to track the natural history of HIV and AIDS. Infants were enrolled in PSD during a span of time (1989–2004) that covered the entire spectrum of the HIV/AIDS epidemic and evolving therapy. There are certain limitations to the PSD data. First, the study is based on pediatric hospital chart review, so maternal information is limited. Second, documentation of LBW and preterm birth trends does not explain why or how these events happened. In addition, the PSD database lacks data about maternal viral load, maternal CD4 counts during pregnancy and at delivery, previous preterm delivery, reason for cesarean section, and maternal socioeconomic status. Each of these factors can influence the outcome of pregnancy, and the lack of such data limits this study’s ability to assess more completely the factors that are associated with the declines in LBW and preterm birth.

**CONCLUSIONS**

Between 1989 and 2004, LBW and preterm birth both have declined among infants of HIV-infected women who were enrolled in the PSD cohort. Both declines occurred among all racial/ethnic groups in contrast to trends in the general US population. Among women who had prenatal care, preterm birth was associated with lack of ARV and HAART therapy that included a PI.

**REFERENCES**


5. Desenclos JC, Scaggs M, Wroten JE. Characteristics of mothers

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**TABLE 2** Risk Factors for Preterm Birth Among 8793 Infants Who Were Born to HIV-Infected Mothers With Prenatal Care During an Era of Changing ARV: PSD, 1998–2004

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preterm (&lt;37 wk; n = 1614), n (%)</th>
<th>Term (≥37 wk; n = 7179), n (%)</th>
<th>Crude OR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
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<tr>
<td><strong>Maternal factors</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug use</td>
<td>593 (37)</td>
<td>1021 (63)</td>
<td>1.69 (1.50–1.89)</td>
<td>1.61 (1.43–1.81)</td>
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<td>No drug use history</td>
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<td>5340 (74)</td>
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<tr>
<td>Unknown HIV/AIDS before delivery</td>
<td>180 (20)</td>
<td>718 (80)</td>
<td>1.13 (0.95–1.35)</td>
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<tr>
<td>Known HIV/AIDS before delivery</td>
<td>1434 (18)</td>
<td>6461 (82)</td>
<td>Reference</td>
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<tr>
<td>Symptomatic HIV</td>
<td>159 (24)</td>
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<td>1.50 (1.24–1.80)</td>
<td>1.34 (1.10–1.62)</td>
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<td>Not symptomatic HIV</td>
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<td>6692 (82)</td>
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<td>ARV</td>
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<tr>
<td>None</td>
<td>548 (21)</td>
<td>2017 (79)</td>
<td>1.64 (1.34–2.01)</td>
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<td>1 drug</td>
<td>457 (17)</td>
<td>2164 (83)</td>
<td>1.28 (1.04–1.57)</td>
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<td>148 (14)</td>
<td>896 (86)</td>
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<td>3 drugs: HAART, PI</td>
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<td>650 (83)</td>
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<td>1.21 (1.04–1.40)</td>
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<tr>
<td>Female</td>
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<td>3509 (82)</td>
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<td>Birth weight, g</td>
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<td>&lt;2500</td>
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<td>20.94 (18.32–23.94)</td>
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<td>≥2500</td>
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<td>6527 (93)</td>
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<td></td>
</tr>
<tr>
<td>Infected</td>
<td>200 (27)</td>
<td>531 (73)</td>
<td>1.77 (1.48–2.11)</td>
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<tr>
<td>Negative/indeterminate</td>
<td>1414 (18)</td>
<td>6648 (83)</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>

All mothers had prenatal care. OR indicates odds ratio; CI, confidence interval; aOR, adjusted odds ratio.
16. European Collaborative Study; Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. AIDS. 2000;14:2913–2920


Nephrotic Syndrome in the First Year of Life: Two Thirds of Cases Are Caused by Mutations in 4 Genes (NPHS1, NPHS2, WT1, and LAMB2)

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. Mutations in each of the NPHS1, NPHS2, WT1, and LAMB2 genes have been implicated in nephrotic syndrome, manifesting in the first year of life. The relative frequency of causative mutations in these genes in children with nephrotic syndrome manifesting in the first year of life is unknown. Therefore, we analyzed all 4 of the genes jointly in a large European cohort of 89 children from 80 families with nephrotic syndrome manifesting in the first year of life and characterized genotype/phenotype correlations.

METHODS. We performed direct exon sequencing of NPHS1, NPHS2, and the relevant exons 8 and 9 of WT1, whereas the LAMB2 gene was screened by enzymatic mismatches cleavage.

RESULTS. We detected disease-causing mutations in 66.3% (53 of 80) families (NPHS1, NPHS2, WT1, and LAMB2: 22.5%, 37.5%, 3.8%, and 2.5%, respectively). As many as 84.8% of families with congenital onset (0–3 months) and 44.1% with infantile onset (4–12 months) of nephrotic syndrome were explained by mutations. NPHS2 mutations were the most frequent cause of nephrotic syndrome among both families with congenital nephrotic syndrome (39.1%) and infantile nephrotic syndrome (35.3%), whereas NPHS1 mutations were solely found in patients with congenital onset. Of 45 children in whom steroid treatment was attempted, only 1 patient achieved a lasting response. Of these 45 treated children, 28 had causative mutations, and none of the 28 responded to treatment.

CONCLUSIONS. First, two thirds of nephrotic syndrome manifesting in the first year of life can be explained by mutations in 4 genes only (NPHS1, NPHS2, WT1, or LAMB2). Second, NPHS1 mutations occur in congenital nephrotic syndrome only. Third, infants with causative mutations in any of the 4 genes do not respond to steroid treatment; therefore, unnecessary treatment attempts can be avoided.

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doi:10.1542/peds.2006-2164

Key Words
nephrotic syndrome, LAMB2, NPHS1, NPHS2, WT1

Abbreviations
NS—nephrotic syndrome
NSFL—nephrotic syndrome manifesting in the first year of life
CNS—congenital nephrotic syndrome
INS—infantile nephrotic syndrome
OMIM—Online Mendelian Inheritance in Man
ESRD—end-stage renal disease

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Fourth, there are most likely additional unknown genes mutated in early-onset nephrotic syndrome.

Nephrotic Syndrome (NS), the association of gross proteinuria, hypoalbuminaemia, edema, and hyperlipidemia, is often a life-threatening condition when manifesting as NS in the first year of life (NSFL). Whereas standardized treatment protocols are widely used for older children, in whom a response rate to steroid treatment of ≤80% can be observed, clinical decision-making in children with NSFL remains challenging. Descriptively, NSFL has been classified as congenital NS (CNS), manifesting in utero or during the first 3 months of life, or infantile NS (INS), with onset between 4 months and 1 year of age.

Over the last few years, inherited impairments of the glomerular filtration barrier have been identified as important causes of NS. The glomerular filtration barrier separates the bloodstream from the urinary space and consists of 3 layers, fenestrated endothelium, glomerular basement membrane, and podocyte foot processes. The interdigitating podocyte foot processes are connected by the slit-diaphragm. The protein nephrin, encoded by the NPHS1 gene, represents a major component of this slit-diaphragm and connects foot processes in a zipper-like fashion. Mutations of NPHS1 were identified by Kestila et al as the cause of CNS of the Finnish type (Online Mendelian Inheritance in Man [OMIM] No. 256300). They result in a disruption of the glomerular filtration barrier and consecutive massive protein loss. Detailed studies on NPHS1 were undertaken, and 2 mutations Finmajor (L411Sx90) and Finminor (R1109X) were identified as the predominant cause of CNS in the Finnish population. Mutations in the NPHS2 gene, encoding podocin, were then identified by Boute et al as a cause of autosomal recessive steroid-resistant NS (OMIM No. 600995) among older children. Podocin represents an essential component of the slit-diaphragm and a close interactor of nephrin. Intracellular retention of podocin mutants and consequentially altered trafficking of nephrin have been demonstrated. Mutations of podocin also result in a dysfunction of the glomerular filtration barrier. The preceding studies demonstrated that children with NPHS2 mutations may manifest as NSFL, and no systematic evaluation focusing on NPHS2 in infants has been undertaken. Furthermore, we recently reported dominant de novo mutations in exons 8 and 9 of the WT1 gene (encoding the transcription factor Wilms tumor suppressor gene 1) as a cause of isolated steroid-resistant NS in infants and children. Transcriptional activation of NPHS1 and upregulation of NPHS1 mRNA by WT1 have been shown. These findings explain why mutations in WT1 result in NS. In addition, WT1 mutations have been detected in patients with Wilms tumor (OMIM No. 194070), Denys-Drash syndrome (OMIM No. 194080), and Frasier syndrome (OMIM No. 136680). Finally, laminin-β2 as a component of the glomerular basement membrane is crucial for podocyte foot process architecture and stability but is also found in other organs, such as the eye. Missense mutations of the LAMB2 present with a spectrum of symptoms reaching from isolated early onset NS to intermediate phenotypes, whereas patients with truncating LAMB2 mutations present with the full syndromic phenotype of Pierson syndrome with NS, diffuse mesangial sclerosis, distinct eye anomalies, and mental retardation (OMIM No. 609049).

Mutations in the genes TRPC6, ACTN4, and CD2AP cause adult-onset NS. They follow a dominant pattern of inheritance and lead to focal segmental glomerulosclerosis. Because they have not been reported in children with NSFL, they were not included in this study.

Mutations in NPHS1, NPHS2, WT1, or LAMB2 in NSFL have been described in small patient cohorts only. These studies mainly focused on 1 of these genes respectively. No reliable data on the relative frequencies of mutations in these genes among children with NSFL are available. We, therefore, examined within a large cohort of 975 children with NS ascertained over 10 years, the subgroup of 89 European infants with NSFL for mutations in NPHS1, NPHS2, WT1, and LAMB2. Here we demonstrate that, in two thirds of children with NSFL, a genetic cause can be identified in 1 of these 4 genes and that children with these mutations do not respond to steroid treatment.

Patients and Methods

Patient and Data Recruitment
In this worldwide study, DNA samples and clinical data from 975 children with NS have been ascertained between 1996 and 2005 (www.renalgenes.org/nephrotic_syndrome.html). Patient recruitment after informed consent has been described by Ruf et al. The focus of this study was on a subgroup of children manifesting with NSFL. Patients were enrolled by pediatric nephrologists from specialized centers only. Diagnosis of NS and, where applicable, response to steroid treatment were classified according to published criteria. Evaluation of clinical characteristics was based on a standard questionnaire described previously (www.renalgenes.org/nephrotic_syndrome.html). Parameters characterized in this analysis were: age of onset, ethnic origin, histology findings on kidney biopsies or nephrectomy, response to standard steroid treatment, and clinical course from first presentation to last clinical examination.

Between 1996 and 2005, 107 children suffering from either sporadic or familial NSFL were enrolled in the...
study. To better define our group by ethnic origin, we excluded 18 non-European children from Asia and North America. The remaining 89 patients were of non-Scandinavian European descent, including 25 patients of Turkish descent. The 89 European patients studied were from 80 different families and included 71 families with 1 affected child and 9 families with 2 affected children with NSFL (Table 1). Parental consanguinity was documented for 4 sibling pairs and 15 children with sporadic NSFL. Fifty-four children from 46 families were classified as having INS with first documented presentation in utero or within 90 days from birth (13 patients of Turkish descent). Thirty-five children from 34 families were classified as having CNS with first documented presentation between 91 and 365 days (12 patients of Turkish descent). Partial data on 31 patients from 25 families have been published previously. In this work, we will refer to the number of patients studied when assessing clinical data and to the number of families studied when assessing genetic data, because affected siblings may follow a different clinical course but should bear the same mutations.

Mutation Analysis by Direct Sequencing for \( \text{NPHS1}, \text{NPHS2}, \) and \( \text{WT1} \)

Genomic DNA was directly isolated from blood samples using the Puregene DNA purification kit (Gentra, Minneapolis, MN) following the manufacturer’s guidelines. Mutation analysis was performed by direct sequencing of all 29 exons of \( \text{NPHS1} \), all 8 exons of \( \text{NPHS2} \), and exons 8 and 9 of \( \text{WT1} \). \( \text{WT1} \) analysis was limited to exons 8 and 9, because mutations of this gene accounting for isolated NS have only been reported in these 2 exons. All of the exons were amplified by PCR and sequenced as described previously. For sequence analysis, the software SEQUENCHER (Gene Codes, Ann Arbor, MI) was used. For all of the detected mutations and new sequence variants, sequencing of both strands was performed. Segregation of these changes was confirmed by direct sequencing of parental DNA samples where available. The absence of previously unreported mutations was shown in 160 control chromosomes from healthy individuals of matched ethnic origin.

**TABLE 1** Frequency of Disease-Causing Mutations in \( \text{NPHS1}, \text{NPHS2}, \text{LAMB2}, \) and \( \text{WT1} \) in 80 Families With NSFL

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>No. of Families</th>
<th>Mutations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total, n (%)</td>
<td>( \text{NPHS1}, n ) (%)</td>
<td>( \text{NPHS2}, n ) (%)</td>
</tr>
<tr>
<td>First year of life (CNS + INS)</td>
<td>80</td>
<td>53 (66.3)</td>
<td>18 (22.5)</td>
<td>30 (37.5)</td>
</tr>
<tr>
<td>CEU</td>
<td>57</td>
<td>43 (75.5)</td>
<td>12 (21.0)</td>
<td>27 (47.4)</td>
</tr>
<tr>
<td>Turkish</td>
<td>23</td>
<td>10 (43.5)</td>
<td>6 (26.1)</td>
<td>3 (13.1)</td>
</tr>
<tr>
<td>CNS</td>
<td>46</td>
<td>39 (84.8)</td>
<td>18 (39.1)</td>
<td>18 (39.1)</td>
</tr>
<tr>
<td>CEU</td>
<td>35</td>
<td>32 (91.4)</td>
<td>12 (34.3)</td>
<td>18 (51.4)</td>
</tr>
<tr>
<td>Turkish</td>
<td>11</td>
<td>7 (63.6)</td>
<td>6 (54.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>INS</td>
<td>34</td>
<td>15 (44.1)</td>
<td>0 (0.0)</td>
<td>12 (35.3)</td>
</tr>
<tr>
<td>CEU</td>
<td>22</td>
<td>12 (54.5)</td>
<td>0 (0.0)</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Turkish</td>
<td>12</td>
<td>3 (25.0)</td>
<td>0 (0.0)</td>
<td>3 (25.0)</td>
</tr>
</tbody>
</table>

CEU indicates central European.
Frequencies of Mutations

Frequencies of detected mutations in *NPHS1*, *NPHS2*, *WT1*, or *LAMB2* in 80 European families with NSFL are summarized in Table 1. The correlation of detected mutations with exact age at first clinical presentation for 89 affected individuals is shown in Fig 1.

Mutation analysis of *NPHS1*, *NPHS2*, *WT1*, and *LAMB2* revealed disease-causing mutations in 66.3% of all of the families with NSFL (Table 1), thereby identifying the molecular cause of NSFL in 53 of 80 of all studied families. Disease-causing mutations in *NPHS1* were found in 22.5% (18 of 80) of all of the families. Mutations in *NPHS2* were identified in 37.5% (30 of 80) of all of the families as the most common cause of NSFL and accounted for 56.6% (30 of 53) of all of the causative mutations. Dominant mutations in *WT1* were found in 3.8% (3 of 80), and recessive mutations in *LAMB2* in 2.5% (2 of 80) of families. Among 33.7% (27 of 80) of our families in whom NSFL was not explained by mutations in *NPHS1*, *NPHS2*, *WT1*, or *LAMB2*, 4 children were carriers of a single heterozygous *NPHS1* mutation, which cannot be considered causative in itself. All 9 of the sibling pairs in this study carried mutations in *NPHS1* (3), *NPHS2* (4), or *LAMB2* (2). Seventeen of these 18 children with “familial” NSFL manifested within the first 3 months of life and 1 child at 4 months of age. The mutation rate of families with >1 affected child was, thus, 100% (9 of 9); the rate among families with 1 affected child only was 62% (45 of 71).

The frequencies of mutations in *NPHS1*, *NPHS2*, *WT1*, and *LAMB2* differed between children with congenital and infantile onset (Table 1). In CNS (onset 0–3 months), mutations were found in 1 of the 4 genes in 84.8% (39 of 46) of all families. The distribution was *NPHS1*, *NPHS2*, *WT1*, and *LAMB2*: 39.1% (18 of 46), 39.1% (18 of 46), 2.2% (1 of 46), and 4.4% (2 of 46). In 15.2% (7 of 46) of families with CNS in whom the disease could not be explained by mutations in these 4 genes, 4 children were carriers of a single heterozygous *NPHS1* mutation, which cannot be considered causative in itself. All 9 of the sibling pairs in this study carried mutations in *NPHS1* (3), *NPHS2* (4), or *LAMB2* (2). Seventeen of these 18 children with “familial” NSFL manifested within the first 3 months of life and 1 child at 4 months of age. The mutation rate of families with >1 affected child was, thus, 100% (9 of 9); the rate among families with 1 affected child only was 62% (45 of 71).

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genes, we detected only 1 heterozygous NPHS1 mutation in 3 families. In NPHS1, all of the patients with disease-causing mutations presented as CNS, that is, within the first 3 months of life. Manifestation of children with NPHS1 mutations was, thus, limited to congenital onset. In INS (onset 4–12 months), mutations were found in 44.1% (15 of 34) of families. The distribution was NPHS1, NPHS2, WT1, and LAMB2: 0.0% (0 of 34), 35.2% (12 of 34), 5.9% (2 of 34), and 2.9% (1 of 34; Table 1). The percentage of patients in whom the disease was explained by mutations in these 4 genes, thus, decreased with increasing age at first presentation. Mutations in LAMB2 and WT1 were a rare cause of NSFL between both groups, CNS and INS, and accounted together for NSFL in only 6.3% (5 of 80) of all families.

The frequencies of mutations in NPHS1, NPHS2, WT1, and LAMB2 were different between children of central European and of Turkish descent (Table 1 and Fig 1). In families of central European descent, mutations were found in 75.5% (43 of 57) of families. The distribution was, respectively, NPHS1, NPHS2, WT1, and LAMB2: 21.0% (12 of 57), 47.4% (27 of 57), 5.3% (3 of 57), and 1.8% (1 of 57; Fig 1A). Mutations were found in 43.5% (10 of 23) of families of Turkish descent. The distribution was, respectively, NPHS1, NPHS2, WT1, and LAMB2: 26.1% (6 of 23), 13.1% (3 of 23), 0.0% (0 of 23), and 4.3% (1 of 23; Fig 1B). Although in families of central European descent, mutations in NPHS2 represented the most frequent cause of CNS (18 of 35 [51.4%]), no mutations of this gene were seen in 13 families of Turkish descent with CNS (Fig 1).

Spectrum of Mutations
An exact reference of all of the detected mutations is given in the Appendix.

NPHS1
A spectrum of 20 different homozygous or compound heterozygous mutations was found in NPHS1. One single Fin_major (F1017) mutation, but no Fin_minor mutations, were seen. In 3 patients presenting with CNS and a fourth patient presenting at 3.5 months of age, only a single heterozygous NPHS1 mutation was detected. Four patients with compound heterozygous disease-causing NPHS1 mutations carried the NPHS2 sequence variant R229Q, in addition, which is considered a polymorphism.

NPHS2
A founder mutation R138Q has been described by Boute et al. We confirm R138Q as the most frequent mutation as follows. In 30 families (18 with CNS and 12 with INS) with NPHS2 mutations, the founder mutation R138Q was detected homozygously in 12 families and compound heterozygously in 8 families. In CNS, all of the patients with NPHS2 mutations carried ≥1 loss of function mutation or R138Q, with the exception of patient F876. In INS, all of the patients with NPHS2 mutations, except for patient F1336, showed either a loss of function mutation or the founder mutation R138Q. The spectrum of detected mutations in NPHS2 was, therefore, similar for patients with CNS and INS.

Genotype Versus Onset of End-Stage Renal Disease
Evaluation of the clinical follow-up was possible for 88.6% (79 of 89) of patients. At last examination, 46.8% (37 of 79) of children had not reached end-stage renal disease (ESRD), 6.3% (5 of 79) were in ESRD and had not received a kidney transplant, 27.8% (22 of 79) had received a kidney transplant and did not experience transplant failure, 7.6% (6 of 79) had suffered from kidney-transplant failure, and 11.4% (9 of 79) were deceased.

Progression to ESRD was more rapid in children with NPHS1 mutations than in children with NPHS2 muta-
tions ($P = .04$). Nine children with $NPHS1$ mutations in ESRD had progressed to ESRD within a mean interval of 4.6 years (range: 1.8–9.3 years) from diagnosis, whereas the equivalent group of 16 children with $NPHS2$ mutations had developed ESRD after a mean of 6.6 years (range: 2.8–10.0 years). Four of the 19 children with $NPHS1$ mutations had died of their disease, whereas all 27 children with $NPHS2$ mutations were alive. Two of 17 children with $NPHS2$ mutations and kidney transplant ($F1221$ and $A674$) showed recurrence of focal segmental glomerulosclerosis in the transplant, and 2 had a rejection of their transplant ($A126$ and $F1030$). In 1 patient with disease-causing $NPHS1$ mutations ($F475$ II-1), no function was obtained, and in 1 patient with a single $NPHS1$ mutation ($A693$), the transplant was rejected.

**DISCUSSION**

We present data on 89 children from 80 different families of European descent manifesting with NS in the first year of life. This is the largest cohort of children with this diagnosis published to date who underwent a combined molecular genetic evaluation of $NPHS1$ and $NPHS2$ and the first to include $WT1$ and $LAMB2$.

We found a high rate of mutations clarifying the molecular pathogenesis in 66.3% of all 80 families with NSFL and in 84.8% of all families with CNS by screening the 4 known genes $NPHS1$, $NPHS2$, $WT1$, and $LAMB2$ only. These data show that NSFL is, to a large extent, a monogenic disease, in which genetic testing should be considered as an early diagnostic step. These findings have additional clinical relevance, because data on the relative frequency of genetically caused NSFL has been missing, and data on the prevalence of steroid responsiveness among children with NSFL is sparse. The efficacy of steroid treatment in infants with NS is considered to be low. However, the documented initiation of steroid treatment in more than half of all patients (45 of 89) reported here illustrates that this treatment remains in clinical practice in children with NSFL.

For 45 children in this study who were treated with steroids, an initial response to treatment was reported in 6 children only. Just 1 of these 6 initially responsive children (A90) achieved a remission but did not carry a disease-causing mutation in 1 of the 4 analyzed genes. In 28 (62.2%) of 45 treated children, we found disease-causing mutations in $NPHS1$, $NPHS2$, $WT1$, or $LAMB2$. None of the children who were treated with steroids and who carried a mutation showed a response. We, therefore, conclude that mutation analysis of $NPHS1$, $NPHS2$, $WT1$, or $LAMB2$ is warranted in children with NSFL. If DNA analysis reveals pathogenic mutations, the children should be spared the adverse effects of unwarranted steroid treatment attempts.

Our data show that children with mutations in $NPHS1$ always manifest within the first 3 months of life. Only small numbers of cases with $NPHS2$ mutations and manifestation during these first 3 months of life have been described. Our findings now identify $NPHS2$ mutations as a frequent cause of CNS among patients of central European descent (51.4%). This finding emphasizes the necessity to include in the mutation analysis of CNS not only $NPHS1$ but also $NPHS2$. If no mutations are found in these 2 genes, the screening of $WT1$ and $LAMB2$ may be indicated, because mutations were found in 3.8% and 2.5% of CNS, respectively.

The relative frequency of mutations in $NPHS1$, $NPHS2$, $WT1$, or $LAMB2$ in patients with NSFL should be seen in the context of the patients’ ethnic origin. Turkish children in our cohort had a higher percentage of absence of mutations in any of the 4 genes (56.5%) compared with central European children (24.5%). In contrast to central European children, no $NPHS2$ mutations were found in Turkish children with CNS. The spectrum of mutations in NSFL has been reported to vary by ethnicity for $NPHS1$ and $NPHS2$. Mutations in $NPHS1$ show a high incidence in the Finnish population and are almost the exclusive cause of CNS there. Two truncating mutations, $F1$ major and $F1$ minor, of $NPHS1$ are predominantly seen in the Finnish population. Outside Finland, however, this Finnish-type CNS is less frequent, and a diversity of different mutations are found in $NPHS1$. Both findings are further supported by our data on mutations, so that further studies will be necessary to evaluate the frequency of mutations in these genes in NSFL among children of different ethnic origin.

Our results reveal a specific spectrum of “severe” $NPHS2$ mutations resulting in NSFL. Twenty-eight (93.3%) of 30 families with $NPHS2$ mutations carried $\geq 1$ truncating mutation or the founder mutation R138Q, a finding also supported by data from Weber et al. Published functional data may provide the first answers as to why these specific alleles cause NS with early onset. It was shown that the $NPHS2$ variant R138Q, which we frequently detected in our patients, is retained in the endoplasmatic reticulum disrupting the targeting of $NPHS1$ to lipid raft microdomains. Based on these experimental findings, Nishibori et al speculated that this altered nephrin positioning resulting from the R138Q mutation in $NPHS2$ could resemble CNS of the Finnish type not only pathophysiologically but also clinically.

**CONCLUSIONS**

Based on our findings, we draw the following conclusions: (1) NSFL is, to a large extent, a monogenic disease, and two thirds of NSFL can be explained by mutations in these 4 genes ($NPHS1$, $NPHS2$, $WT1$, or $LAMB2$) only; (2) children with $NPHS1$ mutations manifest as CNS only, whereas mutations in $NPHS2$ are an additional frequent cause of CNS among central European children; (3) infants with causative mutations in any of the 4 genes do not respond to steroid treatment, and, therefore, unne-
essary treatment attempts can be avoided; and (4) the identification of additional genes as mutated in NSFL can be anticipated.

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REFERENCES

24. Karle S, Uetz B, Ronner V, et al. Novel mutations in NPHS2 are


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<th>First Clinical Presentation With</th>
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<td>CNF</td>
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<td>—</td>
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| F228     | 3          | M German          | N      | 0.0       | Dystrophy     | Mental retardation | DMS            | ND             | 3.4                         | 4.2              | 34              | NA            | NA           | NA             | NA             | NA             | KT, functional  | [c.1738>G] +   | [c.249C>T] +    | [V520 + 2>T]A | [382X7] | 1
| F294     | 3          | M Turkish         | Y      | 0.0       | NS, ED        | —               | ND             | 3.4                         | 4               | 3               | NA            | NA           | NA             | NA             | NA             | KT, functional  | [V520 + 2>T]A | [c.1814delC] + | [c.1814delC]    | [F873W] +       | [F873W] |
| F435     | 3          | M Italian         | NN     | 0.0       | NS            | NN             | NN             | NN             | NN                          | NN               | NN              | NN            | NN           | NN             | NN             | NN             | Deceased         | [c.2617delC] +   | [c.2617delC] +    | [F873W] +        | [F873W] |
| F439     | 3          | M German          | N      | 0.0       | ED, premature | Growth retardation | ND             | ND, NEC        | 2.9                         | 3.8              | 2.9             | NA            | NA           | NA             | NA             | NA             | KT, functional  | [c.1814delC] +   | [c.1814delC]    | [F873W] +        | [F873W] |
| F451     | 3          | M German          | N      | 0.0       | Elevated AFP, postnatal ED | Intracerebral hemorrhage | ND             | NN             | NN                          | —               | —               | Deceased       | NA           | NA             | NA             | NA             | NA             | Deceased         | [c.686G>A] +   | [c.686G>A] +    | [F873W] +        | [F873W] |
| F475     | II-1       | F German          | Y      | 0.0       | Acute ED at birth | Failure to thrive | MCNS           | SR             | 1.8                         | 4.8              | 1.8             | NA            | NA           | NA             | NA             | NA             | KT, relapsing failure | [c.2617delC] +   | [c.2617delC] +    | [F873W] +        | [F873W] |
| F475     | II-2       | F German          | Y      | 0.0       | Discrete ED at birth | Failure to thrive | ND             | SR, CSA, NRF  | 3.5                         | 3               | NA              | 3.5           | NA           | NA             | NA             | NA             | ESRD, no KT     | [c.2617delC] +   | [c.2617delC] +    | [F873W] +        | [F873W] |
| F571     | II-1       | F Turkish         | Y      | 0.1       | Acute ED, HT, hypocalcemia | Pyloric stenosis, bilateral hernia, congenital CMV infection | MCNS           | SR, CSA, NRF  | <4                          | 6                | <4             | NA            | NA           | NA             | NA             | NA             | KT, functional  | [c.1379G>A] +   | [c.1379G>A] +    | [F873W] +        | [F873W] |
| F571     | II-2       | M Turkish         | N      | 0.0       | ED, HT        | —               | ND             | NN             | 5.5                         | NA               | 5.5             | NA            | NA           | NA             | NA             | NA             | ESRD, no KT     | [c.34.54 + 51delACC] + | [c.34.54 + 51delACC] + | [F873W] +        | [F873W] |
| F626     | 3          | F Turkish         | Y      | 0.0       | Congenital SP, SGA, PU, HU | Small for gestational age | MIPCPG         | SR             | —                           | —               | —               | —             | —            | —             | —             | —             | —             | Deceased         | [c.34.54 + 51delACC] + | [c.34.54 + 51delACC] + | [F873W] +        | [F873W] |
| F806     | 3          | F Serbian         | NN     | 0.2       | ED            | —               | MP             | ND             | 7.8                         | 9.1              | 7.6             | —             | —            | NA             | NA             | NA             | KT, functional  | [c.34.54 + 51delACC] + | [c.34.54 + 51delACC] + | [F873W] +        | [F873W] |
| F1017    | 3          | M German          | N      | 0.0       | NN            | Failure to thrive | MS             | ND             | 9.3                         | 10.5             | 9.3             | NA            | NA           | NA             | NA             | NA             | KT, functional  | [c.1258T>C] +   | [c.1258T>C] +    | [F873W] +        | [F873W] |
| F1093    | 3          | F Turkish         | Y      | 0.1       | ED, pallor    | Prematurity, apnoea, bradycardia-syndrome, anemia | CNF            | ND             | NA                         | NA               | NA              | NA            | 3.2          | No ESRD         | NA             | NA             | NA             | No ESRD         | [c.2014G>C] +   | [c.2014G>C] +    | [F873W] +        | [F873W] |
| F1296    | II-1       | F German          | Y      | 0.1       | ED            | —               | ND             | ND             | ND                         | NA               | NA              | NA            | 1.5          | No ESRD         | NA             | NA             | NA             | No ESRD         | [c.2617delC] +   | [c.2617delC] +    | [F873W] +        | [F873W] |
| F1328    | II-1       | M German          | Y      | 0.0       | ED            | Mental retardation, hypertension | FSG5           | SR, ACE-I    | NA                         | NA               | NA              | 2.5           | 2.5          | No ESRD         | NA             | NA             | KT             | [c.385C>T] +   | [c.1868G>T] +    | [L.129F] +       | [G623F] |
| F1328    | II-3       | M German          | Y      | 0.0       | ED            | —               | ND             | ND             | ACE-I                      | NA               | NA              | 2.1           | 2.1          | No ESRD         | NA             | NA             | KT             | [c.385C>T] +   | [c.1868G>T] +    | [L.129F] +       | [G623F] |
| A229     | M Turkish   | N      | 0.2       | ED            | —               | ND             | ND             | NN             | NN                         | NN               | NN              | —             | —            | —             | —             | —             | Deceased         | [c.1001T>C] +   | [c.1007C>T] +    | [L.334P] +       | [L.334P] |
| A650     | II-1       | M Serbian         | N      | 0.0       | ED            | Hydrocephalus, CNS, hemorrhage, low birth weight | CNF            | ND             | —                          | —                | —               | —             | —            | —             | —             | —             | Deceased         | [c.614 + 62 idiCACCGCCGinsSTT] + | [c.614 + 62 idiCACCGCCGinsSTT] + | [T205 + R207delins] + | [T205 + R207delins] | 4

**APPENDIX:** Clinical Data and Spectrum of Detected Sequence Variants in 89 Patients With NSFL

**OS:** NPHS1
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Pediatricians’ Use of Language Services for Families With Limited English Proficiency

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. Patients with limited English proficiency confront multiple barriers to health care access in the United States. Appropriate language services for families with limited English proficiency are essential; however, little is known about pediatricians’ use of language services. The objective of this study was to examine pediatricians’ provision of language services to patients with limited English proficiency and the pediatrician, practice, and state characteristics associated with use of these services.

METHODS. Data were obtained from the Periodic Survey of Fellows No. 60, a nationally representative survey of members of the American Academy of Pediatrics. A total of 1829 surveys were mailed, and responses were obtained from 58%. Use of 6 language services was assessed. Factors associated with language services use were examined after adjusting for physician, practice, and state characteristics.

RESULTS. Bilingual family members (70%) and bilingual staff (58%) were the most frequently reported language services; 40% of respondents report the use of professional interpreters, 28% use telephone interpreters, and 35% of practices report provision of translated written materials. Pediatricians in smaller and rural practices and in states with higher proportions of limited English proficiency persons report less use of professional interpreters. Pediatricians in states with third-party reimbursement for language services are more likely to report use of professional interpreters.

CONCLUSIONS. Most pediatricians report using untrained interpreters to communicate with limited English proficiency patients and their families. Pediatricians in regions with high proportions of limited English proficiency persons may be less likely to provide appropriate language services. Third-party reimbursement for professional language services may increase the use of trained interpreters and quality of care.
RAPID GROWTH IS OCCURRING IN THE NUMBER OF AMERICANS WITH LIMITED ENGLISH PROFICIENCY (LEP), DEFINED AS THOSE WITH A SELF-REPORTED ABILITY TO SPEAK ENGLISH LESS THAN "VERY WELL." 21 TWENTY-ONE MILLION AMERICANS HAD LEP IN 2000, A SUBSTANTIAL INCREASE FROM 14 MILLION WHO HAD LEP IN 1990.1,2 PATIENTS WITH LANGUAGE BARRIERS ARE AT RISK FOR IMPAIRED HEALTH STATUS,3–5 LACK OF HEALTH INSURANCE,6 INCREASED TEST CHARGES AND LENGTHS OF STAY IN EMERGENCY DEPARTMENTS,7 INCREASED ADVERSE EVENTS DURING HOSPITALIZATION,8 DECREASED ADHERENCE TO MEDICATIONS AND FOLLOW-UP APPOINTMENTS,9 AND A LOWER LIKELIHOOD OF RECEIVING FOLLOW-UP APPOINTMENTS AFTER EMERGENCY DEPARTMENT VISITS.10

THE ARRAY OF LANGUAGE SERVICES USED IN HEALTH CARE SETTINGS INCLUDES BILINGUAL PHYSICIANS, BILINGUAL STAFF, BILINGUAL FAMILY MEMBERS AND FRIENDS, PROFESSIONAL INTERPRETERS, TELEPHONE INTERPRETERS, AND WRITTEN MATERIALS IN THE PRIMARY LANGUAGE. DIFFERENT METHODS, HOWEVER, HAVE BEEN SHOWN TO HAVE VARYING LEVELS OF EFFECTIVENESS. THE USE OF BILINGUAL PHYSICIANS AND PROFESSIONAL INTERPRETERS RESULTS IN OPTIMAL COMMUNICATION AND IMPROVED MEDICAL OUTCOMES11 AND HAS BEEN LINKED WITH HIGHER PATIENT ADHERENCE, INCREASED USE OF SCREENING TESTS, AN INCREASED NUMBER OF OFFICE VISITS, HIGHER RATES OF PRESCRIPTIONS BEING FILLED, FEWER LABORATORY TESTS ORDERED, INCREASED ADHERENCE TO GUIDELINES, AND INCREASED PATIENT SATISFACTION.11–13 IN CONTRAST, UNTRAINED AD HOC INTERPRETERS, SUCH AS UNTRAINED STAFF OR FAMILY MEMBERS, FRIENDS, OR STRANGERS FROM THE WAITING ROOM, ARE ASSOCIATED WITH POORER SELF-REPORTED UNDERSTANDING OF DIAGNOSES, INCREASED NUMBERS OF INTERPRETER ERRORS OF CLINICAL CONSEQUENCE,14–18 AND HIGHER RATES OF TESTING AND ADMISSION FROM EMERGENCY DEPARTMENTS.12

Title VI of the Civil Rights Act of 1964 mandates that health care providers receiving federal funds provide "meaningful access to their programs and activities by LEP persons" without cost to the patient.19 The use of trained interpreters among interns and family physicians is low, with cited barriers being cost, inconvenience, limited availability of trained interpreters, and an ongoing perception that ad hoc interpreters are sufficient.20,21 LITTLE IS KNOWN ABOUT PEDIATRICIANS’ USE OF LANGUAGE SERVICES FOR FAMILIES WITH LEP. THE OBJECTIVES OF THIS STUDY WERE TO EXAMINE HOW PEDIATRICIANS COMMUNICATE WITH FAMILIES WITH LEP AND TO EXAMINE THE PEDIATRICIAN, PRACTICE, AND STATE CHARACTERISTICS ASSOCIATED WITH USE OF VARIOUS LANGUAGE SERVICES.

METHODS

DATA FOR THIS STUDY WERE OBTAINED FROM THE 60TH PERIODIC SURVEY OF FELLOWS, CONDUCTED BY THE AMERICAN ACADEMY OF PEDIATRICS (AAP) DIVISION OF HEALTH SERVICES RESEARCH. PERIODIC SURVEYS ARE CONDUCTED 4 TIMES ANNUALLY ON TOPICS OF IMPORTANCE TO PEDIATRICS; EACH SURVEY USES A UNIQUE RANDOM SAMPLE OF US NONRETIRED MEMBERS OF THE AAP.22 PERIODIC SURVEY 60, AN 8-PAGE SELF-ADMINISTERED QUESTIONNAIRE, WAS SENT TO 1829 AAP MEMBERS BETWEEN APRIL AND OCTOBER 2004, WITH 5 FOLLOW-UP MAILINGS. THE SURVEY EXAMINED PEDIATRICIAN INVOLVEMENT IN COMMUNITY CHILD HEALTH ACTIVITIES AND SERVICES PROVIDED IN THEIR PRACTICES. A SUBSET OF QUESTIONS ASKED ABOUT LANGUAGE SERVICES FOR PATIENTS WITH LEP AND THEIR FAMILIES AMONG PEDIATRICIANS WHO REPORTED CARING FOR PATIENTS WITH LEP. SURVEY CONTENT WAS INFORMED BY A NATIONAL ADVISORY GROUP WITH EXPERTISE IN COMMUNITY PEDIATRICS AND BY REVIEW OF THE AAP COMMUNITY PEDIATRICS ACTION GROUP AND MEMBERS OF THE COUNCIL ON COMMUNITY PEDIATRICS. INSTITUTIONAL REVIEW BOARD APPROVAL WAS OBTAINED FROM THE AAP AND THE JOHNS HOPKINS COMMITTEE ON HUMAN RESEARCH. THE SURVEY IS AVAILABLE ON REQUEST FROM THE AAP.

RESPONDENTS ESTIMATED THE PERCENTAGE OF THEIR PATIENTS WITH LEP, DEFINED IN THE QUESTION AS THOSE FOR WHOM ENGLISH WAS NOT THE PRIMARY LANGUAGE AND WAS SPoken LESS THAN "VERY WELL." QUESTIONS WERE ASKED ABOUT THE PRIMARY LANGUAGES SPOKEN BY PATIENTS WITH LEP. FOR EACH PRIMARY LANGUAGE ENCOUNTERED, RESPONDENTS WERE ASKED WHETHER THEY PROVIDED EACH OF 6 DIFFERENT METHODS OF COMMUNICATION: BILINGUAL PHYSICIANS (SELF OR OTHER), BILINGUAL STAFF, BILINGUAL FAMILY MEMBERS, PROFESSIONAL INTERPRETERS, WRITTEN MATERIALS IN THE PRIMARY LANGUAGE, AND TELEPHONE INTERPRETERS.

ADDITIONAL INFORMATION WAS COLLECTED REGARDING PHYSICIAN AND PRACTICE CHARACTERISTICS. PHYSICIAN CHARACTERISTICS INCLUDED AGE, GENDER, RACE, AND HISPANIC/LATINO ETHNICITY (HENCEFORWARD REPORTED AS LATINO). PRACTICES WERE CATEGORIZED BY SETTING (SOL0/2 PHYSICIAN, GROUP WITH 3–10 PHYSICIANS, GROUP WITH >10 PHYSICIANS/MULTISPECIALTY GROUP/STAFF MODEL HEALTH MAINTENANCE ORGANIZATION, OR HOSPITAL/CLINIC/MEDICAL SCHOOL), LOCATION (INNER-CITY, OTHER URBAN, SUBURBAN, OR RURAL), AND REGION (NORTHEAST, MIDWEST, SOUTH, OR WEST). PRACTICES WERE DICHOTOMIZED AT THE MEAN BY THE PERCENTAGES OF PATIENTS WITH PUBLIC INSURANCE AS LOW (≤36%) OR HIGH (>36%) AND ALSO AS HAVING <20% OR ≥20% LATINO PATIENTS.

STATES IN WHICH PEDIATRICIANS PRACTICE WERE CATEGORIZED BY US CENSUS-REPORTED PREVALENCE OF LEP PERSONS, GROWTH IN THE LATINO POPULATION, AND THE AVAILABILITY OF PUBLIC THIRD-PARTY (MEDICAID OR STATE CHILDREN’S HEALTH INSURANCE PROGRAM, SCHIP) REIMBURSEMENT FOR LANGUAGE SERVICES. TEN STATES WERE IDENTIFIED AS HAVING HIGH LEP, WITH ≥9% OF THE POPULATION SPEAKING ENGLISH LESS THAN "VERY WELL" RELATIVE TO THE NATIONAL MEAN LEP PROPORTION OF 8%.23 TEN STATES WERE CATEGORIZED AS HAVING HIGH LEP AMONG SPANISH SPEAKERS, DEFINED AS HAVING ≥5% OF THE POPULATION SPEAKING SPANISH AT HOME AND SPEAKING ENGLISH LESS THAN VERY WELL.23 EIGHT STATES WERE IDENTIFIED AS HAVING HIGH LEP AMONG ASIAN SPEAKERS, DEFINED AS HAVING ≥2% OF THE POPULATION SPEAKING AN ASIAN OR PACIFIC ISLAND LANGUAGE AND SPEAKING ENGLISH LESS THAN VERY WELL.23 TWELVE STATES WERE CATEGORIZED AS HAVING A HIGH INTERVAL POPULATION INCREASE OF LATINOS, DEFINED AS AN
increase of >200 000 Latinos between the 1990 and 2000 US Census. Ten states were categorized as providing Medicaid/SCHIP reimbursement for interpreter services, ranging from direct provider or interpreter reimbursement to contracts with interpreter organizations for language services.

Analyses were conducted using SPSS 12.0 (SPSS Inc, Chicago, IL). Tests for significance of means were conducted by t test and medians by Mann-Whitney and Kruskal-Wallis tests. Bivariate analyses were performed using χ² for categorical and analysis of variance for continuous variables. Multivariate analysis was performed by logistic regression using 3 domains of independent variables selected with health policy significance in mind: physician (age, gender, and Latino ethnicity), practice (setting and location), and state (LEP prevalence and Medicaid/SCHIP reimbursement) characteristics. The 6 methods of communication were selected as dependent variables, and all of the variables were forced in.

RESULTS
Of the 1829 surveys mailed, 1053 were returned, for a response rate of 58%, which is consistent with previous AAP Periodic Surveys. Survey respondents were more likely to be women (P < .01), but no significant difference was found in age or geographic distribution.

Analyses were limited to the 835 respondents who finished their residency training, did not have a specialty fellow (certified by a board other than a pediatric board) designation, reported having patients with LEP, and responded to the subset of questions focusing on language services provided. A total of 51.8% of respondents included for analysis were women, with a mean age of 45.2 years and 7.6% reporting Latino ethnicity. Compared with 2006 national AAP member data, respondents included for analysis were more likely to report a younger age (mean age: 45.2 vs 46.3 years; P < .05); no significant differences were found in gender or geographic distribution. Because the national AAP membership database does not contain sufficient information on ethnicity, aggregate data from AAP Periodic Surveys 59 to 61 were used for national comparison; survey respondents included for analysis were more likely to report Latino ethnicity (7.6% versus 5.2%; P < .001).

Respondents self-reported a median percentage of 5.0% (mean: 13.4%) of patients with LEP. No patients with LEP were seen at 13% of practices, and >20% of patients had LEP in 19.3% of practices. Pediatricians reported 62 different languages spoken at home among their patients with LEP, most commonly Spanish (reported by 94.0%), Chinese (11.8%), and Vietnamese (10.5%). Pediatricians estimated that 53.8% of their patients were non-Latino white, 19.6% were Latino, 18.2% were black, and 5.8% were Asian/Pacific Islander. A mean of 53.2% of the patients had private insurance coverage, 36.7% had public insurance, 3.3% had TRICARE (military) insurance, and 7.0% were uninsured.

Pediatricians who were <45 years old, women, or Latino reported caring for significantly higher proportions of LEP patients (P < .05; Table 1). In addition, higher median proportions of patients with LEP were reported being seen by pediatricians practicing in hospitals, clinics or medical schools, the inner city, the Western United States, and those caring for high percentages of Latino and publicly insured patients.

Pediatricians reported multiple methods of communicating with patients with LEP. For respondents reporting provision of a language service, the most commonly identified methods were bilingual family members (69.6%), bilingual staff (58.3%), and bilingual physicians (52.4%; Table 2). The use of professional interpret-
ers (40.1%) and telephone interpreters (28.2%) was reported by fewer than half of respondents. More than one third (35.2%) of pediatricians reported providing written materials in the primary language. Higher median proportions of LEP patients were associated with pediatricians’ use of all language services except for use of family members.

Language service use varied by selected physician, practice, and state characteristics (Table 3). Higher proportions of Latino than non-Latino pediatricians reported using bilingual physicians, and fewer Latino pediatricians relied on bilingual family members and professional interpreters ($P < .001$). Significantly greater use of most language services was reported for pediatricians with more publicly insured patients and for those in practices located in inner cities and hospitals, clinics, or medical schools. Rural pediatricians reported significantly greater use of bilingual family members ($P < .01$). Clinician age was not associated with language service use, but a greater percentage of female clinicians than male clinicians reported the use of bilingual family members and provision of written materials in the primary language.

Respondents in states with larger proportions of LEP patients, Spanish-speaking LEP patients, and Latino population growth estimated greater use of bilingual physicians and staff but a significantly lower use of professional interpreters (Table 4). In additional analyses limited to respondents who did not report the use of a bilingual physician or staff member, respondents in states with larger proportions of patient with LEP continued to report lower use of a professional interpreter ($P < .01$; data not shown). No significant difference was found in high LEP states on reported professional interpreter use for pediatricians who reported use of a bilingual physician versus those who reported no use of a bilingual physician (data not shown).
States with higher proportions of Asian-language-speaking LEP patients had greater reported use of bilingual physicians and staff (Table 4). Lower rates of telephone interpreter use were described by respondents among states with the highest proportion of LEP persons and Latino population growth. There was significantly greater reported use of professional interpreters and lower use of bilingual staff in states with third party reimbursement for interpreter services.

In multivariate analysis (Table 5), female physicians had increased odds of using a bilingual family member (odds ratio, OR: 1.49; 95% confidence interval, CI: 1.05–2.11) and written materials in the primary language (OR: 1.49; 95% confidence interval, CI: 1.05–2.11) and written materials in the primary language (OR: 1.49; 95% confidence interval, CI: 1.05–2.11). Non-Latino physicians had decreased odds of using a bilingual physician and increased odds of using bilingual family members, bilingual staff, and professional interpreters. Suburban, rural, and noninner city urban practices were substantially less likely to use professional interpreters. Smaller practices had 8 to 9 times lower odds of using professional interpreters. Physicians in states with higher proportions of LEP persons were more likely to use bilingual physicians (OR: 2.17; 95% CI: 1.55–3.05) and bilingual staff (OR: 4.63; 95% CI: 3.22–6.67) but less likely to use professional interpreters (OR: 0.46; 95% CI: 0.31–0.69). Physicians in states with public third-party reimbursement for language services were more likely to use professional interpreters (OR: 2.05; 95% CI: 1.10–3.83).

**DISCUSSION**

More than two thirds of US pediatricians report using family members as interpreters during encounters with...
LEP patients and their families. Less than half of pediatricians report use of professional interpreters, and only approximately one third report provision of written materials in the primary language. Even in states with high proportions of LEP persons, less than half of pediatricians report using professional interpreters, and almost three quarters report using family members as interpreters. Pediatricians in high LEP states are more likely to use bilingual providers but less likely to use professional interpreters, after adjusting for physician, practice, and state characteristics. Finally, reported use of professional and telephone interpreters were low in all states, regardless of demographics. Given the documented association between language barriers and compromised health care quality and patient safety, the study findings highlight the need to develop policies and programs to promote the provision of adequate language services in pediatric practices caring for the rapidly growing population of families with LEP.

Several findings have key policy implications. Smaller and rural practices are less likely to use professional interpreters, even after adjustment for state LEP prevalence and third-party reimbursement for interpreter services. Further research is needed to determine whether this finding relates to insufficient availability of professional interpreters, inadequate reimbursement for language services, or the need for greater education on the importance of professional interpreters in providing high-quality care and optimal communication. Non-Latino physicians report greater use of bilingual staff and family members, possibly reflecting the need for improved training on cultural competency and on the hazards of using family members as interpreters. Physicians in states with higher proportions of persons with LEP report lower use of a professional interpreter; similar reported use of professional interpreters among respondents who report use of bilingual physicians or staff members compared with respondents reporting no use suggests that this finding cannot be explained by higher use of bilingual personnel in such states. Our results may suggest an inadequate supply of professional interpreters to meet the increasing demand in states with a high LEP population.

It is encouraging that third-party reimbursement for language services is associated with greater use of professional interpreters, suggesting an important intervention that could increase the use of appropriate language services. States with public third-party reimbursement for language services may have a paucity of bilingual providers and staff; according to the 2000 US Census, 8 of 10 states providing Medicaid and SCHIP reimbursement for interpreter services (at the time of the survey) have an LEP population proportion that is less than or equal to the median LEP population proportion for the United States, with only Hawaii having both a high proportion of LEP patients and third-party language services reimbursement. Although there was a significant association between third-party reimbursement and professional interpreter use in adjusted analysis, reported use of professional interpreters was <60% even in states with third-party reimbursement. Levels of and mechanisms for payment vary by state, and we do not know how often practices bill for these services, making it difficult to fully assess the effect of third-party reimbursement. We also have no information regarding private third-party reimbursement, but patients with LEP disproportionately have public insurance.

The distribution of LEP patients is uneven across pediatricians, practices, and states and offers starting points to improve the delivery of language services. The higher proportion of LEP patients reported by female and younger pediatricians highlights the importance of education on proper language services use during the early years of physician training. Despite an emphasis on providing culturally effective care in residency training, a recent study found that 22% of pediatric residents report being very or somewhat unprepared to treat patients with LEP. Misperceptions exist among practicing physicians that family members provide sufficient interpretation services, highlighting the need for provider education and practice policies that ensure uniform delivery of effective language services. Successful strategies already being used by small practice providers include determining language needs at initial contact, use of trained bilingual staff, extensive use of written translations available either through community resources or the Internet, and use of telephone language lines. Finally, an increase in interpreter use has been reported among physicians with previous training in interpreter use.

The overall cost of providing language services may be relatively modest. A federal report by the Office of Management and Budget estimated that the cost of interpreter services for LEP persons, when averaged over all inpatient, outpatient, and dental visits, would be an average of $4.04 more per visit, equivalent to 0.5% of the average cost per health care visit. Latinos and Asians incur annual medical costs 20% to 60% less than the mean of non-Latino whites, and the overall cost of providing interpreter services is less than existing cost disparities. However, health care providers in many states currently assume the burden of the cost of language services, potentially creating disincentives for providing language services. Outpatient providers, in particular, bear a disproportionate share of the cost. Third-party reimbursement would alleviate the burden and may increase preventative medical services, which could further lower the overall cost of interpreter services.

Certain study limitations should be noted. First, the response rate was 58%; however, this is similar to that of other large national physician postal surveys, and analysis of response rates in previous AAP surveys reveals
minimal nonresponse bias.\textsuperscript{29} Respondents included for analysis tended to be younger relative to national AAP membership and to have a higher proportion reporting Latino ethnicity compared with overall Periodic Survey respondents, which could overestimate LEP patient prevalence and frequency of language service provision. Second, survey data were self-reported and subject to recall bias. Providers may vary in how they estimate the percentage of their patients with LEP, and reported use of a language service may not reflect actual frequency of use; for example, it is unlikely that the 52\% of respondents reporting use of a bilingual physician provide a bilingual physician for each encounter with a patient with LEP. Third, no additional definitions for methods of communication were provided for survey respondents, possibly resulting in respondents having differing definitions of what may compose a “professional” interpreter or “written materials in the primary language.” Finally, our study does not address the quality or effectiveness of language services that are provided, and the quality of the training of individual interpreters is not known. Health care interpreter standards were issued recently by the National Council on Interpreting in Health Care\textsuperscript{37}; how interpreter standards will impact the supply and costs of interpreter services is unknown.

CONCLUSIONS

The provision of language services for LEP patients is inadequate in many pediatricians’ offices. The problem is particularly severe in smaller and rural practices and in states with high proportions of LEP patients. Given the documented risks of inadequate interpretation, including adverse health status, decreased preventative screening, compromised patient safety, and decreased patient satisfaction, there is an urgent need to promote appropriate language services through the use of interpreters, translated written materials, provider training, and third-party reimbursement.

ACKNOWLEDGMENTS

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REFERENCES


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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. This study examines changing patterns of inequalities in US infant, neonatal, and postneonatal mortality rates between 1969 and 2001 by area deprivation and maternal education.

METHODS. A deprivation index was linked to county vital records data to derive annual infant mortality rates by deprivation quintiles from 1969 to 2000. Rates by maternal education were computed for 1986, 1991, 1996, and 2001 using national linked birth/infant death files. Log-binomial regression was used to estimate relative risks of infant mortality by deprivation and time period. Cox regression was used to model overall and birth weight–specific infant mortality risks by maternal education after adjusting for covariates. Temporal disparities were summarized by log-linear regression and inequality indices.

RESULTS. Although absolute disparities have narrowed over time, relative socioeconomic disparities in infant mortality have increased since 1985. In 1985–1989, infants in the most deprived group had, respectively, 36% and 57% higher risks of neonatal and postneonatal mortality than infants in the least deprived group. The corresponding relative risks increased to 43% and 96% in 1995–2000. The adjusted risk of infant mortality was 22% higher in 1986 for mothers with <12 years of education than for those with ≥16 years of education, with the relative risk increasing to 41% in 2001. Disparities were greatest among normal birth weight infants, with education-specific relative risks of neonatal and postneonatal mortality increasing significantly between 1986 and 2001.

CONCLUSIONS. Dramatic declines in infant mortality among all of the socioeconomic groups during 1969–2001 represent a major public health success. However, substantial socioeconomic disparities persisted in both neonatal and postneonatal mortality. Relatively larger declines in infant and postneonatal mortality among higher socioeconomic groups have contributed to the widening gap in mortality since 1985. Persistent disparities in infant mortality may reflect increasing polarization among socioeconomic groups in material and social conditions, smoking during pregnancy, and health care services.
INFANT MORTALITY RATES have declined dramatically in the United States over the past 6 decades, from a rate of 47.0 infant deaths per 1000 live births in 1940 to 6.8 in 2003.1,2 Yet, racial, ethnic, and social class disparities in infant mortality remain marked. In 2003, black infants and infants born to women with less than a high school education experienced more than twice the mortality rate of white infants and infants born to women with a college degree, respectively.2

Existence of such large social disparities in current infant mortality rates is in sharp contrast to the goals of Healthy People 2000 and 2010 that were launched a decade and a half ago.3 Their primary goal has been to reduce and ultimately eliminate health inequalities among various segments of the US population, including disparities in infant mortality among ethnic and socioeconomic groups.3,4

Although trends in health inequalities by race/ethnicity, gender, and geographical area are analyzed routinely in the United States, the analysis of changes in the extent of health inequalities over time according to socioeconomic characteristics is far less common. The studies that have examined temporal social patterning in health have shown increasing socioeconomic inequalities in overall US mortality, life expectancy, and mortality from cardiovascular diseases and certain cancers.6–11 Previous studies have also shown substantial socioeconomic inequalities in infant mortality,2,12–14 although the extent to which such disparities have changed over time has received little attention.2,16 To our knowledge, no attempt has yet been made to conduct a systematic analysis of how US infant mortality rates have changed in recent decades in relation to individual socioeconomic status (SES) and area-based deprivation. The aim of this article is to examine changes in the extent of inequalities in US infant, neonatal, and postneonatal mortality rates between 1969 and 2001 by area socioeconomic deprivation and maternal education.

METHODS
To analyze temporal inequalities in US infant mortality by area deprivation, we used birth and infant death data from the National Vital Statistics System (NVSS) and the decennial census.1,17,18 Area socioeconomic patterns in infant mortality were derived indirectly by linking county-level SES data from the 1990 decennial census with the NVSS data via the common county Federal Information Processing Standards geocodes.1,17,18 We used a factor-based deprivation index that consisted of 17 census-based social indicators, which may be viewed as broadly representing educational opportunities, labor force skills, and economic and housing conditions in a given county. Selected indicators of education, occupation, wealth, income distribution, unemployment rate, poverty rate, and housing quality were used to construct the index.6–11 The factor loadings (correlations of indicators with the index) ranged from 0.92 for 150% of the poverty rate to 0.45 for household plumbing.8,10 The US deprivation index was constructed at the county level for the 1970, 1980, and 1990 censuses.6,10,11 Substantive and methodologic details underlying the construction of the US deprivation index are provided elsewhere.6,10

To analyze trends in infant mortality by deprivation, we used the weighted population quintile distribution of the 1990 deprivation index that classified all of the US counties into 5 groups of approximately equal population size. The groups thus created ranged from being the most deprived (first quintile) to the least disadvantaged (fifth quintile) population groups. The 1990 index was used to compute annual rates from 1969 through 2000. Specifically, county-specific infant, neonatal, and postneonatal deaths from 1969 through 2000 were obtained using the national mortality database,1 whereas county-specific live births, obtained from the natality component of NVSS, served as denominators for computing infant mortality rates.17 Each of the 3097 counties in the NVSS database was assigned 1 of the 5 deprivation categories. In the case of Alaska and Hawaii, state- rather than county-level data were used.

To estimate SES trends at the individual level, we computed infant mortality rates by maternal education using the national linked birth and infant death files for the 1986, 1991, 1996, and 2001 birth cohorts.19–22 Availability of the linked file since 1983 permits the analysis of educational trends in infant mortality over time. Maternal education was measured by the number of years of school completed and was grouped into 4 categories: <12, 12, 13 to 15, and ≥16 years. Other measures of individual SES, such as income, occupation, or employment status, are not available in the linked files.2,19–22

Cox proportional hazards regression model, fitted by the SAS PHREG procedure (SAS Institute, Inc, Cary, NC), was used to estimate relative risks (RRs; hazard ratios) of infant, neonatal, and postneonatal mortality associated with maternal education before and after adjusting for such covariates as maternal age (≥19, 20–34, or ≥35 years), race/ethnicity (non-Hispanic white, black, Hispanic, Asian/Pacific Islander, or American Indian/Alaska Native), marital status (married or unmarried), live birth order (1, 2–3, or ≥4), infant sex, plurality (singleton or twin/multiple birth), prenatal care use (first trimester, second trimester, third trimester, or no care), smoking during pregnancy (unavailable for the 1986 cohort), gestational age (<33, 33–36, or ≥37 weeks), and birth weight (<1500, 1500–2499, or ≥2500 g).14,23,24 We preferred the Cox model to the logistic model, because the latter fails to take into account the varying survival times of infants dying in the first year of life.14 Hazards proportionality assumption of the Cox model was tested and confirmed by inspecting the plots of log-log survivor functions against survival time for various covariate categories, including those for mater-
nal education. Survival times were measured in days. In estimating the risk of infant mortality, all of the live births surviving beyond the first year of life were treated as right-censored observations. Analyses for the 1986, 1991, 1996, and 2001 linked birth cohorts were based on 2,906,066, 4,111,059, 3,892,133, and 4,026,323 live births, respectively.

Log-binomial regression, estimated by the SAS GENMOD procedure (SAS Institute, Inc, Cary, NC), was used to estimate RRs of infant, neonatal, and postneonatal mortality for each deprivation group and time period. Although rates for each deprivation group were computed annually from 1969 to 2000, we modeled infant mortality as a function of area deprivation for four 5-year and two 6-year time periods, 1969–1974, 1975–1979, 1980–1984, 1985–1989, 1990–1994, and 1995–2000, to reduce variability associated with annual rates and to provide more stable RR estimates. Other than RRs, disparities in infant mortality were also measured by the absolute difference in rates between the least deprived group (or the highest education group) and each of the other deprivation or education groups. Log-linear regression was used to calculate average annual exponential rates of decline in infant mortality for each deprivation group. An index of disparity, which approximated in relative terms the average deviation of the rates from the rate for the highest SES group, was used to summarize disparities over time across all of the deprivation and education groups. This relative mean deviation index of disparity was calculated as follows:

\[ ID = \left( \frac{\sum \left| Q_{i} - Q_{5} \right|}{5} \right) \times 100, \]

where “\( Q_{i} \)” is the rate for the \( i \)th quintile (\( i = 1, 2, 3, 4, 5 \)), “\( Q_{5} \)” is the rate for the 5th quintile, and “\( I \)” is the number of groups or quintiles being compared. In addition, a measure of excess mortality, defined as the difference between the rates for the total population and the highest SES group, was computed to assess the extent of improvement in infant mortality if all of the groups were to have the rate of the highest SES group.

RESULTS

Trends in Area Socioeconomic Disparities in Infant, Neonatal, and Postneonatal Mortality

Figure 1 shows county socioeconomic gradients in annual infant mortality rates between 1969 and 2000. Although rates declined over time for all of the deprivation groups, more deprived groups had higher infant mortality than less deprived groups each year, and the gradients (rate ratios) seemed to be greater in the 1990s than in the 1980s. Infant mortality in the least through the most deprived groups declined at average annual rates of 3.50%, 3.39%, 3.24%, 3.21%, and 3.37%, respectively, between 1969 and 2000.

Figure 1 also presents trends in neonatal and postneonatal mortality rates. Neonatal mortality refers to infant deaths occurring in the first 27 days of life, whereas postneonatal mortality refers to infant deaths between 28 days and 1 year of age. All of the deprivation groups showed a decreasing trend in neonatal and postneonatal mortality between 1969 and 2000, although county socioeconomic gradients (rate ratios) were larger for postneonatal mortality than for neonatal mortality. Postneonatal mortality declined faster in the least deprived group than in the other deprivation groups, thus contributing to increasing rate ratios, particularly since 1985. In the least deprived group, the postneonatal mortality rate declined by 4.62% per year between 1985 and 2000, whereas it declined by just 2.64% per year in the most deprived group over the same time period. Neonatal mortality in all of the deprivation groups showed similar declines, with the rates declining at ~3.8% per year during 1969–2000.

Tables 1 and 2 summarize changing county socioeconomic differentials in infant mortality across different time periods. Between 1969 and 1984, both absolute and relative socioeconomic disparities in infant, neonatal, and postneonatal mortality declined. For example, the interquintile differences (Q1–Q5) in infant, neonatal, and postneonatal mortality rates declined from 8.3, 5.3, and 3.0 deaths per 1000 live births in 1969–1974 to 3.7, 1.9, and 1.8 in 1980–1984, respectively (Table 1). The RRs of infant, neonatal, and postneonatal mortality between the least and most deprived groups dropped significantly from 1.56, 1.46, and 1.86 in 1969–1974 to 1.38, 1.28, and 1.62 in 1980–1984, respectively (Table 2).

Beginning with the 1985–1989 period, however, the RRs of infant, neonatal, and postneonatal mortality associated with area deprivation generally increased. In 1985–1989, infants in the most deprived group had, respectively, 36% and 57% higher risks of neonatal and postneonatal mortality than infants in the least deprived group. In 1995–2000, the deprivation gradient in infant mortality widened significantly, with infants in the most deprived group experiencing 43% and 96% higher RRs of neonatal and postneonatal mortality, respectively, than their least deprived counterparts (Table 2). The summary index of inequality in Table 1, which quantifies the magnitude of disparities across all of the deprivation groups, also indicates generally increasing socioeconomic disparities in infant mortality, particularly in postneonatal mortality since 1985. The relative overall disparity in infant and postneonatal mortality across deprivation groups, for example, widened from 23% and 33% in 1985–1989 to 31% and 52% in 1995–2000, respectively. The excess mortality estimates in Table 1 indicate that infant and postneonatal mortality rates in 1995–2000 would have declined by 23% and 34% if infants in the more deprived groups experienced mortality rates similar to those of the least deprived group.
Trends in Educational Disparities in Overall Infant, Neonatal, and Postneonatal Mortality

Table 3 shows changes in individual-level educational disparities in infant mortality between 1986 and 2001. Although area deprivation quintiles are substantively not equivalent to the 4 maternal educational strata, the absolute and relative socioeconomic disparities in infant mortality are indeed greater at the individual level than at the area level. All of the education groups showed substantial declines in mortality, with the mortality rate for infants born to mothers with <12 years of education decreasing by 45% from 15.32 in 1986 to 8.49 deaths per 1000 live births in 2001. The rate for infants born to mothers with ≥16 years of education fell by 38% from 6.85 in 1986 to 4.24 deaths per 1000 live births in 2001. Between 1986 and 2001, the neonatal mortality rates for infants born to mothers with <12 and ≥16 years of education decreased by 44% and 35% respectively.

FIGURE 1
Trends in US infant, neonatal, and postneonatal mortality according to area (county) socioeconomic deprivation, 1969–2000. A, infant mortality rates; B, RR of infant mortality; C, neonatal mortality rates; D, RR of neonatal mortality; E, postneonatal mortality rates; F, RR of postneonatal mortality.
TABLE 1 Infant, Neonatal, and Postneontal Mortality Rates per 1000 Live Births by Area (County) Socioeconomic Deprivation, Interquintile
(Qi–Q5) Rate Differences, Excess Mortality (%), and Index of Disparity: United States, 1969 –2000
Year

Infant mortality
1969–1974
1975–1979
1980–1984
1985–1989
1990–1994
1995–2000
Neonatal mortality
1969–1974
1975–1979
1980–1984
1985–1989
1990–1994
1995–2000
Postneonatal mortality
1969–1974
1975–1979
1980–1984
1985–1989
1990–1994
1995–2000

Rate

Interquintile Difference in Mortality Rates

All
Groups

Q1
(Low SES)

Q2

Q3

Q4

Q5
(High SES)

Q1-Q5

Q2-Q5

Q3-Q5

Q4-Q5

Excess
Mortality
(Total-Q5)/
Total

Index of
Disparitya

19.23
14.56
11.72
10.48
8.88
7.53

23.18
17.40
13.38
12.15
10.87
9.13

20.62
15.45
12.61
11.27
9.95
8.48

18.57
13.82
11.51
10.31
8.84
7.57

17.20
13.29
10.92
9.98
8.12
6.81

14.88
11.57
9.67
8.52
6.76
5.77

8.29
5.83
3.71
3.63
4.11
3.36

5.74
3.88
2.94
2.75
3.19
2.71

3.69
2.25
1.84
1.79
2.09
1.80

2.32
1.72
1.26
1.47
1.36
1.03

22.59
20.51
17.56
18.71
23.92
23.30

26.93
23.65
20.18
22.65
31.83
30.83

14.26
10.21
7.78
6.73
5.61
4.97

16.64
11.99
8.64
7.75
6.77
5.83

15.43
10.80
8.34
7.22
6.26
5.55

14.01
9.75
7.67
6.58
5.48
4.96

12.76
9.25
7.22
6.32
5.13
4.52

11.36
8.47
6.73
5.71
4.51
4.09

5.27
3.52
1.91
2.03
2.26
1.74

4.07
2.33
1.61
1.50
1.75
1.46

2.65
1.29
0.94
0.86
0.97
0.87

1.39
0.78
0.49
0.61
0.62
0.43

20.33
17.08
13.49
15.14
19.66
17.77

23.55
18.74
14.71
17.54
24.80
21.97

4.96
4.35
3.95
3.74
3.27
2.55

6.54
5.41
4.74
4.40
4.10
3.29

5.19
4.65
4.27
4.06
3.69
2.93

4.57
4.07
3.84
3.73
3.37
2.61

4.45
4.04
3.70
3.66
2.99
2.29

3.52
3.11
2.94
2.80
2.25
1.68

3.02
2.31
1.81
1.60
1.85
1.61

1.67
1.55
1.33
1.25
1.45
1.25

1.05
0.96
0.90
0.93
1.12
0.93

0.93
0.93
0.77
0.85
0.74
0.61

29.08
28.57
25.59
25.13
31.24
34.07

37.87
37.03
32.71
33.08
45.95
52.39

Area socioeconomic deprivation quintiles, Q1 through Q5, represent the lowest to highest socioeconomic status groups.
a The relative mean deviation index of disparity was calculated as ID ⫽ {关(Q ⫺ Q ⫹ Q ⫺ Q ⫹ Q ⫺ Q ⫹ Q ⫺ Q )/5兴/Q } ⫻ 100, where Q through Q are the rates for 5 socioeconomic
r1
r5
r2
r5
r3
r5
r4
r5
r5
r1
r5
deprivation quintiles, respectively.

TABLE 2 RRs of Infant, Neonatal, and Postneonatal Mortality by Area (County) Socioeconomic Deprivation (SES) Index, (Derived From LogBinomial Regression Models): United States, 1969 –2000
Time Period

Infant mortality
1969–1974
1975–1979
1980–1984
1985–1989
1990–1994
1995–2000
Neonatal mortality
1969–1974
1975–1979
1980–1984
1985–1989
1990–1994
1995–2000
Postneonatal mortality
1969–1974
1975–1979
1980–1984
1985–1989
1990–1994
1995–2000

SES I (Low SES)

SES II

SINGH, KOGAN

SES IV

SES V (High SES)

95% CI

RR

95% CI

RR

95% CI

RR

95% CI

RR

Ptrend

1.56
1.50
1.38
1.43
1.61
1.58

1.54–1.57
1.48–1.52
1.36–1.40
1.41–1.45
1.58–1.63
1.56–1.61

1.39
1.34
1.30
1.32
1.47
1.47

1.37–1.40
1.32–1.35
1.29–1.32
1.30–1.34
1.45–1.50
1.45–1.49

1.25
1.19
1.19
1.21
1.31
1.31

1.23–1.26
1.18–1.21
1.17–1.21
1.19–1.23
1.29–1.33
1.29–1.33

1.16
1.15
1.13
1.17
1.20
1.18

1.14–1.17
1.13–1.17
1.11–1.15
1.15–1.19
1.18–1.22
1.16–1.20

1.00
1.00
1.00
1.00
1.00
1.00

⬍.0001
⬍.0001
⬍.0001
⬍.0001
⬍.0001
⬍.0001

1.46
1.42
1.28
1.36
1.50
1.43

1.45–1.48
1.39–1.44
1.26–1.31
1.33–1.38
1.47–1.53
1.40–1.45

1.36
1.28
1.24
1.26
1.39
1.36

1.34–1.37
1.26–1.30
1.22–1.26
1.24–1.29
1.36–1.41
1.33–1.38

1.23
1.15
1.14
1.15
1.21
1.21

1.22–1.25
1.13–1.17
1.12–1.16
1.13–1.17
1.19–1.24
1.19–1.24

1.12
1.09
1.07
1.11
1.14
1.10

1.11–1.14
1.07–1.11
1.05–1.09
1.09–1.13
1.12–1.16
1.08–1.13

1.00
1.00
1.00
1.00
1.00
1.00

⬍.0001
⬍.0001
⬍.0001
⬍.0001
⬍.0001
⬍.0001

1.86
1.74
1.62
1.57
1.82
1.96

1.82–1.90
1.70–1.79
1.58–1.66
1.53–1.61
1.78–1.87
1.91–2.01

1.48
1.50
1.45
1.45
1.64
1.74

1.44–1.51
1.46–1.54
1.42–1.49
1.41–1.48
1.60–1.69
1.70–1.79

1.30
1.31
1.31
1.33
1.50
1.55

1.27–1.33
1.27–1.35
1.27–1.34
1.30–1.37
1.46–1.54
1.51–1.60

1.26
1.30
1.26
1.30
1.33
1.36

1.23–1.29
1.26–1.34
1.23–1.29
1.27–1.34
1.30–1.37
1.32–1.40

1.00
1.00
1.00
1.00
1.00
1.00

⬍.0001
⬍.0001
⬍.0001
⬍.0001
⬍.0001
⬍.0001

CI indicates conﬁdence interval. SES V was treated as the reference category. P values are 2-sided.

e932

SES III

RR


whereas the corresponding postneonatal mortality rates decreased by 46%.

The index of inequality, summarizing the magnitude of disparities across all 4 of the education groups, shows an increasing overall disparity in postneonatal mortality between 1986 and 2001, with the index score increasing from 90% in 1996 to 98% in 1996 to 123% in 2001. However, the index shows stable educational disparities in neonatal mortality over the same time period. The excess mortality estimates in Table 3 indicate that neonatal and postneonatal mortality in 2001 would have declined by 29% and 55% if the mortality rate for all of the educational groups were the same as the rate for infants born to mothers with a college degree (model 1). Crude RRs of infant mortality in 2001 decreased for mothers with <12 years of education (RR: 2.00) but increased significantly for mothers with 12 and 13 to 15 years of education (RR: 1.75 and 1.44, respectively). Adjusting for maternal age, race/ethnicity, marital status, birth order, infant sex, plurality, and prenatal care in model 2 decreased the RRs in all 4 of the birth cohorts, but the adjusted relative educational disparities were greater in 2001 than in 1986. The inclusion of prenatal smoking, gestational age, and birth weight, along with all of the other covariates in model 2 further decreased the RRs associated with education, but they all remained statistically significant (model 3). Compared with ≥16 years of education, the fully adjusted risk of infant mortality associated with <12 and 12 years of education was 22% and 10% higher in 1986 and 41% and 28% higher in 2001, respectively, with the increase in the RRs being statistically significantly during 1986–2001.

Although the crude RRs show a consistent narrowing

<table>
<thead>
<tr>
<th>Maternal Education (Years of Schooling)</th>
<th>Live Births</th>
<th>Infant Deaths</th>
<th>Infant Mortality Rate</th>
<th>Neonatal Deaths</th>
<th>Neonatal Mortality Rate</th>
<th>Postneonatal Deaths</th>
<th>Postneonatal Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;12</td>
<td>524,433</td>
<td>8,035</td>
<td>15.32</td>
<td>46,355</td>
<td>8.84</td>
<td>340,00</td>
<td>6.48</td>
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<tr>
<td>12</td>
<td>1,081,095</td>
<td>10,935</td>
<td>10.11</td>
<td>73,515</td>
<td>6.80</td>
<td>358,40</td>
<td>3.32</td>
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<tr>
<td>13–15</td>
<td>510,351</td>
<td>4,243</td>
<td>8.31</td>
<td>29,091</td>
<td>5.70</td>
<td>133,40</td>
<td>2.61</td>
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<tr>
<td>≥16</td>
<td>440,241</td>
<td>3,014</td>
<td>6.85</td>
<td>21,885</td>
<td>4.97</td>
<td>82,60</td>
<td>1.88</td>
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<tr>
<td>All levels</td>
<td>2,906,066</td>
<td>30,332</td>
<td>10.44</td>
<td>19,962</td>
<td>6.87</td>
<td>103,70</td>
<td>3.57</td>
</tr>
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<td>Excess mortality, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>34.39</td>
<td></td>
<td></td>
<td></td>
<td>27.66</td>
<td></td>
<td>47.34</td>
</tr>
<tr>
<td>Index of disparity&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90.03</td>
</tr>
<tr>
<td>1991&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
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<td>&lt;12</td>
<td>949,466</td>
<td>10,863</td>
<td>11.44</td>
<td>60,525</td>
<td>6.37</td>
<td>481,10</td>
<td>5.07</td>
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<td>1,491,753</td>
<td>13,147</td>
<td>8.81</td>
<td>82,735</td>
<td>5.55</td>
<td>487,40</td>
<td>3.27</td>
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<td>13–15</td>
<td>816,927</td>
<td>5,532</td>
<td>6.77</td>
<td>37,200</td>
<td>4.55</td>
<td>181,20</td>
<td>2.22</td>
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<tr>
<td>≥16</td>
<td>719,619</td>
<td>3,825</td>
<td>5.32</td>
<td>27,185</td>
<td>3.78</td>
<td>110,75</td>
<td>1.54</td>
</tr>
<tr>
<td>All levels</td>
<td>4,111,059</td>
<td>35,496</td>
<td>8.63</td>
<td>22,384</td>
<td>5.44</td>
<td>131,12</td>
<td>3.19</td>
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<tr>
<td>Excess mortality, %&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>38.35</td>
<td></td>
<td>51.72</td>
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<tr>
<td>Index of disparity&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>51.97</td>
<td></td>
<td>96.43</td>
</tr>
<tr>
<td>1996&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>&lt;12</td>
<td>859,956</td>
<td>8,002</td>
<td>9.31</td>
<td>45,475</td>
<td>5.29</td>
<td>345,55</td>
<td>4.02</td>
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<td></td>
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<td>54.66</td>
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<td>122.77</td>
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</table>

<sup>b</sup> [(Qr1 - Qr4)/Qr4] × 100, where “Tr” is the rate for the total population and “Qr4” is the rate for the ≥16 education category.
<sup>c</sup> The relative mean deviation index of disparity was calculated as ID = [(Qr1 - Qr4 + Qr2 - Qr4 + Qr3 - Qr4)/(Qr4)] × 100, where “Qr1” through “Qr4” are the rates for 4 educational groups, respectively.
of the gap in neonatal mortality between 1986 and 2001 (model 1), the adjustment for all of the covariates, including gestational age and birth weight in model 3, show no statistically significant difference between educational groups in 1986 and 1991 but a slightly increased RR of neonatal death associated with lower education in 1996 and 2001. The adjusted RRs associated with education increased significantly between 1986 and 2001 (model 3).

The crude RRs show particularly marked differentials in postneonatal mortality by maternal education, with the risk being ≥3.3 times greater in each cohort for mothers with <12 years of education than for those with ≥16 years of education (model 1). Even after the adjustment for all of the covariates, lower maternal education was associated with substantially increased postneonatal mortality, with the RRs associated with high school education or less significantly higher in 2001 than in 1986 (model 3).

Trends in Educational Disparities in Birth Weight–specific Infant Mortality

Although the RRs in Table 4 adjust for educational differences in the birth weight composition, they do not reflect the extent to which educational differences in infant mortality vary across different birth weight strata. Birth weight–specific analyses should reveal whether educational disparities in infant mortality are more pronounced among the low or normal birth weight (NBW) infants and whether such disparities have changed over time. Infant, neonatal, and postneonatal mortality rates show dramatic declines between 1986 and 2001 for the 3 birth weight strata (Table 5). The rate of decline in neonatal mortality during 1986–2001, however, was greater for very low birth weight (VLBW) and moderately low birth weight (MLBW) neonates in the highest educational category than in the lower educational categories. The adjusted RRs indicate significant educational differences in neonatal mortality risks of VLBW infants in 2001 but not in 1986. However, the adjusted RRs of neonatal mortality associated with education did not increase significantly between 1986 and 2001. Lower education was associated with a significantly decreased neonatal mortality risk for MLBW infants in 1986, which is consistent with a higher survival of socially disadvantaged infants at low birth weights (LBWs). However, this survival advantage disappeared by 2001. Among the NBW infants, the adjusted RRs of neonatal mortality associated with <12 years of education increased from 1.30 in 1986 to 1.62 in 2001 (Table 5).

The rate of decline in postneonatal mortality during 1986–2001 was markedly greater for VLBW and MLBW infants in the highest educational category than in the lower educational categories. Although maternal education, adjusted for covariates, was not significantly related to postneonatal mortality among VLBW and MLBW infants in 1986, it was significantly associated with increased mortality in 2001 (RR: 1.53 and 1.46 for <12 years of education, respectively). Among the NBW infants, the adjusted RRs of postneonatal mortality associated with <12 and 12 years of education increased from 1.97 and 1.35 in 1986 to 2.65 and 2.04, respectively, in 2001. The adjusted infant mortality risk associated lower education increased significantly between 1986 and 2001 for each birth weight stratum.

DISCUSSION

In this study, using a comprehensive area-based deprivation index and an individual SES measure of maternal education, we have analyzed the extent to which socioeconomic patterns in US infant, neonatal, and postneonatal mortality have changed in the last 3 decades. Infant mortality declined dramatically among all of the SES groups, and the absolute socioeconomic disparities generally narrowed in both neonatal and postneonatal mortality during 1969–2001, which should be viewed as a major public health success. To illustrate the public health impact of such declines, consider the following example (based on the data in Table 1). If all US infants experienced the mortality rate of infants in the highest SES group, there would have been ~87 434 fewer infant deaths during 1969–1974, compared with 39 867 fewer deaths during 1995–2000. Moreover, the absolute change during 1969–2000 also favored the most deprived group (a decline of 14 infant deaths per 1000 live births) compared with the least deprived group (a reduction of 9 deaths). A similar calculation shows more infants saved per 1000 live births during 1986–2001 for mothers with <12 years of education than for mothers with ≥16 years of education.

The success in reducing absolute disparities in infant mortality must be weighed against changes in the relative measures of disparity, which are particularly important for assessing the progress of various social groups relative to the best-off group toward reaching a health policy goal, such as the elimination of health disparities. Despite the impressive overall reductions in mortality over the long term, large socioeconomic inequalities in infant mortality persisted throughout the study period. Interestingly, socioeconomic disparities in infant mortality declined markedly between 1969 and 1984 both in absolute and relative terms. However, the absolute socioeconomic disparities in infant and postneonatal mortality, as measured by the summary inequality indices and crude and adjusted RRs, increased substantially since 1985. Improvements in infant mortality would be substantial if infants in the lower SES groups experienced mortality rates similar to those of the highest SES group.
<table>
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<tr>
<th>Maternal Education, y</th>
<th>Infant Mortality Model 1, Crude</th>
<th>Infant Mortality Model 2, Adjusted</th>
<th>Infant Mortality Model 3, Adjusted</th>
<th>Neonatal Mortality Model 1, Crude</th>
<th>Neonatal Mortality Model 2, Adjusted</th>
<th>Neonatal Mortality Model 3, Adjusted</th>
<th>Postneonatal Mortality Model 1, Crude</th>
<th>Postneonatal Mortality Model 2, Adjusted</th>
<th>Postneonatal Mortality Model 3, Adjusted</th>
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<td>RR 95% CI</td>
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<td>RR 95% CI</td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
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<td>1.78 (1.69–1.87)</td>
<td>1.33 (1.26–1.41)</td>
<td>1.01 (0.96–1.07)</td>
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<td>1.21 (1.15–1.27)</td>
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<td>1.26 (1.19–1.33)</td>
<td>1.03 (0.97–1.08)</td>
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a RRs are unadjusted for the effects of other covariates.

b RRs are adjusted for maternal age, race/ethnicity, marital status, birth order, infant sex, plurality, and prenatal care.

c RRs are adjusted for maternal age, race/ethnicity, marital status, birth order, infant sex, plurality, prenatal care, smoking during pregnancy (not available for the 1986 cohort), gestational age, and birth weight.
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<th>MLBW (1500–2499 g)</th>
<th>NBW (≥2500 g)</th>
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<td>Live Births</td>
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<td>Crude&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>Neonatal mortality, 2001</strong></td>
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<td><strong>Postneonatal mortality, 2001</strong></td>
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<td>13404</td>
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<td>1.98</td>
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<td>19.9</td>
<td>1.00</td>
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</tbody>
</table>

CI indicates confidence interval. Rates are per 1000 live births. Data are derived from the National Center for Health Statistics’ 1986 and 2001 National Linked Birth and Infant Death data files.

<sup>a</sup> All of the rates and RRs are based on all live births (100% data).

<sup>b</sup> RRs are unadjusted for the effects of other covariates.

<sup>c</sup> RRs are adjusted for maternal age, race/ethnicity, marital status, birth order, infant sex, plurality, and prenatal care.
The pattern of continuing socioeconomic disparities in US infant mortality over the past 3 decades is consistent with the persistent occupational social class inequalities in infant mortality in the United Kingdom between 1975 and 2001.\textsuperscript{10–32} Moreover, the recent pattern of increasing socioeconomic inequalities in US infant mortality coincides with increasing inequalities in US life expectancy and mortality among working-age adults and the elderly.\textsuperscript{8–10} However, the recent patterns in infant mortality differed from those for the United States during 1930–1960.\textsuperscript{19} Kitagawa and Hauser\textsuperscript{19} showed substantial gradients in infant mortality by census tract SES for the Chicago, IL, area in 1930, 1940, and 1960. Although infant mortality among white infants generally decreased with increasing SES levels in each period, the difference in infant mortality between the lowest and highest SES groups diminished markedly between 1930 and 1960. Our national findings also differed from those of an ecological study of birth outcomes in 30 health districts of New York City, NY, which showed a significantly decreasing income gradient in infant mortality during 1988–2001: the relative rate ratio of infant mortality between the lowest and highest income quartiles decreased from 1.66 in 1988 to 1.25 in 2001.\textsuperscript{16} A recent Canadian study also showed a narrowing of the SES gap, both in terms of rate differences and rate ratios.\textsuperscript{35} Infant mortality in urban Canada in 1971 was 97% higher in the poorest quintile compared with the richest quintile. However, by 1996, the inequality between the richest and poorest quintiles had diminished to 61%.

Changing socioeconomic inequalities in infant mortality over time may reflect temporal inequalities in the material and social living conditions between SES groups, both in absolute and relative terms. Absolute differences between deprivation groups in income, wealth, assets (as measured by homeownership and median home value), poverty, unemployment, female-headed households, and health care personnel per capita widened between 1970 and 2000 and were more pronounced in the 1990s than in the 1970s and 1980s.\textsuperscript{8–10} Similarly, the gap in relative income disparity between deprivation groups increased markedly.\textsuperscript{8–10} Income differentials between educational strata also widened considerably. The mean earnings differential between those without a high school diploma and those with more than a bachelor’s education increased from $10 527 in 1975 to $54 076 in 2001, and the ratio of mean earnings increased from 2.7 in 1975 to 3.9 in 2001.\textsuperscript{34}

Temporal socioeconomic inequalities in infant mortality may also be related to geographical and SES inequalities in the other important social, behavioral, and health care factors known to be associated with infant mortality. The key risk factors, smoking during pregnancy, delayed or no prenatal care, and lack of health care coverage, all strongly associated with increased infant mortality risks, vary substantially by county deprivation levels and maternal education.\textsuperscript{2,35} Although rates of smoking during pregnancy have declined for all educational groups, the pace of decline has been faster for women in the higher educational strata.\textsuperscript{38} As a result, educational disparities in smoking during pregnancy increased during the last decade. In 1992, women with less than a high school education were 7.1 times more likely to smoke during pregnancy than those with a college degree.\textsuperscript{37} In 2002, this differential increased to 11.8 times.\textsuperscript{17} Although long-term trend data on prenatal smoking are lacking, they are expected to be similar to the trend of consistently increasing educational disparities in smoking prevalence in the general female population.\textsuperscript{36} SES disparities in prenatal care use have also persisted in the past 2 decades.\textsuperscript{17,38}

Declining rates of teenage childbearing (births to mothers ≤20 years) and improved survival of LBW infants may also have contributed to the declines in overall US infant mortality. As shown here and based on other linked data, SES disparities have persisted despite substantial reductions in the incidence of teenage childbearing and in mortality of VLBW and MLBW infants over the long term.\textsuperscript{36} Socioeconomic differences in maternal health status, particularly such medical conditions as chronic and pregnancy-related hypertension, heart and lung disease, diabetes (including gestational diabetes), and anemia,\textsuperscript{22} may also have contributed to the declines in overall infant mortality. Other than reductions in smoking during pregnancy and improved medical care, the introduction of Medicaid in 1965, a federally funded public insurance program for poor and deprived children and socially disadvantaged groups, may have been responsible for declines in overall infant mortality and narrowing of the socioeconomic gap during 1969–1984.\textsuperscript{36} During the 1960s and 1970s, mortality from such leading causes of infant death as congenital anomalies, LBW, pneumonia and influenza, and infections all fell dramatically, possibly because of improved perinatal and neonatal medical care.\textsuperscript{12,36}

What might explain increasing socioeconomic disparities in US infant mortality since 1985? Controlling for such risk factors as prenatal smoking, prenatal care, preterm birth, and LBW partly accounted for the observed SES differences in infant mortality. However, significant differences remained, particularly for the more recent cohorts, indicating that maternal education has become an increasingly important predictor of infant survival in both the neonatal and postneonatal periods.

Birth weight–specific analyses presented here may shed some light on the potential factors responsible for the increasing disparity in infant mortality. Substantial absolute declines in the mortality of VLBW and MLBW infants between 1986 and 2001 across all of the education groups undoubtedly reflect the prominent role of improved access and use of obstetric and neonatal intensive care in reducing mortality.\textsuperscript{36,40} However, the rela-
tively slower declines in mortality among LBW infants from the lower SES groups have resulted in a widening of the educational gradient in neonatal and postneonatal mortality over time, thus suggesting a continuing gap in access to high-quality neonatal and infant health care across various SES groups.

Educational inequalities in total infant mortality are driven largely by educational gradients in mortality among NBW infants (because they compose >90% of all births), which not only have increased over time but have become quite steep. This may reflect an increasingly important role of social and environmental influences on infant mortality risks in the United States. Cause-specific mortality analyses are needed to identify more precisely what factors might have been responsible for increasing or persistent socioeconomic inequalities in infant mortality. A recent US study showed substantial and persistent area SES disparities in infant mortality from such major causes of death as congenital anomalies, sudden infant death syndrome (SIDS), LBW, and injuries. Although birth defects mortality declined impressively during 1969–2000 for all groups, the deprivation gradient widened substantially since 1985, a temporal pattern consistent with that shown here in overall infant mortality. SIDS mortality showed much steeper deprivation gradients in the 1990s than in the 1980s. Infant mortality because of LBW rose significantly between 1986 and 1998 for more deprived groups but remained stable for less deprived groups, leading to increasing SES disparities in mortality from this cause.

When first introduced in the general population, specific behavioral and public health interventions and advances in medical care may lead to an improved overall population health but may very well increase health disparities, particularly in the short run. Such is the case with SIDS mortality in the United States, which declined dramatically in the 1990s but saw social inequalities widen between 1989 and 1998 despite the introduction in June 1994 of the Back to Sleep campaign. Two recent Norwegian studies also found an increasing educational inequality in postneonatal and SIDS mortality in Norway between 1969 and 1995.

Differentials in infant mortality between deprivation groups shown here are probably underestimated, because we used counties, rather than smaller and more homogeneous geographic areas, such as census tracts or neighborhoods, to define deprivation groups. Many US counties are large geographic areas or population units with substantial socioeconomic heterogeneity. Unfortunately, national vital records data do not identify geographic areas smaller than counties for confidentiality protection of individual information on birth and death certificates. Vital records for some states, such as those for California, Massachusetts, North Carolina, Virginia, and Kansas, may contain census tract or block group geocodes for the 1990 and 2000 censuses that could allow investigators to define deprivation levels at the neighborhood level, resulting in less misclassification of area-based SES. However, because the 1970 and 1980 censuses were not fully tracted, temporal analyses of census tract-based disparities in infant mortality, unlike our county-based analysis, may not extend as far back as 1969. The 1990 deprivation index has been shown to provide a stable socioeconomic classification of counties over time, and the use of the 1980 index produced infant mortality trends similar to those based on the 1990 Index. The deprivation indices for the 1970, 1980, and 1990 censuses were highly correlated. The correlation of the 1990 index with the 1970 and 1980 indices was 0.90 and 0.94, respectively. Thus, the sole use of the 1990 index to construct deprivation quintiles for the entire study period is unlikely to have caused any substantial area misclassification, and the general trend of persistent inequalities in infant mortality holds regardless of which index is used.

Although this study focused on trends in overall socioeconomic disparities, it is important to note that both area- and individual-level SES gradients in infant mortality do vary by race/ethnicity. Our analysis revealed that the area deprivation gradients were more pronounced and consistent for whites than for blacks (data not shown). Disparities in infant mortality by maternal education were also greater for whites than for blacks, Hispanics, and Asian/Pacific Islanders. Changes in the extent of SES disparities in infant mortality over time for major racial/ethnic groups will be explored more fully in a subsequent article.

Behavioral and health policy interventions (e.g., smoking reduction, tobacco regulation and advertising, improving access to and use of early and comprehensive prenatal care, and universal health care coverage) have the potential to reduce socioeconomic inequalities in infant mortality in both absolute and relative terms. Large socioeconomic disparities in infant mortality remain one of the primary reasons for the continued unfavorable international standing of the US infant mortality rate when compared with rates for the other industrialized countries; the US ranking dropped from being the 11th best in 1960 to only the 28th best in 2002. Continuing SES disparities in infant mortality may also prove to be a major obstacle in reaching the Healthy People 2010 goals. As shown here, the infant mortality rates for the 3 most deprived groups in 2000 (representing ~60% of the total population) and for those with high school education or less in 2001 (representing 53% of all mothers) were all greater than the year 2000 national target of 7 deaths per 1000 live births. It will be a formidable challenge to meet the 2010 target of 4.5 deaths per 1000 live births, particularly for infants in the most disadvantaged SES groups, of which the mortality rates would have to be reduced by 50% during this decade.
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A Cross-sectional Survey of Levels of Care and Response Mechanisms for Evolving Critical Illness in Hospitalized Children

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ABSTRACT

OBJECTIVES. Recognition and treatment of evolving critical illness is a fundamental element of hospital care. Hospital systems should triage patients to receive appropriate levels of care. We describe here the levels of care, the frequency of near or actual cardiopulmonary arrest (code-blue events), identification mechanisms, and responses to evolving critical illness in hospitalized children.

METHODS. A cross-sectional telephone survey of Canadian and American hospitals with ≥50 pediatric acute care beds or ≥2 pediatric wards was performed. Regression analysis identified factors associated with the frequency of code-blue events after adjustment for hospital volume.

RESULTS. Responses from 388 (84%) hospitals identified the 181 eligible pediatric hospitals included in this survey. All had a PICU, 99 (55%) had high-dependency units, 101 (56%) had extracorporeal membrane oxygenation therapy, and 69 (38%) used extracorporeal membrane oxygenation therapy for refractory cardiopulmonary arrest. All of the hospitals had immediate-response teams. They were activated 4676 times in the previous 12 months. Twenty-four percent of hospitals had activation criteria for immediate-response teams. Urgent-response teams to treat children who were clinically deteriorating but not at immediate risk of cardiopulmonary arrest were available in 136 (75%) hospitals; 29 (17%) had formal medical emergency teams, and 92 (51%) consulted the PICU. Code-blue events were more common in hospitals with extracorporeal membrane oxygenation therapy, cardiopulmonary bypass, and larger PICU size.

CONCLUSIONS. Currently, the organization of Canadian and American pediatric hospitals includes dedicated areas to match patient acuity and additional personnel to stabilize and facilitate transfer. The functioning of these systems of care results in calls for immediate medical assistance for ward patients ~5000 times annually.
The recognition and treatment of children admitted to hospital wards with evolving critical illness is a fundamental element of hospital care. The ultimate consequence of incomplete recognition or ineffective treatment is cardiopulmonary arrest. High mortality and neurocognitive morbidity in survivors makes cardiopulmonary arrest extremely undesirable. Near arrest is also associated with considerable morbidity and hospital mortality.

Multiple safeguards exist to prevent and treat cardiopulmonary arrest including the frontline care provided by ward nurses and physicians, the use of urgent-response teams, such as medical emergency teams (METs), and in cases of immediate medical need by formal resuscitation (“code-blue”) teams. The purpose of urgent-response teams is to provide required care to improve the child’s condition, thus preventing the need for escalation in the level of care, to facilitate timely admission to the HDU or ICU, or to discuss appropriate end-of-life care. METs have been widely implemented in adult hospitals despite limited evidence to support their introduction. The current frequency of implementation of METs and other urgent-response mechanisms in pediatric hospitals is unknown. To better understand current practice in large- and medium-sized North American pediatric hospitals, we conducted a cross-sectional survey to describe the available levels of care and response mechanisms to evolving critical illness in children.

Methods
A telephone survey was designed, pretested, and administered to clinician administrators in Canadian and American acute care pediatric hospitals. Its purpose was to describe the number and capacity of the levels of care provided in the hospital, the types of response teams for children who were recognized to be clinically deteriorating, their composition, and frequency of activation. Eligible hospitals had ≥2 (nonneonatal) pediatric wards and/or ≥50 acute inpatient beds for patients aged ≤18 years of age.

Survey Development
The questionnaire was developed by 2 investigators (Ms VandenBerg and Dr Parshuram) and consisted of 42 questions. The levels of care available in each hospital were documented by asking respondents about the numbers of acute care, HDU and ICU beds, and the availability of pediatric cardiopulmonary bypass, extracorporeal membrane oxygenation therapy (ECMO), and the use of ECMO, through extracorporeal cardiopulmonary resuscitation (ECPR), to restore circulation in children with refractory cardiopulmonary arrest.

Respondents were asked to describe the availability, composition, activation criteria, and frequency of activation for “immediate” (code-blue or cardiac arrest) and “urgent” response teams. We defined immediate (code-blue) response teams as those who were called to treat ward patients with impending or actual cardiopulmonary arrest. Urgent-response teams were defined as those who treated ward patients who were appreciated to be clinically deteriorating but who were not at risk of imminent cardiopulmonary arrest. When a hospital had 1 team functioning as both the immediate and urgent-response team, the team was classified as an immediate-response team, and the composition of the urgent-response team was described as a code-blue team. Ward patients were defined as all of the hospital inpatients aged ≤18 years who were cared for outside the ICU, operating room, or delivery room areas. The survey was reviewed by members of the Canadian Critical Care Trials Group for content and face validity and was pretested in 5 health care professionals representing 5 different hospitals.

Hospital Identification
A database of potentially eligible hospitals was created from an existing database of the investigators. Internet searches for hospitals by province or state, and local knowledge of respondents in surveyed hospitals. The American Hospital Directory was searched to identify freestanding pediatric hospitals and general hospitals with >450 acute care beds. These were included in the list of hospitals to be contacted.

Survey Administration and Data Collection
The survey was administered by telephone. The informed respondents included resuscitation committee chairs, pediatric intensive care directors, and acute care clinical nurse specialists. Contact with potential respondents was either made directly, or telephone appointments were made. The professional background and administrative position of the respondent and the number of contact episodes were recorded. We did not ask respondents to specify the source of their information.

Analysis
The data about levels of care and response teams were represented by median and interquartile ranges (IQRs). Linear regression analyses were performed to evaluate the association of the occurrence of urgent and immediate-response teams with available level of care and...
response team variables. The number of acute care beds was kept in all of the models to control for the effect of hospital volume. The raw data from the survey data were entered into a custom-made Microsoft Access Database (Redmond, CA) and were analyzed using SAS 9.1 (SAS Inc, Cary, NC).

RESULTS
The survey was conducted over an 8-week period ending July 26, 2005. A total of 464 eligible North American hospitals from 51 states or commonwealths of the United States of America and 12 provinces of Canada were identified and contacted. Responses were received after 1091 contact episodes with 964 health care professionals from 388 hospitals, for a response rate of 84%. The main reason for nonresponse was failure to contact the potential respondent directly. Of the responding hospitals, 181 (47%) hospitals met inclusion criteria; 16 (8%) were Canadian hospitals; 165 (92%) were American; and 85 (47%) were freestanding pediatric acute care hospitals. These hospitals represented 24 874 acute care pediatric beds, composed of 6861 NICU, 2811 PICU, 715 HDU, and 14 487 general beds. The primary respondents from these hospitals were PICU staff physicians or chairs of code-blue committees in 87 hospitals (48%) and acute care nurse specialists in the remaining 103 hospitals (52%).

Levels of Care
All 181 of the hospitals had a PICU. 170 hospitals (94%) had a NICU, 99 (55%) had an HDU, 108 (60%) had cardiopulmonary bypass, 101 (56%) used ECMO, and 69 (38%) used ECMO for ECPR. The median number of acute care beds was 113 (Table 1). There were 64 hospitals (35%) with ≥150 acute care beds.

PICUs and HDUs
All 181 of the hospitals had a PICU. The median number of PICU beds was 14 (IQR: 9.5–20). PICUs were larger in hospitals with cardiopulmonary bypass, ECMO, and rapid response ECMO. Respondents in the 99 hospitals with HDU beds differentiated HDU beds from ward beds, by “higher acuity” of patients, the availability of additional therapies (13%), and a higher nurse/patient ratio (84%). The median number of HDU beds per hospital was 4 (IQR: 2–7); 47 HDUs (47%) were located within the PICU, whereas 52 (53%) were separate from the PICU. The child’s primary service directed care in the HDU in 37 hospitals (37%), a PICU physician directed care in 54 (55%), in 7 (7%) the care was shared between PICU and ward physicians, and in 1 (1%) hospital this was not known.

Urgent-Response Mechanisms
The child who was appreciated to be clinically deteriorating but was not at risk of imminent cardiopulmonary arrest was treated by a team other than the primary service in 136 hospitals (75%). These urgent-response personnel were staff from the PICU in 92 (51%), a team identified as a pediatric MET (PMET) in 29 (17%), the pediatric code-blue team in 14 (8%), and an adult MET in 1 (0.6%) of the hospitals surveyed. Having a specific PMET was not associated with the numbers of acute care beds (P = .85), PICU beds (P = .65), HDU beds (P = .47), or with hospitals having cardiopulmonary bypass (P = .62), ECMO (P = .95), or using ECPR (P = .29).

The 29 PMETs were composed of 1 to 9 members, with a median number of members of 3 (IQR: 1–6) in the day and 2.5 (IQR: 1–5) at night (P = .13). In the daytime there were 12 “teams” with 1 member. These were staff physicians (n = 9), registered nurses (n = 2),

| TABLE 1 | Hospital Attributes Versus the Frequency of Near or Actual Cardiopulmonary Arrest |
|-----------------|-----------------|-----------------|-----------------|
| Hospital Attribute | Total | Hospital Frequency of Code Blue | p* |
| Capacitya | | | |
| Acute care (total) | 113 (80–200) | 105 (82–134) | 118 (76–200) | .600 |
| HDU | 4 (2–7) | 2 (2–4) | 3 (2–7) |
| PICU | 14 (9.5–20) | 11 (8–17) | 14.5 (10–24) | .024 |
| Service characteristicsb | | | |
| Closed PICU | 85 (47) | 18 (20) | 22 (25) | .605 |
| Cardiopulmonary bypass | 108 (60) | 17 (16) | 30 (28) | .016 |
| ECMO | 101 (56) | 15 (15) | 26 (26) | .044 |
| ECPR | 69 (38) | 11 (16) | 19 (28) | .084 |
| Urgent-response team | | | |
| Any team | 136 (75) | 25 (18) | 33 (24) | .168 |
| Code-blue team | 14 (8) | 2 (14) | 4 (29) | — |
| PMET | 29 (16) | 11 (38) | 5 (17) | — |
| PICU team | 92 (51) | 12 (13) | 24 (26) | — |

To illustrate associations between hospital attributes and the frequency of code-blue events, we describe the 25% hospitals with the fewest (least frequent column) and 25% of hospitals with the greatest (most frequent column) number of code-blue events per hospital bed.

a P values were calculated by using generalized linear regression incorporating adjustment for the number of acute care beds.

b The numbers of hospital beds (acute care, PICU, and HDU) are represented as the median plus IQR in parentheses.

c The service characteristics of hospitals are represented as the number of hospitals with the percentage in parentheses.
and a pediatric resident ($n = 1$). Two of the 29 hospitals provide PMET only during the day. There were 9 single-member teams composed of staff physicians ($n = 5$), registered nurses ($n = 2$), and pediatric residents ($n = 2$). There was a designated leader in all but 1 team, and a designated airway staff in 14 teams (Table 2). Team members were required to have a formal pediatric resuscitation qualification in 27 hospitals (93%).

Respondents indicated that “anyone” was able to activate the urgent-response personnel in all of the hospitals. Criteria to determine when to activate a PMET response were reported to be used in 6 (21%) of 29 hospitals. The stated criteria included seizures, “unstable” vital signs, “abnormal” heart rate, decreasing oxygen saturation, “increased work of breathing,” “nurse concern,” “uncontrolled” hemorrhage, and attempted suicide. The frequency of training for urgent-response teams was reported in 13 of the 29 hospitals: teams trained weekly ($n = 1$), twice each month ($n = 1$), monthly ($n = 6$), quarterly ($n = 2$), and annually ($n = 2$).

Urgent-response personnel were called a median of 48 times per year (IQR: 12–144). This was not associated with the number of acute care, HDU, or PICU beds or the number of code-blue events per year (all $P > .47$).

Immediate-Response Teams
A team was organized to respond to a call for immediate medical assistance to treat near or actual cardiopulmonary arrest in all of the hospitals. Formal pediatric resuscitation teams were used in 173 hospitals (96%). The remaining 8 hospitals used either an adult cardiac arrest team ($n = 2$) or an informal pediatric team ($n = 6$). Immediate-response teams had 2 to 15 members, 169 (98%) had a predesignated leader, and 159 (91%) had predesignated airway staff. The median team size was 7 (IQR: 5–9) at night and 8 (IQR: 6–9) in the day ($P < .0001$). At night there were fewer teams with a staff physician (76 vs 41; $P < .0001$; Fig 1). Training for immediate-response teams occurred in 173 hospitals (96%). The median frequency of training was 12 (IQR: 4–12) times per year. The maximum training frequency was twice per week.

In all of the hospitals, anyone was able to call the immediate-response team. There were 43 hospitals (24%) with calling criteria. These included some specific items, such as heart rate <$60$ beats per minute, apnea, and “unresponsive.” Code-blue teams were activated a median of 14 (IQR: 6–36) times per annum in each hospital and a total of 4676 times each year in the surveyed hospitals (Fig 2).

After adjustment for the number of acute care beds in each hospital, there were 3 factors associated with the frequency of code-blue calls at the $P = .05$ level (Table 1). More code-blue events occurred in hospitals with cardiopulmonary bypass, ECMO, and larger PICUs. Having an urgent-response team was not associated with the frequency of code-blue events ($P = .17$).

DISCUSSION
Our survey provides a cross-sectional description of large- and medium-sized pediatric hospitals in Canada.
and the United States. We found that comprehensive infrastructure existed in the 181 hospitals surveyed. All had ≥2 levels of care (ward, HDU, PICU, and ECMO) to deliver care to children as determined by their severity of illness. Children admitted to hospital wards who were clinically deteriorating could be treated by their primary service in all and by urgent-response personnel in 75% of hospitals. Children who had progressed to near or actual cardiopulmonary arrest were treated by immediate-response (code-blue) teams in all of the hospitals. Despite this comprehensive system of care, code-blue teams were activated ≥5000 times each year to provide immediate treatment for children with near or actual cardiopulmonary arrest. This represents a significant source of acquired morbidity and mortality, which may be preventable. Assuming a bed occupancy of 80%, this translates into a mean of 0.71 events per 1000 bed days. With bed occupancy at 100%, the event rate is 0.52 events per 1000 patient days. These rates are lower than the 1.5 code-blue events per 1000 patient days in our center.

The reasons for the disconnect between the existing systems of care and the high frequency of near or actual cardiac arrest are likely to be complex. Several explanations may be extrapolated from our data. First, we found 3 hospital characteristics that were associated with the frequency of calls for immediate medical assistance to treat near or actual cardiopulmonary arrest. Hospitals with cardiopulmonary bypass, ECMO, and those with larger PICUs may tend to care for children who are, on average, more complex and at higher risk for clinical deterioration.

Unlike the ACADEMIA (Antecedents to Cardiac Arrests, Deaths, and Emergency Intensive Care Admissions in Australia and New Zealand) investigators, we found that hospitals with more PICU beds had more frequent code-blue events. Several factors associated with larger PICUs may explain this finding: the patients in inpatient wards of hospitals with larger PICUs may be sicker; the health care professionals working outside the PICUs of hospitals with greater centralization of critical care expertise may be either relatively deskilled or have a higher threshold for calling for help; and the movement of patients between the inpatient wards and the PICU may be relatively inefficient, or premature ICU discharges may be more common in larger hospitals. Other factors, including patient acuity, the nurse/patient ratio, and local arrest or near-arrest reporting practices may be important determinants that were not measured in this survey.

Having an MET or HDU beds was not associated with lower rates of near or actual cardiopulmonary arrest. It seems reasonable to suggest that hospitals with higher baseline (pre-MET) rates of near or actual cardiopulmonary arrest are more likely to have either implemented a MET team or to have an HDU. However, it cannot be assumed that METs are effective in the light of limited pediatric data and a negative-cluster randomized trial of 120,000 adult admissions in 23 hospitals. Despite this, an additional 23 hospitals (13%) reported that they were in the process of developing a PMET.

Second, we found that less than a quarter of hospitals had specific criteria to identify patients in need of referral to urgent and immediate-response teams. Delays in
the identification and referral of patients with evolving critical illness to response teams in hospitals with and without identification criteria have been described previously. The MET calling criteria listed by respondents were generally subjective and imprecise (unstable vital signs and decreasing oxygen saturation). Items such as “clinical concern,” judgment, and experience can also be used to identify sick patients. Although this approach is widely used, it has not eradicated the need for immediate assistance to prevent cardiopulmonary arrest in this and other reports.

Third, diurnal staffing patterns of hospital inpatient wards may be contributing to the frequency of near or actual cardiopulmonary arrest. We found reduced staffing of code-blue and intermediate-response teams at night versus the day and, specifically, reductions in the inclusion of staff physician(s) on the team. Although the delivery of health care is predominantly organized on a Monday to Friday daytime basis, critical illness is a 24-hour, 7-day phenomenon. Reduced hospital staffing at night is likely to increase rather than decrease the need for staff to respond to children who are clinically deteriorating and to increase the risk of adverse events, such as cardiopulmonary arrest.

Finally, it may be that the roles of urgent and immediate-response teams are merging. Formal resuscitation teams, such as the code-blue team, may already be performing the role anticipated of the MET or vice versa. This phenomenon was described in the Australian adult MET study and in 1 pediatric hospital. Our data taken with recent data from the National Registry of Cardiopulmonary Resuscitation suggest that the proportion of code-blue calls that are for children with actual cardiopulmonary arrest is probably small. In turn, this suggests that the roles of pediatric MET and code-blue teams may have significant overlap.

LIMITATIONS
There are several limitations to this survey. First, this cross-sectional survey was administered by telephone to voluntary respondents. Respondents had limited time to confirm the data that they provided, and the investigators did not verify the accuracy of the responses, nor did we ask the source of the data on which the response was based. However, respondents were senior clinician administrators, from physician and nursing backgrounds, thus, we believe that the information is likely to be representative in each institution. Second, the results may not be generalizable to other hospitals. The 84% response rate suggests that the results are likely to be representative of large- and medium-sized pediatric hospitals; however, they may not apply to hospitals with <50 beds or in other cultural and geographic areas. Third, our data are cross-sectional, and we are unable to provide information about the temporal trends in pediatric inpatient resuscitation. Finally, whereas it can be argued that immediate calls for medical assistance are a manifestation of system failure, the clinical significance of late recognition and treatment of critical illness in children has not been well quantified. Previous work suggests that adults and children can be identified well before near or actual cardiopulmonary arrest and that “near” cardiac arrests are associated with morbidity and mortality. However, further work is required to evaluate the clinical impact of timely identification and referral of children with evolving critical illness to urgent-response teams.

CONCLUSIONS
This cross-sectional survey of 181 North American pediatric hospitals found that the infrastructure exists to meet the requirements that the spectrum of disease severity anticipated in hospitalized children. The systems of care included specific response personnel to facilitate that transfer of sicker children to higher levels of care in three quarters of hospitals. Calls for immediate medical assistance were made ~5000 times in the preceding year. Reorganization of current systems of care is required if cardiopulmonary arrest is to be prevented and the outcomes of hospitalization improved.

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REFERENCES
Follow-up Care for Infants With Chronic Lung Disease: A Randomized Comparison of Community- and Center-Based Models

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ABSTRACT

OBJECTIVES. Premature infants with chronic lung disease benefit from comprehensive care, which typically is based in tertiary medical centers. When such centers are not easily accessible, alternative models of care are needed. The purpose of this work was to compare community-based follow-up, provided via telephone contacts, to traditional center-based follow-up of premature infants with chronic lung disease.

PATIENTS AND METHODS. After discharge from neonatal intensive care, 150 premature infants with chronic lung disease were randomly assigned to either community-based (n = 75) or center-based (n = 75) follow-up. In community-based follow-up, a nurse specialist maintained telephone contact with the infant’s primary caregiver and health care providers. Center-based follow-up consisted of visits to a medical center–based multidisciplinary clinic staffed by a neonatologist, a nurse specialist, and a social worker. The outcomes of interest were Bayley Scales of Infant Development mental developmental index and psychomotor developmental index, Vineland Adaptive Behavioral Composite, and growth delay (weight for length <5th percentile) at 1-year adjusted age and respiratory rehospitalizations through 1-year adjusted age.

RESULTS. In each randomization group, 73 infants survived, and 69 were evaluated at 1-year adjusted age. The median mental development index (corrected for gestational age) was 90 for both groups. The median psychomotor developmental index was 82 for the center-based group and 81 for the community-based group. The median Vineland Adaptive Behavioral Composite was 100 and 102 for the center-based and community-based groups, respectively. In the center-based and community-based groups, respectively, the proportions with growth delay were 13% and 26%, and the proportions rehospitalized for respiratory illness were 33% and 29%.

CONCLUSIONS. Infants randomly assigned to community-based, as compared with those randomly assigned to center-based follow-up, had similar developmental and health outcomes. The former approach might be a preferred alternative for families in rural settings or families for whom access to a tertiary care medical center is difficult.
The American Academy of Pediatrics recommends that children with special health care needs receive comprehensive and coordinated care.1 Such care, provided to very low birth weight infants, decreases the risk of serious illness requiring hospitalization in the first year of life after discharge from neonatal intensive care.2 Among very low birth weight infants, chronic lung disease (CLD) is the most prevalent chronic illness and underlies many of their special health care needs.3

Infants with CLD are prone to frequent respiratory illnesses, feeding difficulties,4 growth failure,5–7 and rehospitalization during infancy,6,8 and their families incur financial and psychosocial costs during and after their infants’ neonatal intensive care.9,10 After resolution of severe pulmonary symptoms, children recovered from CLD are at increased risk for cognitive impairment,11,12 motor11 and language impairment,13–15 hearing loss,16 and poor academic performance.14

We and others have described models for providing special health services and support to children with CLD and their families after hospital discharge.17–20 Children with CLD who received multidisciplinary comprehensive care at a regional medical center, when compared with historical control subjects, had improved health and developmental outcomes.17 Although multidisciplinary care clinics seem to benefit children with special health care needs, such clinics may not be easily accessible to some families, for whom alternative models of care may be preferable.

On the basis of a model developed for providing prenatal support to mothers at high risk for preterm delivery,21 we developed an alternative to medical center–based follow-up of prematurely born infants with CLD. In this model, which we will refer to as community-based care, medical management was coordinated by a nurse specialist through frequent telephone contacts with the infants’ primary caregiver. Here we report the primary results of a randomized comparison of community-based care with the more traditional model of multidisciplinary medical center–based care for prematurely born infants recovering from neonatal CLD. We hypothesized that the 2 models would lead to similar developmental and health outcomes during the first year of life.

METHODS

Study Design
The study was a randomized comparison in which participants were not blinded as to the intervention, but those who assessed the primary outcome were blinded. The study was approved by the Wake Forest University Health Sciences Institutional Review Board.

Study Participants
Study infants were born between March 1996 and April 1999; follow-up assessments were completed between June 1997 and August 2000. Infants who were eligible for the study were identified by weekly contact with 5 NICUs, which, at the time of the study, were the only sites providing neonatal intensive care in a 20-county region in northwest North Carolina. Infants were eligible if they were born before 33 weeks’ gestational age, required supplemental oxygen at 36 weeks’ postmenstrual age, and were discharged from the hospital after neonatal intensive care. Neonates who had a major congenital anomaly or a tracheostomy were excluded, as well as families in which the mother did not speak English (because the intervention depended on verbal communication with the nurse specialist) and families who lived >150 miles from our clinic (because such families typically are referred to regional neonatal centers closer to their homes). The nurse specialist (Ms Hiatt) visited the family in their home to establish a relationship before random assignment. Written informed consent to participate in the study was obtained from the parent of each randomly assigned infant.

Random Assignment
For each of the sites at which infants were recruited, a list of randomization assignments, in block sizes of 2 or 4, was prepared by a biostatistician (Dr Legault). These lists were kept in a sealed envelope in a locked drawer, and after each study participant arrived home from the NICU, a research assistant informed the nurse specialist (Ms Hiatt) of the randomization assignment. The nurse specialist then informed the family, primary care provider, and study neonologists. Within 24 hours after random assignment, the principal investigator called each infant’s primary care provider to inform him or her of the study and the infant’s randomization assignment. Although data were collected from all members of multiple gestations, only 1 member was selected at random for inclusion during the analysis of data, because infants from a multiple gestation were not regarded as independent observations. The randomization process and the patient flow are described in Fig 1.

Intervention
For the center-based group, the intervention team included the nurse specialist, a social worker, and 2 study neonologists (Drs O’Shea and Dillard). The community-based group received direct contact only from the nurse specialist, although the nurse specialist involved the study neonologists in specific circumstances, as described below.

If a family lacked telephone service when their infant was discharged, a telephone was installed at no cost to the family, within 1 week of the infant’s discharge from the hospital. All of the families who participated in the study were reimbursed for the cost of local telephone service for the duration of the study. Families assigned to either intervention could contact the nurse specialist on...
a toll-free long-distance line; a voice mail system recorded messages when the telephone was not attended.

Community-Based Follow-up
The nurse specialist called the infants’ primary caregiver twice weekly in the first month after discharge, weekly in months 2 through 4, and monthly thereafter until the infant attained 12 months’ adjusted age. At each telephone contact, the nurse specialist used a questionnaire to inquire about the infant’s health, community resources used by the infant, potential stressors and sources of support for the family, and the infant’s medications and feedings. If she judged that the infant would benefit from a change in medical management, additional assessments (eg, pulse oximetry), or a subspecialty referral, she discussed the infant with 1 of the study neonatologists and then communicated recommendations to the family and the infant’s primary care provider. The nurse specialist also coordinated care by communicating with home health nurses, public health nurses, early intervention specialists, physical therapists, and pediatric subspecialists. The primary care provider was contacted by the nurse specialist whenever she believed that a change in care was indicated.

Medical Center–Based Follow-up
For infants who were discharged from the hospital using supplemental oxygen, the nurse specialist made a home
visit 1 to 2 weeks after discharge. During this visit, she obtained an interim medical history, performed a physical assessment including pulse oximetry, and reviewed discharge instructions regarding medications and durable medical equipment. If concerned about the infant, she consulted a study neonatologist and, if appropriate, recommended a change in the plan of care.

All of the infants in the center-based care group were seen in a multidisciplinary clinic for high-risk infants at Wake Forest University School of Medicine. Each visit included assessments by the social worker, nurse specialist, and a study neonatologist. The social worker assessed family stressors and resources; the nurse specialist obtained an interim medical history (feeding, respiratory status, medication use, illnesses, and health-services use) and anthropometric measurements; and the neonatologist performed a physical examination. Together, the 3 developed a plan of care, which the nurse specialist communicated to the family.

For all of the infants, the first clinic visit was scheduled for ~1 month after their discharge, and subsequent visits were scheduled at 4, 8, and 12 months’ adjusted age. In addition, infants using supplemental oxygen were scheduled for visits every 1 to 2 months until they were no longer using supplemental oxygen, medications, or an apnea monitor and their growth rate was 15 to 30 g per day. After each clinic visit, a letter describing findings, impressions, and recommendations was sent to the primary care provider.

Care During Rehospitalizations
When an infant in the community-based follow-up group was rehospitalized, the study neonatologists were not involved in medical decisions during the hospitalization. When an infant randomly assigned to center-based care was rehospitalized at our medical center, the study neonatologist visited the infant in the hospital and served as a consultant to the attending physician.

Guidelines Used for Both Groups
A written protocol for management of CLD in neonates was developed on the basis of a National Institutes of Health consensus conference, and a copy was mailed to each infant’s primary care provider. The general underlying principle was that infants’ health was considered satisfactory if they gained 15 to 45 g of body weight per day and had no clinical features of the following: (1) gastroesophageal reflux (irritability and/or back arching during feeding or frequent regurgitation with poor weight gain); (2) excessive fluid retention (tachypnea, retractions, rales, excessive weight gain, liver enlargement, poor feeding, and oxygen saturations <92%); (3) obstructed airways (wheezing, prolonged expiratory phase of respirations, and liver edge felt >2 cm below the costal margin); or (4) delayed motor development (25% delay in the attainment of gross motor milestones). These signs and symptoms were assessed at each clinic visit of infants in the center-based follow-up group, and on the basis of the findings, the care plan was developed. In the community-based group, symptoms of gastroesophageal reflux and respiratory distress were based on parents’ or guardians’ report, as ascertained by the nurse specialist during telephone contacts; and data about oxygen saturations were collected each month by home health respiratory therapists.

While at home, infants for whom supplemental oxygen was prescribed received oxygen by nasal cannula, as 100% oxygen from H cylinders; portable D or E cylinders were used outside the home. Before discharge from the hospital, a respiratory therapist met with families and instructed caregivers on the use of oxygen and cardiorespiratory monitors. Respiratory therapists visited the infants’ homes every 4 to 6 weeks to ensure appropriate functioning of the equipment. Pulse oximetry was performed at least monthly on all of the infants who were using supplemental oxygen (for the center-based care group, within our multidisciplinary clinic; for the community-based follow-up group, by home health respiratory therapists). According to the manufacturer’s specifications, the pulse oximeter used in our clinic had a time-averaging interval of 4 to 7 seconds and was accurate to within 3%. Pulse oximetry was performed at rest, during an entire feeding, and for ~10 minutes after a feeding. If the oxygen saturations were consistently above 95%, the oxygen flow rate was decreased by 0.1 L/min, and pulse oximetry was repeated. If the saturations remained consistently >92%, the flow rate was maintained at this new (lower) level until the next clinic visit. Infants whose oxygen requirements increased over consecutive visits to the clinic were referred to a pediatric pulmonologist for consultation.

A cardiorespiratory monitor was prescribed for infants who used supplemental oxygen or had persistent apnea at the time of discharge from the hospital. Typically, the monitor was discontinued within 1 to 2 months after the infant was weaned to room air, except when the parent requested that the monitor be continued beyond that point.

For all of the infants, 100.42 J (24 cal)/oz of formula or fortified human milk was prescribed until the infant had weaned to room air. The adequacy of nutrition was assessed by computing the average daily weight gain between clinic or telephone patient encounters. If the average weight gain was >15 g per day, no changes were made in the infant’s nutrition. If the average weight gain was <15 g per day, a plan was developed to address the presumed cause, such as hypoxemia or inadequate caloric intake.

Most infants who required supplemental oxygen at discharge were treated with chlorothiazide and spironolactone. Serum potassium and sodium had been assessed during the hospitalization, and hypokalemia and hypo-
natremia were not present in any of the infants at the time of discharge. Electrolytes were not monitored routinely after discharge, except in the small number of infants who were treated with furosemide. Inhaled albuterol and corticosteroids were prescribed for infants with wheezing. Gastroesophageal reflux was treated with cisapride or metoclopramide, plus ranitidine. Monthly immunoprophylaxis against respiratory syncytial virus was prescribed for all of the subjects. At the discretion of the attending neonatologists, postdischarge private duty nursing was prescribed before discharge (and randomization).

Measurements

Prerandomization Measures
A research assistant collected baseline data (eg, gestational age and neonatal complications) from medical charts. Information about the family demographics, stressors, resources, and rehospitalizations were collected by questionnaires completed by the mother or primary caregiver before random assignment.

Gestational age was based on the date of the mother’s last menstrual period unless this was not available, in which case an obstetrician’s estimate was used; when no prenatal estimate was available, gestational age was based on assessment of the neonate.24 “Small for gestational age” was defined as a body weight less than the 10th percentile for gestational age and gender.25 The radiologist’s reports on cranial ultrasound were abstracted from medical charts. If the results of the cranial ultrasound were reported as normal by the radiologist, the ultrasound was classified as normal. Reports of abnormal cranial ultrasounds were reviewed by 1 of the study neonatologists (not blinded to treatment assignments) and classified as described by Stewart et al.26 Posthemorrhagic hydrocephalus, persistent ventricular dilatation, and periventricular echolucency were considered to be major abnormalities. The severity of lung disease was classified by a pediatric radiologist, using the severity scale described by Weinstein et al (grades 1–6, with 6 being the most severe).27 To estimate the number and duration of telephone contacts in the 2 groups, the study nurse recorded the data about the number and duration of telephone contacts for the first 92 infants randomly assigned (45 in the center-based group and 47 in the community-based group).

Outcomes Assessed at 1-Year Adjusted Age
The primary outcome of interest was the Bayley Scales of Infant Development–Second Edition (BSID) mental developmental index (MDI), a widely used measure of early cognitive functioning.28,29 Secondary outcomes were BSID psychomotor developmental index (PDI), Vineland Adaptive Behavioral Composite, growth delay, neurodevelopmental impairments, and rehospitalizations through 1-year adjusted age.

All of the children were evaluated at 1-year adjusted age at the Wake Forest University Development Evaluation Clinic. For most participants, this was ~12 months after random assignment, because most infants were discharged within a few weeks of the estimated date of confinement. Child psychologists or psychology graduate students supervised by a child psychologist, who were not aware of the child’s intervention group or medical history, administered the BSID-MDI, PDI, and Vineland Adaptive Behavioral Scales. After the testing was completed, the psychologist was informed of the infant’s gestational age at birth so that the BSID scores could be corrected for the degree of prematurity. When the raw score yielded a MDI or PDI score <50, we derived extrapolated scores as described by Robinson and Mervis.30 The Vineland Adaptive Behavior Scales are a parent-reported measure of child adaptive development, which yield an adaptive behavior composite.31

Anthropometric measurements were performed by the nurse specialist or 1 of the neonatologists using a pediatric scale for weight, a length board for length, and a tape measure for head circumference. Growth delay was defined as weight for length less than the fifth percentile at 1-year adjusted age.32 On the basis of the neonatologist’s neurologic examination, infants with hypertonia and hyperreflexia in ≥1 extremity, accompanied by delayed motor milestones, were classified as having definite cerebral palsy. Infants were classified as having suspect cerebral palsy if they had hyperreflexia or hypertonia but were not delayed in attaining motor milestones.23 A research assistant, who was not aware of intervention group assignments, reviewed each infant’s clinic chart to collect data about the presence of the following: hearing impairment (for which a hearing aid had been prescribed), blindness (diagnosed by a pediatric ophthalmologist), and seizure disorder (for which anti-convulsant agents had been prescribed). Neurodevelopmental impairment was defined as the presence of any 1 of the following: cerebral palsy, blindness, need for hearing aid, MDI of <70, or PDI of <70.

A research assistant reviewed the discharge summary from each rehospitalization and recorded the reason for the hospitalization. The principal investigator, without knowledge of the infant’s identity, categorized the hospitalizations as follows: respiratory syncytial virus-related respiratory illness, respiratory illness without documentation of respiratory syncytial virus infection, elective surgery, or other.

Statistical Analysis
Descriptive statistics were obtained for prerandomization characteristics and outcomes. For comparisons between 2 groups for the primary outcome and for secondary outcomes measured as continuous variables, the
Wilcoxon rank sum test was used. Associations between intervention group and dichotomous outcomes were expressed as odds ratios (ORs) and exact 95% confidence intervals (CIs). A $P < .05$ was considered statistically significant. Analysis was by intention to treat. Assuming a rate of sample attrition of 10% and an SD of 15 (the SD in the Bayley Scales standardization sample), 75 infants would provide 80% statistical power to detect a group difference of 0.5 SD (7.5 Bayley points) at the 5% 2-sided level of significance. In a previous study of infants with CLD, we had observed an SD of 23, and if this degree of variation is assumed, the minimal difference detectable at 80% statistical power would be 10.5. We used SAS 8.2 (SAS Institute, Cary, NC) and STATXACT (Cytel Software Corporation, Cambridge, MA) for statistical analysis.

RESULTS

Study Participants
Of 185 consecutive infants identified with CLD, 164 infants were eligible for the study, and the parents of 150 (92% of those eligible) agreed to participate. Seventy-five children each were randomly assigned to the community- and center-based groups (Fig 1). There was no crossover from 1 intervention arm to the other. The center-based group received or initiated a median of 16 calls (5th and 95th percentiles: 2 and 53), as compared with a median of 27 calls (5th and 95th percentiles: 3 and 73) in the community-based group ($P = .02$). The median total duration of calls was 68 (5th and 95th percentiles: 2 and 414) minutes for the center-based group and 212 (5th and 95th percentiles: 31 and 732) minutes for the community-based group ($P < .001$).

Prerandomization Attributes
Of the entire sample, nearly one third of mothers were black, one half were not married, and approximately one half were eligible for Medicaid. The median birth weight of study infants was 830 g, and the median gestational age was 26 weeks. At the time of discharge from the NICU, more than one half of the infants were using supplemental oxygen, and three quarters were using a cardiorespiratory monitor. Postdischarge private duty nursing was prescribed for 2 infants before discharge (and random assignment); both were randomly assigned to community-based care. Maternal and sociodemographic attributes before random assignment are described in Table 1. As shown in Table 2, infant attributes before random assignment were similar for the 2 intervention groups.

Outcomes
In the center-based group, 2 children died suddenly at home. One death was classified as because of sudden infant death syndrome and the other because of right ventricular failure secondary to pulmonary hypertension. In the community-based group, 1 infant died at home of presumed sudden infant death syndrome, and 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Center-Based Group ($N = 75$)</th>
<th>Community-Based Group ($N = 75$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age, median (5th–95th percentiles), y</td>
<td>26 (18–37)</td>
<td>26 (17–34)</td>
</tr>
<tr>
<td>Receipt of prenatal care, n (%)a</td>
<td>60 (94)</td>
<td>64 (98)</td>
</tr>
<tr>
<td>Prenatal steroid treatment, n (%)b</td>
<td>54 (78)</td>
<td>58 (78)</td>
</tr>
<tr>
<td>Chorioamnionitis, n (%)c</td>
<td>17 (26)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Preeclampsia, n (%)d</td>
<td>12 (16)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Twin pregnancy, n (%)</td>
<td>20 (27)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Sociodemographic characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (self-reported), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>53 (71)</td>
<td>47 (63)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>21 (28)</td>
<td>26 (35)</td>
</tr>
<tr>
<td>Hispanic or Asian</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Insurance, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>36 (48)</td>
<td>36 (48)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>39 (52)</td>
<td>39 (52)</td>
</tr>
<tr>
<td>Annual household income, n (%), $</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥19 999</td>
<td>26 (36)</td>
<td>32 (45)</td>
</tr>
<tr>
<td>20 000–49 999</td>
<td>34 (47)</td>
<td>30 (42)</td>
</tr>
<tr>
<td>≤50 000</td>
<td>12 (17)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Mother married, n (%)</td>
<td>47 (63)</td>
<td>43 (57)</td>
</tr>
<tr>
<td>Smoker(s) at home, n (%)</td>
<td>29 (39)</td>
<td>31 (41)</td>
</tr>
</tbody>
</table>

a Data were available for 65 infants in the center-based group and 65 in the community-based group.
b Data were available for 69 infants in the center-based group and 74 in the community-based group.
c Data were available for 66 infants in each group.
infant died of cardiopulmonary failure after being readmitted to the hospital. Three of the infants who died were using supplemental oxygen when they died; in none of these infants was the oxygen flow weaned after discharge from neonatal intensive care. Of the 146 survivors, 4 in each group did not return for the 12-month follow-up visit. We obtained information about the developmental outcome of 7 of these children from local sources, including development evaluation centers (3 children), a local physician (1 child), and parents (3 children). Four were thought to have abnormal development and 3 to have possibly abnormal development.

The 12 infants who died or did not return for evaluation at 12 months’ adjusted age, as compared with those evaluated, were similar with respect to birth weight, gestational age, gender, race, and the proportion discharged using supplemental oxygen.

The median age at follow-up, adjusted for gestational age, was 12.3 months (5th and 95th percentile was 11.7 and 14.7 months, respectively). Outcomes for infants whom we evaluated at 12 months’ adjusted age are shown in Table 3. No difference was found in the group medians for the primary outcome of interest (the BSID-MDI), nor were differences found for the other developmental or health outcomes. The difference (community-center) in mean MDI was 3.4 (95% CI: 2.7 to 9.5), and the difference in mean PDI was 0.1 (95% CI: 0.67 to 0.69). Weight for length less than the fifth percentile was found more frequently among infants randomly assigned to community-based follow-up, although the difference was not statistically significant (ORcommunity/center: 2.31; 95% CI: 0.96 to 5.60). Similar proportions of the 2 groups were rehospitalized for respiratory illness (ORcommunity/center: 0.82; 95% CI: 0.40 to 1.68).

DISCUSSION

The results of this clinical trial indicate that, for prematurely born infants with CLD, community-based follow-up, coordinated by a nurse specialist via frequent telephone contacts, is a safe alternative to the prevailing model of health services for such infants, that is, a multidisciplinary medical-center based follow-up. Our study suggests that telephone follow-up, like multidisciplinary

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Clinical Characteristics of Infants Before Random Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Characteristic</td>
<td>Center-Based Group (N = 75)</td>
</tr>
<tr>
<td>Birth weight, median (5th–95th percentiles), g</td>
<td>800 (500–1475)</td>
</tr>
<tr>
<td>Head circumference, median (5th–95th percentiles), cm</td>
<td>24 (21–29)</td>
</tr>
<tr>
<td>Gestational age, median (5th–95th percentiles), wk</td>
<td>26 (23–31)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>45 (60)</td>
</tr>
<tr>
<td>Small for gestational age, n (%)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Birth at a perinatal referral center, n (%)</td>
<td>64 (85)</td>
</tr>
<tr>
<td>Cesarean section delivery, n (%)</td>
<td>48 (64)</td>
</tr>
<tr>
<td>Surfactant treatment, n (%)</td>
<td>71 (95)</td>
</tr>
<tr>
<td>Postnatal steroid treatment, n (%)</td>
<td>52 (69)</td>
</tr>
<tr>
<td>Days of postnatal steroid treatment, median (5th–95th percentiles)</td>
<td>21 (0–51)</td>
</tr>
<tr>
<td>Patent ductus arteriosus (surgically closed), n (%)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis, n (%)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Retinopathy of prematurity treated with laser surgery, n (%)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Major abnormality in cranial ultrasound, n (%)a</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Pulmonary interstitial emphysema, n (%)</td>
<td>18 (24)</td>
</tr>
<tr>
<td>Severity of CLDb</td>
<td></td>
</tr>
<tr>
<td>Grades 1, 2, and 3, n (%)</td>
<td>47 (75)</td>
</tr>
<tr>
<td>Grades 4, 5, and 6, n (%)</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Medication for gastroesophageal reflux, n (%)c</td>
<td>60 (80)</td>
</tr>
<tr>
<td>Diuretic, n (%)</td>
<td>61 (81)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, median (5th–95th percentiles), d</td>
<td>21 (2–91)</td>
</tr>
<tr>
<td>Length of stay in NICU, median (5th–95th percentiles), d</td>
<td>90 (50–162)</td>
</tr>
<tr>
<td>Nasogastric tube feeds at discharge, n (%)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Supplemental oxygen at discharge, n (%)</td>
<td>44 (59)</td>
</tr>
<tr>
<td>Home apnea monitor at discharge, n (%)</td>
<td>59 (79)</td>
</tr>
</tbody>
</table>

a Abnormalities include posthemorrhagic hydrocephalus, persistent ventricular dilatation, or periventricular echolucency.

b n = 63 for center-based group and n = 67 for community-based group.

c Medication includes cisapride, ranitidine, or metoclopramide.
clinics, can be used to facilitate compliance with medical recommendations, such as those developed for CLD,22 and to provide social and emotional support for the parents, referrals to subspecialty and early intervention services, developmental surveillance, and care coordination. In separate reports, we will compare the 2 approaches to follow-up in terms of costs, processes of care, satisfaction with the care provided, and psychosocial outcomes for families.

Children with chronic medical conditions like diabetes and asthma have improved clinical outcomes from comprehensive and coordinated care.33–36 Such care decreases life-threatening illnesses and hospitalizations of high-risk infants.2 In addition, coordinated care improves parents’ satisfaction with health care and decreases health care use of children with special health care needs.18 There is one method by which comprehensive care can be provided to children with chronic conditions in rural areas, where access to a complex level of care is limited.

Telephone intervention has been successfully used for the management of chronic illnesses in adults.39,40 In children, telephone management used in diabetes care did not significantly improve glycemic control, but it increased knowledge about diabetes care and adherence to care.41,42 In a randomized trial in low-income pregnant women, frequent telephone calls from a registered nurse were not associated with a statistically significant difference in the rate of low birth weight births; but in the subgroup of study participants who were black and <19 years of age, a statistically significant difference was found (relative risk: 0.56; 95% CI: 0.38 to 0.84; \( P = .004 \)).21 We are aware of no published descriptions of longitudinal telephone follow-up for infants with special health care needs.

Community-based follow-up was associated with a twofold greater risk of growth delay, which, although

<table>
<thead>
<tr>
<th>TABLE 3 Developmental and Health Outcomes of Children With CLD at 1 Year</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Median (5th–95th percentiles) BSID-MDI</td>
</tr>
<tr>
<td>BSID-MDI score, n (%)</td>
</tr>
<tr>
<td>&lt;55</td>
</tr>
<tr>
<td>55–69</td>
</tr>
<tr>
<td>&gt;64</td>
</tr>
<tr>
<td>Median (5th–95th percentiles) BSID-PDI</td>
</tr>
<tr>
<td>BSID-PDI score, n (%)</td>
</tr>
<tr>
<td>&lt;55</td>
</tr>
<tr>
<td>55–69</td>
</tr>
<tr>
<td>&gt;64</td>
</tr>
<tr>
<td>Vineland Adaptive Behavior Composite, median (5th–95th percentiles)</td>
</tr>
<tr>
<td>Weight &lt;5th percentile, n (%)</td>
</tr>
<tr>
<td>Length &lt;5th percentile, n (%)</td>
</tr>
<tr>
<td>Weight for length (&lt;5th percentile), n (%)</td>
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<tr>
<td>Head circumference (&lt;5th percentile), n (%)</td>
</tr>
<tr>
<td>Cerebral palsy, definite, n (%)</td>
</tr>
<tr>
<td>Cerebral palsy, suspect, n (%)</td>
</tr>
<tr>
<td>Blindness, n (%)</td>
</tr>
<tr>
<td>Hearing aid prescribed, n (%)</td>
</tr>
<tr>
<td>Neurodevelopmental impairment, n (%)</td>
</tr>
<tr>
<td>Anticonvulsant medication prescribed for seizures, n (%)</td>
</tr>
<tr>
<td>Using supplemental oxygen, n (%)</td>
</tr>
<tr>
<td>Median duration of supplemental oxygen postdischarge, median (5th–95th percentiles), d</td>
</tr>
<tr>
<td>Reason for rehospitalization, n (%)</td>
</tr>
<tr>
<td>Respiratory illness</td>
</tr>
<tr>
<td>RSV-related illness</td>
</tr>
<tr>
<td>Elective surgery</td>
</tr>
</tbody>
</table>

*Length was not measured on 1 infant in the center-based group.

\( P \) value computed using \( \chi^2 \) analysis without Yates continuity correction.

Impairments included MDI of <70, PDI of <70, cerebral palsy, blindness, or need for hearing aid.

Supplemental oxygen data were only for infants who were discharged home on oxygen (\( n = 42 \) for the center-based group and 34 for community-based group).
not a statistically significant effect, does raise the possibility that some aspect community-based follow-up care was inferior to center-based care. Observational studies suggest that discontinuation of supplemental oxygen can result in a slowing of weight gain among infants with CLD, particularly those who experience oxygen saturations <92% during sleep. The oxygen saturation target that was used in our study is very close to that used in the largest randomized trial of home oxygen therapy reported to date. However, if pulse oximetry in our clinic, as compared with pulse oximetry in the home, more accurately reflected an infant’s minimum saturations during sleep, then the group difference in growth during the first year might be attributable to more optimal oxygen saturations in the center-based follow-up group. Of note, however, is that the weaning of this group of infants from supplemental oxygen was not slower.

In addition to the slowing of weight gain, other adverse outcomes that are possibly related to hypoxemia during sleep include sudden infant death syndrome, the cause of death in 1 study participant in each group, and right ventricular heart failure, a factor in the other 2 deaths. The flow of supplemental oxygen was not weaned for any of the infants who died, but because we did not measure oxygen saturations continuously, it is plausible that these infants might have benefited from even higher oxygen flows than were used. Regarding the assessment of oxygen saturations in infants with CLD, a panel of experts suggested that “multiple determinations [be] made in various states including rest, sleep, feeding, and high activity, and in various positions.” Although this panel described continuous oxygen saturation monitoring at home as “helpful,” no explicit recommendation was made regarding its application.

Despite numerous advances in neonatology during the last 5 decades and remarkably improved rates of survival, the prevalence of CLD has not decreased. The impact of CLD increases with increasing severity, and patients who continue to require supplemental oxygen at 36 weeks’ postmenstrual age, as was true of the infants whom we studied, are at highest risk for adverse health and developmental outcomes during early childhood. The rates of mortality, rehospitalization, and neurodevelopmental impairment described here are similar to those reported by Ehrenkranz et al, who studied 2269 extremely low birth weight infants with moderate or severe bronchopulmonary dysplasia (ie, requirement for supplemental oxygen at 36 weeks’ postmenstrual age). In that study, 3% of infants died after discharge from neonatal intensive care (2.7% in the current study), 36.6% were readmitted for respiratory disease (31% in the current study), and 50.8% were found to have neurodevelopmental impairment, that is, MDI or PDI of <70, cerebral palsy, blindness, or deafness, at 18 months’ adjusted age (35% at 12 months’ adjusted age, in the current study).

We should acknowledge that the benefit of several interventions used in this study to infants with resolving CLD and no longer requiring mechanical ventilation, such as diuretics, medications for gastroesophageal reflux, and bronchodilators, is not supported by randomized clinical trials. Although at the time that this trial was conducted many experts recommended treatment of infants with CLD with diuretics, the routine use of diuretics for infants with CLD is discouraged in recent reviews. Whereas there is agreement about the benefit of supplemental oxygen to infants with CLD, controversy still exists regarding the oxygen saturations that should be targeted. More research is needed related to the care of infants with CLD after discharge from neonatal intensive care.

Limitations of our study should be noted. First, our failure to detect certain group differences might be because of limited statistical power. For example, although the twofold group difference in the rate of growth delay was not statistically significant, posthoc power calculations indicate that our study had only 50% power to detect a twofold increase in the frequency of growth delay. Second, only 1 intervention team was used, which limits the generalizability of our conclusions. Furthermore, because we included only English-speaking families in the study, we cannot generalize our findings to non–English-speaking families. The study team and other health care providers were not blinded to the randomization assignment, so cointerventions might have been differentially applied, leading to bias. Finally, neurodevelopmental status was evaluated at 1-year adjusted age, when assessments of early cognitive functioning and neurologic status (eg, presence of cerebral palsy) are only moderately predictive of status later in childhood.

CONCLUSIONS
This study indicates that telephone follow-up is a safe alternative to multidisciplinary clinic follow-up for ≥1 group of infants with complex medical needs, that is, those with CLD. This approach might be the preferred option for families who live far from a tertiary medical center. To the extent that CLD is an appropriate paradigm for chronic illness during infancy, our findings could apply to infants with other complex medical conditions.

ACKNOWLEDGMENTS
The Agency for Healthcare Research and Quality (grant R01 HS07928; principal investigator: Dr O’Shea) provided financial support for the design and conduct of the study and collection, management, and interpretation of the data. The assessment of the primary outcome was
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Injury-Prevention Counseling and Behavior Among US Children: Results From the Second Injury Control and Risk Survey

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ABSTRACT

OBJECTIVES. The purpose of this work was to provide recent national prevalence estimates of pediatric injury-prevention counseling by health care providers, to compare these latest findings with those from a similar survey conducted in 1994, and to ascertain the association between counseling and safety behaviors.

METHODS. We conducted a cross-sectional, list-assisted random-digit-dial telephone survey of randomly selected children in English- or Spanish-speaking households in all 50 US states and the District of Columbia. The main outcome measures were respondents’ reports that they or their children received injury-prevention counseling from their child’s health care provider in the 12 months preceding the interview, children’s practices of safety behaviors, and the association of injury-prevention counseling and such behaviors.

RESULTS. The overall proportion of US children receiving any injury-prevention counseling (42.4%) remained relatively unchanged, whereas counseling on selected injury-prevention topics increased significantly compared with reports based on the 1994 survey. Topic-specific injury-prevention counseling was positively associated with the posting of the poison control center telephone number in homes with children <6 years of age and with bicycle-helmet use among children 5 to 14 years of age.

CONCLUSIONS. Although the prevalence of pediatric injury-prevention counseling remains low, such counseling was associated with safer behaviors. This suggests the importance of pediatric injury-prevention counseling and indicates the need for health care providers to increase pediatric injury-prevention counseling in clinical practices.
Injury, although highly preventable, continues to be an important cause of mortality and morbidity. In 2003, there were >164,000 injury deaths and an estimated 29.2 million nonfatal injuries treated in US emergency departments.1

Various means have been used to reduce the burden of injury. An array of legislation (eg, child-proof safety caps on medicines, child safety seat and seatbelt use, and laws that hold gun owners responsible for safe storage practices) and regulations (eg, vehicle safety standards, sprinkler systems in new construction, and building codes to guard against fire) has been enacted to create a safer environment. Offering injury-prevention counseling by health care providers is another strategy to reduce the risk for injury by convincing people to modify their environment or behavior. The importance of injury-prevention counseling is recognized by the health care community and supported by the American Academy of Pediatrics,2 the American Academy of Family Physicians,3 the American Medical Association,4 and the US Preventive Services Task Force.5

In 1994, the Centers for Disease Control and Prevention (CDC) initiated a national Injury Control and Risk Survey (ICARIS-1994) in all 50 states and the District of Columbia to assess injury risk factors and the prevalence of injury-prevention counseling. Data collection covered a wide range of injury-related topics, including children’s safety behaviors and pediatric counseling on injury prevention. Research based on the ICARIS-1994 data and other earlier studies has shown that injury-prevention counseling by health care providers promotes safer behaviors.6–8

The CDC recently conducted the Second Injury Control and Risk Survey (ICARIS-2), the only national survey of this scope since ICARIS-1994. The purpose of this article is to provide recent prevalence estimates of pediatric injury-prevention counseling on the basis of ICARIS-2 data, to compare these new findings with the prevalence estimates from ICARIS-1994, and to reassess the association between injury-prevention counseling and safety behaviors.

METHODS

Study Design

ICARIS-2, conducted from July 23, 2001, through February 7, 2003, was a cross-sectional, list-assisted random-digit-dial (RDD) telephone survey of English- or Spanish-speaking adults in all 50 US states and the District of Columbia. The survey, conducted by the CDC National Center for Injury Prevention and Control, covered a wide range of injury-related topics. In addition to injury-prevention counseling, survey questions covered residential fire and smoke alarm use, bicycle-helmet use, sports and recreation safety, motor vehicle safety, falls among the elderly, firearm ownership and storage, dog bites, alcohol consumption, and violence. After the terrorist attacks on the World Trade Center and the Pentagon in September 2001, a set of questions was added to the survey to assess the relationship between exposure to these events and posttraumatic stress disorder. The survey questionnaire and interview protocol were approved by the CDC Institutional Review Board.

The sampling frame for this survey was the Genesys (Pitt Washington, PA) Sampling System “1+ banks” composed of blocks of 100 telephone numbers, with each block containing ≥1 residential directory listing. This frame covered ~96% of all households with landline telephones in the 50 US states and the District of Columbia.9 To ensure adequate racial and ethnic minority representation in the sample, telephone exchanges were stratified into high- (≥10% black or Hispanic households) and low-minority (all others) strata. Seventy percent of the ICARIS-2 sample was drawn from the high-minority stratum. With the addition of questions assessing posttraumatic stress disorder prevalence after the events of September 11, 2001, the sampling procedure was altered to incorporate a 10% oversample in the areas of New York and Washington, DC.

An eligible household was defined as a private residence that did not meet the US Bureau of the Census definition of a group quarter.10 Residents of institutions, dormitories, and dwelling units without working telephone landlines were not included in the sample.

One adult (aged ≥18 years) was selected from each eligible household. In households with both male and female adults, a gender category was selected with a higher probability of choosing a man. The gender distribution of the sample was monitored throughout the survey fielding period, and the probability of selecting a man was adjusted as needed to obtain a final sample with equal numbers of male and female respondents. The adult with the most recent birthday was chosen in households with multiple eligible adults of the selected gender.

The selected English- or Spanish-speaking adults who gave verbal consent to participate in the survey were interviewed using a computer-assisted telephone interviewing system. The respondent was asked to provide information about a variety of individual (eg, age, education, and employment status) and household (eg, type of dwelling and household income) characteristics and the age and gender of each child <15 years of age in the household. In households with ≥1 child <15 years of age, a child was randomly selected, and the respondent was asked to provide additional information specific to that child. The entire interview took an average of 21.5 minutes to complete. In recognition of survey participants’ contribution to our study, we offered all of the respondents the option of receiving a $5 telephone card or approving a donation of $5 to either the United Way or the Safe Kids Worldwide.
A total of 113,476 telephone numbers were sampled. Of these, 59% were ineligible (business or nonworking telephone numbers), 28% were of unknown eligibility, and 13% were eligible. From the 14,724 eligible households (including eligible noninterviews, such as refusals and breakoffs), data from 9,684 completed interviews were collected. We obtained a response rate of 48% using the standard definitions published by the American Association for Public Opinion Research (formula RR3). Formula RR3 uses a conservative approach by defining the response rate as the percentage of all definite and possible eligible adults who completed the entire interview. Thus, respondents who completed or partially completed the interview and those who refused to participate in the interview plus an estimated number of potentially eligible adults from households of unknown eligibility were all included in the denominator of this computational formula.

**Measures**

**Counseling**

To assess the opportunity for pediatric injury-prevention counseling, each respondent selected from households with children <15 years of age was asked, “During the past 12 months, how many times have you taken (the randomly selected child) to see a doctor, nurse, or health care provider about a health-related issue?” Consistent with ICARIS-1994 analysis for comparative purposes, an answer of “don’t know” to this question was treated as a “no.” Counseling received on any of these topics was defined as “counseled.” This coding scheme causes only negligible differences in analysis results compared with those produced when “don’t know” was left unchanged. Children who had no reported health care visits, including well-child visits, in the past 12 months were not asked if they had received any injury-prevention counseling.

**Behavior**

To assess safety practices related to children, respondents were asked if any smoke detectors were installed in the home, whether firearms were stored unloaded and locked, and if the randomly selected child “always used a car seat/seat belt while riding in a motor vehicle in the past 30 days.” Respondents with children <9 years of age were asked if the poison control center telephone number was posted on or near a telephone. For children 5 to 14 years of age, respondents were also asked if the randomly selected child “always wore a bicycle helmet when riding a bicycle in the past 30 days.” Respondents’ seat belt use as a driver or a passenger was also assessed. An answer of “don’t know” in response to whether firearms were safely stored at home was treated as missing (0.21% response), because respondents may not be able to observe other household members’ firearm ownership and storage practices. An answer of “don’t know” for other behaviors was coded as a “no” (range: 0.07%–0.18%).

**Analysis**

Survey data were weighted to account for the complex sample design, noncoverage, and nonresponse. Data were then poststratified by household composition to the US population estimates as provided by the March 2002 Current Population Survey and the 2000 US Census. Each respondent and randomly selected child was further ratio adjusted to their age-gender-race group in the population using data from the July 2002 Bridged Population data file prepared by the US Bureau of the Census in collaboration with the National Center for Health Statistics.

We used SUDAAN survey data analysis software to address the complex sample design and to compute national pediatric injury-prevention counseling prevalence estimates along with 95% confidence limits. The denominators for computing counseling prevalence were composed of all of the children for whom the counseling topics were age appropriate and for whom ≥1 past 12-month medical visit was reported. The denominators for computing safety behavior prevalence contain all of the children for whom the specific behaviors were age and environmentally appropriate. We examined the difference between the prevalence of injury-prevention counseling reported in ICARIS-2 with that reported in ICARIS-1994 using a standard t test. To control for the potential confounding effect of demographic factors on the relationship between the receipt of injury-prevention counseling and the practice of corresponding safety behaviors, we conducted multivariable logistic regression modeling adjusting for selected demographic characteristics.
RESULTS

Characteristics of Those Counseled

Among 9684 English- or Spanish-speaking US households, 3091 (35.1%) reported the presence of ≥1 child age 0 to 14 years in the household. Of these, 2541 (83.0%) reported that their children had visited a health care provider at least once “in the past 12 months.” Of the children who had any reported visit with a health care provider in the 12 months preceding the interview, 1046 (42.4%) were counseled on ≥1 of the injury-prevention topics examined (Table 1).

Receipt of any injury-prevention counseling among children with ≥1 medical visit “in the past 12 months” decreased with increasing age (0–1 year: 62.8%; 2–6 years: 44.6%; 7–12 years: 39.0%; 13–14 years: 27.3%; \( P < .01 \), test for linear trend; Table 1). Counseling was also significantly associated with the adult’s race/ethnicity. Among children who had ≥1 medical visit “in the past 12 months,” those who were living with an adult of Hispanic origin were more likely than those living with an adult of white non-Hispanic origin to be counseled on any of the injury-prevention topics covered in the survey (\( P = .03 \)). However, reported receipt of counseling was not associated with the gender of the child, number of children 0 to 14 years of age in the household, health

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Demographic Characteristics of US Children Receiving Any Pediatric Injury Prevention Counseling Among Those Who Visited a Health Care Provider at Least Once in the 12 Months Preceding the Interview, ICARIS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>No. Visited&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Total</td>
<td>2541</td>
</tr>
<tr>
<td>Child’s age group, y&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>305</td>
</tr>
<tr>
<td>2–6</td>
<td>884</td>
</tr>
<tr>
<td>7–12</td>
<td>960</td>
</tr>
<tr>
<td>13–14</td>
<td>392</td>
</tr>
<tr>
<td>Child’s gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1320</td>
</tr>
<tr>
<td>Female</td>
<td>1221</td>
</tr>
<tr>
<td>Race/ethnicity of the adult&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>413</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>307</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>1666</td>
</tr>
<tr>
<td>Other non-Hispanic</td>
<td>118</td>
</tr>
<tr>
<td>Household poverty status</td>
<td></td>
</tr>
<tr>
<td>Below threshold</td>
<td>276</td>
</tr>
<tr>
<td>At or above threshold</td>
<td>2001</td>
</tr>
<tr>
<td>Highest household educational attainment level</td>
<td></td>
</tr>
<tr>
<td>≤High school</td>
<td>659</td>
</tr>
<tr>
<td>&gt;High school but ≤college</td>
<td>527</td>
</tr>
<tr>
<td>College graduate</td>
<td>829</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>508</td>
</tr>
<tr>
<td>Adult has health insurance</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2252</td>
</tr>
<tr>
<td>No</td>
<td>287</td>
</tr>
<tr>
<td>No. of kids (aged 0–14 y) in the household</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1133</td>
</tr>
<tr>
<td>2</td>
<td>927</td>
</tr>
<tr>
<td>≥3</td>
<td>481</td>
</tr>
<tr>
<td>Census region</td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>557</td>
</tr>
<tr>
<td>North central</td>
<td>426</td>
</tr>
<tr>
<td>South</td>
<td>1056</td>
</tr>
<tr>
<td>West</td>
<td>502</td>
</tr>
<tr>
<td>Urbanicity</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>2502</td>
</tr>
<tr>
<td>Rural</td>
<td>39</td>
</tr>
</tbody>
</table>

<sup>a</sup> Sample data show children who reported having had ≥1 visit to any health care provider in the 12 months preceding the interview.

<sup>b</sup> Sample data show children who were counseled on any of the injury-prevention topics examined in ICARIS-2 among children who had ≥1 medical visit in the 12 months preceding the interview.

<sup>c</sup> Characteristic is statistically significantly associated with receiving any counseling (\( P < .05 \)).
insurance status of the adult, or other household-level demographic characteristics, such as the highest level of educational attainment, census region, urbanicity, or poverty status.

**Comparison With ICARIS-1994**

Current prevalence estimates indicate that reported pediatric counseling ranges from a low of 10% for children ages 2 to 14 years for proper firearm storage to a high of 39% for car seat/seat belt use for children ages 0 to 6 years (Table 2). Among children who had ≥1 reported medical visit in the past 12 months, the overall estimated 42% who reported receiving counseling was no higher than that in the 1994 survey (39.3%; P = .12). The number of injury-prevention topics discussed, however, increased among those who reported receiving counseling. Data from ICARIS-2 show that whereas 34.3% of the children counseled received counseling on ≥3 topics, only 18.3% did so in 1994. As a result, we saw a statistically significant gain in reported counseling on several injury-specific topics. We observed the largest absolute increase (11.8%) in counseling on bicycle-helmet use for children ages 5 to 14 years (from 18.6% in 1994 to 30.4% in the current survey; P < .01), followed by counseling on car seat/seat belt use for children ages 0 to 6 years (7.8%; P < .01), smoke detectors for 0- to 14-year-olds (6.1%; P < .01), and proper firearm storage practices for 2- to 14-year-olds (3.7%; P < .01). We saw no significant change from the 1994 prevalence estimates in counseling on the poison control center telephone number for 0- to 6-year-olds and seat belt use for 7- to 14-year-olds.

**Association Between Injury-Prevention Counseling and Safety Behaviors**

We saw a statistically significant association between reported injury-specific counseling and some reported safety behaviors (Table 3). Seventy-three percent of adults with children ages 0 to 6 years who received counseling reported posting the poison control center telephone number compared with 48% of those who were not counseled (P < .01). The association between reported receipt of counseling and reports of always using a bicycle helmet when biking also reached statistical significance. Children ages 5 to 14 years who were counseled were more likely to “always use a helmet in the past 30 days” compared with those without such counseling (58% vs 44%, respectively; P < .01). These associations remained unchanged after controlling for the age and gender of the child, number of children ages 0 to 14 years in the household, whether the adult had health insurance, race/ethnicity of the adult, and household-level demographic characteristics, such as urbanicity, poverty status, and the highest level of educational attainment. Although there was no statistically significant association found between child counseling and practice with respect to having ≥1 working smoke detector in the home or always using a seat belt when riding in a vehicle among children ages 7 to 14, there is some indication of a positive association between receiving counseling and practicing safe firearm storage and between receiving counseling and always using a car seat/seat belt when riding among children ages 0 to 6 years (bivariable analysis: 0.05 < P < 0.07). However, in both instances, these associations failed to hold after adjusting for person- and household-level demographic characteristics. For car seat/seat belt use among children, the multivariable analysis also controlled for seat belt use of the adult, either as a driver or a passenger. Children living with adults who always used a seat belt were more likely to always use car seats/seat belts compared with children living with adults who did not always do so (P < .01). This association held, regardless of the child’s age.

**DISCUSSION**

Although >7 years had passed since the ICARIS-1994 survey at the start of ICARIS-2, the percentage of US children counseled on any of the injury-prevention topics examined remained steady at ~40%. With few exceptions, receipt of counseling was not dependent on demographic characteristics of the adult, the child, or the household. This suggests that characteristics of the health care visit explain some of the variation in counseling and calls our attention to the barriers for health care providers to more actively engage in injury-prevention counseling. A body of literature has cited mixed findings in the determinants of counseling in primary care pediatric practices. Factors such as physician attitudes toward the importance of a health issue; their confidence in their ability to counsel; their perceptions about the effectiveness of counseling; demographics of the physician, specialty, training, office time constraints, and patient factors, such as the number of visits a child has in the previous year, have been hypothesized to influence the counseling practices of pediatricians.
and professional and personal experience; and practice settings have been found to be associated with a physician’s decision to incorporate injury-prevention counseling into routine patient care.13–16

The finding of an association between pediatric injury-prevention counseling and safety behaviors is supported by previous research. The ICARIS-1994 survey found an association between counseling and behavior for posting the poison control center telephone number (for children 6 years of age), proper firearm storage (2–14 years of age), always using a helmet when biking (5–14 years of age), and always using car seats/seat belts when riding in a motor vehicle (≤6 years of age).6 The consistent association between counseling and some safety behaviors revealed by both the ICARIS-1994 and the recent ICARIS-2 surveys underscores the need for the pediatric health care community to overcome the barriers to routine injury-prevention counseling. While health care providers who already practice injury-prevention counseling should be encouraged to continue,17,18 others who support counseling more in theory than in practice should be urged to include age-appropriate injury-prevention counseling in their clinical practices.19–21 A clinical norm of active injury-prevention counseling among pediatric health care providers is a crucial step toward increased practice of children’s safety behaviors. In turn, increasing the public’s awareness of injury prevention through counseling will help to shape the developing norm for health care providers. Patients’ interest in injury-prevention and health promotion could further encourage health care providers to increase their knowledge in injury prevention and to include such counseling as a regular component in clinical practices.

Several limitations of the ICARIS-2 survey warrant discussion. First, this study was subject to the potential of recall bias. While recognizing the varying ability and effort on the part of respondents to recall information, we lack the data to conclusively ascertain how well our survey respondents remembered and reported receipt of counseling or practice of safety behaviors. The counseling data were collected from respondents’ reports, rather than independent observation, that they or their randomly selected children received counseling on age-appropriate injury-prevention topics at the time of the child’s medical visit(s). The respondent may not be the child’s primary caregiver or may not be the adult who took the child to the doctor. In the case of an older child, the child may not have told the adult about information that he or she received while alone with the health care provider. Either of these instances could lead to an underreporting of receipt of counseling and, hence, an underestimation of pediatric counseling prevalence. This might help explain why only 2 of the 5 injury topics were statistically linked to safety behaviors. On the other hand, because respondents were also asked about injury-prevention counseling (on the use of seat belt, smoke detector, and proper firearm storage) received in conjunction with their own medical visit(s) “in the past 12 months,” they may recall counseling at their own visit and attribute the experience to that of their child’s visit(s) resulting in an overreporting of pediatric injury-prevention counseling. In addition to the potential recall bias, reporting of behaviors may also be influenced by social desirability such that reports of safety behaviors were inflated. This potential for overreporting, however, is expected to be similar among counseling recipients and nonrecipients, and, hence, it is unlikely that the significant associations observed between counseling and behaviors are explained by differences in overreporting across counseling status. We were able to verify neither the reported practice of safety behaviors nor the proper use of safety equipment. Readers should use caution when interpreting findings shown in Table 3, because these associations do not mean that the safety behaviors were performed properly.

### Table 3

<table>
<thead>
<tr>
<th>Injury Topic</th>
<th>Practiced Safety Behavior, (Unweighted Counts)</th>
<th>Weighted Percentages</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoke detectors, 0–14 y</td>
<td>Counseled: 319 (97.3%)</td>
<td>Not Counseled: 2148 (97.6%)</td>
<td>0.87 (0.41–1.82)</td>
<td>.95</td>
</tr>
<tr>
<td>Poison control number, 0–6 y</td>
<td>(227) 73.4</td>
<td>(397) 47.8</td>
<td>3.02 (2.08–4.40)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Firearm storage, 2–14 y</td>
<td>(38) 95.6</td>
<td>(527) 80.0</td>
<td>2.94 (0.95–9.09)</td>
<td>.22</td>
</tr>
<tr>
<td>Bicycle helmets, 5–14 y</td>
<td>(148) 57.9</td>
<td>(287) 44.4</td>
<td>1.87 (1.29–2.71)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Car seats/seat belts, y</td>
<td>0–14: 660 (94.9%)</td>
<td>0–14: 1702 (92.4)</td>
<td>1.51 (0.92–2.47)</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>0–6: 451 (96.7)</td>
<td>0–6: 678 (93.5)</td>
<td>2.05 (0.94–4.46)</td>
<td>.17</td>
</tr>
<tr>
<td></td>
<td>7–14: 209 (91.1)</td>
<td>7–14: 1024 (91.6)</td>
<td>0.94 (0.49–1.79)</td>
<td>.88</td>
</tr>
</tbody>
</table>

a Column contains P values from Wald F test.
b Analyses were adjusted for child’s age, gender, race/ethnicity (adult), health insurance (adult), urbanicity, poverty status, highest household educational attainment, and the number of children <15 years of age in the household.
Second, given the cross-sectional nature of this study, we cannot establish a causal relationship between injury-prevention counseling and injury-prevention practice. We cannot ascertain whether injury-prevention counseling led to injury-prevention practice, nor can we detect whether injury-prevention counseling, when it occurred, was prompted by the medical issues that brought the child to the attention of the health care provider.

A third limitation to consider in the interpretation of our findings is the unknown extent to which the likelihood of counseling varied by type of health care visit. Although a well-child visit may provide the time for a comprehensive injury-prevention counseling, an acute care visit might prompt an opportunity for counseling on a specific injury-prevention topic. Because information on the type of health care visit was not collected, we cannot know definitively whether pediatric counseling was a part of well-child visit or related to certain kinds of visits for treating acute illness or injury.

Finally, ICARIS-2 was conducted amid rapid changes in the telecommunication environment. The impact of changes, such as increased use of Privacy Manager, caller ID, answering machines, and cell phones, and the introduction of “do-not-call” lists contributed to the difficulties in telephone data collection. As noted, our response rate was calculated by using American Association for Public Opinion Research formula RR3 and assumed that households of unknown eligibility contained the same percentage of eligible adults as households with confirmed eligibility. Such a conservative assumption tends to overestimate the eligibility rate among those of unknown eligibility, thereby lowering the response rate. Our response rate is comparable to those calculated for other RDD studies conducted during the same time period using the same definitions and formula.22,23 Researchers have shown that low response rates in RDD studies do not necessarily equate to high nonresponse bias and that telephone survey results may still be generalizable.24,25 To assess the representativeness of our data, we compared the demographics of our sample at various stages of the weighting process with those from the 2000 US Census, the July 2002 US Bureau of the Census/National Center for Health Statistics Bridged Population data file, and the March 2002 Current Population Survey. Data comparisons indicate that the ICARIS-2 sample was representative with respect to age, gender, race/ethnicity, household income, and employment status. Respondents in our sample were slightly more likely to be married, to be more highly educated, and to own their own homes compared with the general US population; however, even here, differences were <10%.26 We controlled for educational attainment in multivariable analyses. Because marital status and home ownership are not strongly associated with our outcomes of interest, we do not expect this slight overrepresentation to have impacted our findings.

Although much remains to be studied about the degree of modification in behavior attributable to pediatric counseling, the positive associations between injury-prevention counseling and safety behaviors observed in this study and others are encouraging and support the recommendation to continue to increase injury-prevention counseling by pediatric health care providers. Injuries are the leading cause of preventable death in children, and progress can be made in reducing this burden by implementing effective strategies while continuing to search for other practical solutions. We lack the evidence to identify effective prevention strategies in many areas of public health. This study and the previous ICARIS-1994 study indicate that, for ≥2 safety behaviors (posting the poison control center telephone number and bicycle-helmet use), counseling is significantly associated with protective behaviors. In 2003, poisoning was the cause of 130 deaths and ≥89,335 visits to the emergency departments among children ages 0 to 14 years, and bicycle-related injury caused 127 deaths and >286,020 visits in this population.1 These grim statistics impart a responsibility to adopt now what we know works while we learn more about how to encourage injury-prevention counseling by health care providers and to maximize the behavioral impact of such counseling.

ACKNOWLEDGMENTS

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REFERENCES


Masculine Beliefs, Parental Communication, and Male Adolescents’ Health Care Use

Arik V. Marcell, MD, MPH, Carol A. Ford, MD, Joseph H. Pleck, PhD, Freya L. Sonenstein, PhD

OBJECTIVES. Male adolescents frequently become disconnected from health care, especially as they get older, which limits physicians’ abilities to address their health needs and results in missed opportunities to connect them to the health care system as they enter adulthood. In this study we tested the ability of modifiable (beliefs about masculinity, parental communication, sex education, and health insurance) and nonmodifiable (age, race/ethnicity, and region of residence) factors to prospectively predict health care use by male adolescents.

PATIENTS AND METHODS. We conducted a prospective analysis of data from 1677 male participants aged 15 to 19 years who completed the National Survey of Adolescent Males, a household probability survey conducted throughout the United States in 1988 (wave 1, participation rate: 74%) and in 1990–1991 (wave 2, follow-up rate: 89%). We present percentages and adjusted relative risks of the factors that predict male adolescents’ self-report of a physical examination by a regular provider in the past year measured at wave 2.

RESULTS. On average, 1067 (66%) of 1677 male adolescents at wave 2 reported having a physical examination within the last year. Factors associated with a lower likelihood of a physical examination included living in the South, Midwest, and West; being older in age; and holding more traditional masculine beliefs. Factors associated with a higher likelihood of a physical examination included communicating about reproductive health with both parents and being insured. Male adolescents who were sexually active or engaged in ≥2 other risk behaviors had neither a higher nor lower likelihood of a physical examination.

CONCLUSIONS. Efforts to enhance male adolescents’ health through health care should include work to modify masculine stereotypes, improve mothers’ and fathers’ communication about health with their sons, expand health insurance coverage, and identify interventions to connect male adolescents at increased risk for health problems with health care.
Most causes of adolescent male morbidity and mortality are preventable.1–2 This is the basis for practice guidelines that recommend clinical preventive services for all adolescents as part of annual or tailored visits.3–7 Two adolescent clinical preventive services supported by research include that physicians provide reproductive health services (eg, sexually transmitted infection [STI]/HIV screening, counseling, and testing) to male patients between 11 and 21 years of age and age-appropriate immunizations.1–8 Whether physicians are able to provide preventive health services to adolescent male patients depends on this populations’ involvement in the health care system.

Male adolescents frequently become disconnected from health care, especially as they get older.9,10 A better understanding of modifiable factors that influence adolescent male health care use would improve our ability to develop interventions to increase adolescent male connections to health care. The Andersen’s Behavioral Model of Health Services Use has been used to examine factors that influence health care use and proposes that use is influenced by enabling factors that provide resources, predisposing factors that provide motivation, and health needs that provide actual stimulus to engage in care.11 Previous studies show that enabling factors that represent adolescent barriers to care include lower socioeconomic status,12 lack of health insurance,13,14 and lack of a regular source of care,15 whereas factors that promote adolescent male access to care include the availability of confidential services,16,17 gender of the provider,18 assistance with appointment making,19,20 and school-based health clinics.9 Predisposing factors associated with the lower use of health care by male adolescents include being older in age,9 being of minority race/ethnicity,21 and lacking knowledge/sources of health care information.22 Few studies have examined how adolescent male health needs19 and, in particular, needs related to reproductive health, influence their health care use.

Two modifiable factors that may influence adolescent male health care use have been largely ignored in the research literature. First, although parent-teen communication has been shown to be an important contributor to adolescent health, the relationship between parental communication and access to care for sons has received little attention. Second, the way in which men are socialized in the United States (eg, to be tough, competitive, and inexpressive), defined as beliefs about masculinity,10 has been shown to influence adult men’s health care use23–25 but has not been examined in adolescence.

The National Survey of Adolescent Males (NSAM) provides a unique opportunity to address gaps in our knowledge. The main objective of this prospective study is to test the combined influence of modifiable and nonmodifiable factors, organized around Andersen’s Behavioral Model of Health Services Use framework, to predict the report of health care use by male adolescents. We also specifically focus on the relationship among beliefs about masculinity, parental communication, and health care use while controlling for other factors.

METHODS

Population and Procedures
Data for these analyses come from the first and second waves of the NSAM. NSAM used an area probability sampling frame based on census data that provides a racially and ethnically representative household sample of noninstitutionalized never-married US male adolescents ages 15 to 19.26 NSAM wave 1 was conducted in 1988 (response rate: 74%; N = 1880). NSAM wave 2 was conducted 2 years later in 1990–1991 (follow-up rate: 89%; N = 1677). Temple University and Brandeis University human subjects review boards approved NSAM procedures. Adult participants provided verbal consent; parental consent and verbal assent was obtained for minors. Survey administration consisted of a 1-hour in-person interview followed by a self-administered paper-and-pencil questionnaire to collect more sensitive information.

Measures of Predictor Variables
Anderson’s Behavioral Model of Health Services Use,11 coupled with variables known to be associated with adolescent male health care use, guided variable selection for this analysis. Unless specified, variables were assessed by self-report at wave 1.

Predisposing Factors

Demographics
Demographics included participant’s age and race/ethnicity coded as non-Hispanic white, non-Hispanic black, Hispanic, or other race. Region of residence, measured by census tract information, was coded categorically as Northeast, South, Midwest, or West. Urbanicity, measured by census tract information, was coded categorically as urban or nonurban. Family composition at age 14 years was coded as living in a single- or 2-parent household.

Reproductive Health Information
Parental communication about reproductive health was measured by asking whether participants communicated with parents or people who raised them about any of 6 reproductive health topics (eg, pregnancy, STIs, contraception, HIV/AIDS, menstruation, and what happens if he got a girl pregnant) with responses coded categorically as no communication with parent(s), communication about ≥1 topic with only 1 parent, or communication about ≥1 topic with both parents (together or separately). Hours of sex education ever received in
school or an organized program was coded as <5 hours or ≥6 hours.

**Attitudes and Beliefs**

Beliefs about masculinity were assessed using a 12-item scale that is conceptualized as beliefs in the importance that men adhere to culturally defined standards for male behavior.28 Scale items were introduced by the question, “How much do you agree or disagree with the following statements?” Item examples included “men are always ready for sex,” “it is essential for a guy to get respect from others,” and “I could be friends with a gay person.” Responses were coded on a 4-point Likert-type scale ranging from 1 (strongly disagree) to 4 (strongly agree; Cronbach α = .67). For these analyses, using cut points of 1 SD below and above the mean, scale scores were classified as representing less, neutral, and more traditional beliefs about masculinity, respectively.

**Enabling Factors**

**Socioeconomic Status**

Mother’s education level was measured by highest schooling level completed and coded as an ordered categorical variable. Annual family income was coded as an ordered categorical variable (with $10 000 increments up to $50 000 or more).

**Health Insurance**

Insurance status during the past 12 months was measured at wave 2 and coded as insured (any type) or uninsured (no insurance).

**School Performance**

School performance was measured by participants’ response to “how well they did in school” with responses coded on a 5-point Likert-type scale ranging from 1 (well below average) to 5 (well above average).

**Need Factors**

Wave 1 measures for risk of health problems were “have you ever had sex?” and “have you ever had any STI including gonorrhea, syphilis, herpes, warts and HIV/AIDS?” Measure also include sum composite comorbidity risk score developed from responses to involvement in 5 risk behaviors22: “Have you ever drunk alcohol?”; “. . .used tobacco?”; “. . .used cocaine?”; “. . .been picked up by the police for doing something wrong?”; and “. . .tricked or forced someone to have sex?” This score was coded categorically on the basis of responses indicating involvement in 0 to 1 vs ≥2 risk behaviors. At wave 2, participants were also asked “have you had a serious illness or injury since the last interview?”

**Measure of Outcome Variable**

Health care use was measured by response to, “When was the last time you saw your regular care provider for a physical examination?” with responses coded as >12 months or ≤12 months.

**Analysis**

The University of Maryland’s human subjects review board provided approval to perform secondary data analysis. Data were prepared and analyzed using SPSS 12.0 (SPSS Inc, Chicago, IL) and Stata 9.0 (Stata Corp, College Station, TX), respectively. Descriptive analyses reported for the full sample are weighted. Sample weights were calculated as the product of the basic sampling rate that takes into account sampling framework, screening nonresponse rate, interview nonresponse rate, and attrition.27,29

Unweighted univariate logistic regression analyses were first conducted to examine relationships between predictor variables and health care use. A P value of <.10 determined variables to include in the final model. Two nonsignificant yet conceptually important health needs (eg, sexual activity and engaging in other high-risk behaviors) were included in the final model, because male adolescents involved in these behaviors are at risk for experiencing negative health outcomes.

Next, the final set of covariates was assessed for multicollinearity, and none was found. Unweighted multivariate analyses were then performed. A Poisson model was applied in the multivariate analyses to calculate the relative risk (RR).30 because odds ratios overestimate RR when main outcomes are common (>10%) and, thus, lead to inaccurate estimates of health care use.31 All of the predictor variables were entered simultaneously into the regression model to produce adjusted incidence rate ratios.30 Thus, RR represents the association of each predictor variable with the dependent variable after accounting for the influence of all of the other variables.

**Missing Data**

For multivariate analyses, participants who had missing data for mother’s education (n = 170 [10%]) and family income (n = 104 [6.2%]) were replaced with the sample’s mean for that variable. Dummy variables were created for each of these variables to represent missing data and were included in the final model.32 Multivariate analyses were performed with and without mean replacement for missing data, and findings were not significantly different; because 10% of participants had missing data for mother’s education, multivariate analyses presented here use mean replacement.

**RESULTS**

**Participants**

Participants had a mean (±SD) age of 16.9 (±1.4) years and were predominantly non-Hispanic white (73.2%).
Approximately one third lived in the South, two thirds in urban settings, and one fifth in single-parent households. Approximately three quarters communicated about reproductive health with 1 or both parents, and approximately half reported they had received ≥6 hours of sex education in school or an organized program. The participant mean (±SD) beliefs about masculinity score was 2.6 (±0.4); that is, on average, male adolescents had neutral masculine beliefs (Table 1).

Participants’ mean (±SD) mother’s education level was 12.9 (±2.6) years. There was equal representation from all of the family income levels. During the 12 months preceding the second interview, 85.4% of participants were insured. Behaviors associated with health needs were reported by many: 59.6% ever had sex, 3.6% ever had an STI, 16.3% had a serious illness or injury, and 20.3% engaged in ≥2 risk behaviors (Table 2).

### Table 1: Percentage of Male Subjects Reporting Physical Examination in Past Year by Predisposing Factors (N = 1677)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last physical examination by regular care provider</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥12 mo</td>
<td>602</td>
<td>33.8</td>
<td>—</td>
</tr>
<tr>
<td>≤12 mo</td>
<td>1067</td>
<td>66.0</td>
<td>—</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>211</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Overall</td>
<td>1677</td>
<td>100</td>
<td>66.1</td>
</tr>
<tr>
<td>Predisposing factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>675</td>
<td>73.2</td>
<td>68.6 (ref)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>608</td>
<td>14.5</td>
<td>62.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>340</td>
<td>9.3</td>
<td>53.8</td>
</tr>
<tr>
<td>Other race</td>
<td>54</td>
<td>3.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Region of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>287</td>
<td>19.0</td>
<td>74.4 (ref)</td>
</tr>
<tr>
<td>South</td>
<td>798</td>
<td>37.4</td>
<td>60.9</td>
</tr>
<tr>
<td>Midwest</td>
<td>308</td>
<td>23.7</td>
<td>69.8</td>
</tr>
<tr>
<td>West</td>
<td>284</td>
<td>19.9</td>
<td>63.8</td>
</tr>
<tr>
<td>Urbanicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonurban</td>
<td>527</td>
<td>35.5</td>
<td>66.6 (ref)</td>
</tr>
<tr>
<td>Urban</td>
<td>1150</td>
<td>64.5</td>
<td>65.3</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>362</td>
<td>20.1</td>
<td>72.3 (ref)</td>
</tr>
<tr>
<td>16</td>
<td>359</td>
<td>19.6</td>
<td>70.1</td>
</tr>
<tr>
<td>17</td>
<td>371</td>
<td>21.8</td>
<td>65.7</td>
</tr>
<tr>
<td>18</td>
<td>345</td>
<td>23.4</td>
<td>60.7</td>
</tr>
<tr>
<td>19</td>
<td>239</td>
<td>15.1</td>
<td>62.1</td>
</tr>
<tr>
<td>Family composition at age 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-parent household</td>
<td>466</td>
<td>20.8</td>
<td>55.9 (ref)</td>
</tr>
<tr>
<td>2-parent household</td>
<td>1209</td>
<td>79.1</td>
<td>68.9</td>
</tr>
<tr>
<td>Reproductive health information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental communication about reproductive health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No communication</td>
<td>398</td>
<td>22.0</td>
<td>55.6 (ref)</td>
</tr>
<tr>
<td>Communication with only 1 parent</td>
<td>543</td>
<td>26.3</td>
<td>59.8</td>
</tr>
<tr>
<td>Communication with both parents</td>
<td>728</td>
<td>51.4</td>
<td>73.7</td>
</tr>
<tr>
<td>Hours of sex education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>607</td>
<td>44.5</td>
<td>61.7 (ref)</td>
</tr>
<tr>
<td>≥6</td>
<td>1070</td>
<td>53.3</td>
<td>69.4</td>
</tr>
<tr>
<td>Attitudes and beliefs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beliefs about masculinity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less traditional beliefs</td>
<td>372</td>
<td>22.2</td>
<td>68.8</td>
</tr>
<tr>
<td>Neutral beliefs</td>
<td>1104</td>
<td>65.9</td>
<td>66.9 (ref)</td>
</tr>
<tr>
<td>More traditional beliefs</td>
<td>197</td>
<td>11.8</td>
<td>51.3</td>
</tr>
</tbody>
</table>

— indicates not applicable; ref, reference.

* Data are unweighted.

b Data are weighted.

c Data show a significant difference between Midwest and South (P < .05).

d Data show a significant difference between communication with both and 1 parent (P < .05).

e Data show a significant difference between male subjects with more and less traditional beliefs.
Approximately two thirds of the participants (66%) reported that the last time they saw their regular care provider for a physical examination was within the last year (Table 1).

Predisposing Factors and Health Care
Bivariate analyses revealed that male adolescents who were less likely to have a physical examination in the past year were Hispanic versus non-Hispanic white (53.8% vs 68.6%; Table 1); lived in the South (60.9%) and West (63.8%) versus Northeast (74.4%); lived in the South versus Midwest (60.9% vs 69.8%); were age 19 vs 15 (62.1% vs 72.3%); lived in single-parent versus 2-parent households (55.9% vs 68.9%); and held more traditional masculine beliefs (51.3%) versus neutral (66.9%) or less traditional beliefs (68.8%). Male adolescents who communicated about reproductive health with both parents (73.7%) were more likely to have a physical examination than male adolescents who had no communication with either parent (55.6%) or who communicated with only 1 parent (59.8%).

Enabling Factors and Health Care
Bivariate analyses revealed that male adolescents who were more likely to have a physical examination in the past year had mothers with higher educational versus mothers with lower educational levels; were from higher versus lower income families; and were insured versus uninsured (Table 2).

Need Factors and Health Care
Male adolescents who were sexually active or engaged in ≥2 risk behaviors were neither more nor less likely to have a physical examination than those who were not sexually active or engaged in any risk behaviors (Table 2).

### Table 2: Percentage of Male Subjects Reporting Physical Examination in Past Year by Enabling and Need Factors (N = 1677)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Physical Examination in Past Year, %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enabling factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11th grade</td>
<td>384</td>
<td>14.7</td>
<td>55.7</td>
</tr>
<tr>
<td>High school diploma or GED</td>
<td>668</td>
<td>42.5</td>
<td>69.3</td>
</tr>
<tr>
<td>College or more</td>
<td>455</td>
<td>36.2</td>
<td>68.6&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Missing</td>
<td>170</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>Annual family income, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 000</td>
<td>202</td>
<td>6.5</td>
<td>58.2</td>
</tr>
<tr>
<td>10 000–20 000</td>
<td>381</td>
<td>15.6</td>
<td>53.8</td>
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<tr>
<td>20 000–30 000</td>
<td>320</td>
<td>18.2</td>
<td>67.9</td>
</tr>
<tr>
<td>30 000–40 000</td>
<td>275</td>
<td>17.3</td>
<td>67.5</td>
</tr>
<tr>
<td>40 000–50 000</td>
<td>162</td>
<td>13.3</td>
<td>73.1</td>
</tr>
<tr>
<td>50 000–60 000</td>
<td>84</td>
<td>8.0</td>
<td>80.6</td>
</tr>
<tr>
<td>≥60 000</td>
<td>149</td>
<td>16.4</td>
<td>69.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Missing</td>
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<td>4.7</td>
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<tr>
<td>No</td>
<td>307</td>
<td>14.6</td>
<td>33.9&lt;sup&gt;a&lt;/sup&gt; (ref)</td>
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<td>1368</td>
<td>85.4</td>
<td>71.7&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>School performance</td>
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<tr>
<td>Well below and below average</td>
<td>166</td>
<td>8.0</td>
<td>48.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Average</td>
<td>840</td>
<td>43.5</td>
<td>67.0&lt;sup&gt;a&lt;/sup&gt; (ref)</td>
</tr>
<tr>
<td>Above and well above average</td>
<td>665</td>
<td>48.0</td>
<td>68.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Need factors</strong></td>
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<tr>
<td>Serious illness or injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1387</td>
<td>83.7</td>
<td>66.3&lt;sup&gt;a&lt;/sup&gt; (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>289</td>
<td>16.3</td>
<td>65.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ever had sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>552</td>
<td>40.2</td>
<td>69.2&lt;sup&gt;a&lt;/sup&gt; (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>1121</td>
<td>59.6</td>
<td>63.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ever had any STI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1496</td>
<td>92.7</td>
<td>66.1&lt;sup&gt;a&lt;/sup&gt; (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>104</td>
<td>3.6</td>
<td>66.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Comorbidity of risk behaviors&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>1346</td>
<td>78.0</td>
<td>67.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥2</td>
<td>293</td>
<td>20.3</td>
<td>60.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

GED indicates general equivalency diploma; ref, reference; —, not applicable.
<sup>a</sup> Data are unweighted.
<sup>b</sup> Data are weighted.
<sup>c</sup> Bivariate analysis was performed with predictor in the form of a continuous variable.
<sup>d</sup> Data are the sum of involvement in risk behaviors, including ever used alcohol last year, tobacco use last year, cocaine use, ever picked up by police, and ever forced someone to have sex.
have a physical examination than male adolescents who were not sexually active or engaged in less risk behavior (Table 2).

**Predictors of Health Care Use: Multivariate Analyses**

Multivariate analyses showed that region of residence, age, parental communication about reproductive health, beliefs about masculinity, and insurance prospectively predicted having a visit to a regular care provider for a physical examination in the last year while controlling for all other factors (Table 3). Male adolescents who were less likely to have a physical examination in the past year lived in the South, Midwest, and West versus Northeast (RR [95% confidence interval (CI)]: 0.81 [0.74–0.89], 0.89 [0.80–0.98], and 0.87 [0.77–0.97], respectively); were age 19 vs 15 years (0.86 [0.75–0.98]); and held more traditional masculine beliefs versus neutral beliefs (0.86 [0.77–0.96]). Male adolescents who were more likely to have a physical examination within the past year communicated about reproductive health with both parents versus no communication with either parent (1.14 [1.04–1.26]) and were insured versus uninsured (1.62 [1.40–1.87]). The other significant bivariate relationships did not persist in multivariate analyses.

**Exploratory Analysis: Parent Communication According to Age, Family Composition, and Beliefs About Masculinity**

We conducted an exploratory posthoc analysis to determine whether the impact of different sources of parental communication on health care use varied according to age, family composition, and beliefs about masculinity.

### TABLE 3 Unadjusted Odds Ratio and Adjusted RR for Predictors of Adolescent Male Health Care Use in the Past Year

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Bivariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI P</td>
<td>RRc 95% CI P</td>
</tr>
<tr>
<td>Predisposing factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity (reference = non-Hispanic white)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>0.94 (0.75–1.18) .596</td>
<td>1.05 (0.96–1.15) .283</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.69 (0.53–0.91) .007</td>
<td>0.95 (0.85–1.06) .326</td>
</tr>
<tr>
<td>Other race</td>
<td>0.74 (0.42–1.30) .287</td>
<td>0.99 (0.78–1.25) .910</td>
</tr>
<tr>
<td>Region of residence (reference = Northeast)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>0.56 (0.42–0.75) &lt;.001</td>
<td>0.81 (0.74–0.89) &lt;.001</td>
</tr>
<tr>
<td>Midwest</td>
<td>0.74 (0.52–1.06) .101</td>
<td>0.89 (0.80–0.98) .024</td>
</tr>
<tr>
<td>West</td>
<td>0.61 (0.43–0.87) .007</td>
<td>0.87 (0.77–0.97) .015</td>
</tr>
<tr>
<td>Age (reference = 15), y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.88 (0.64–1.20) .412</td>
<td>0.97 (0.88–1.07) .538</td>
</tr>
<tr>
<td>17</td>
<td>0.81 (0.59–1.10) .168</td>
<td>0.95 (0.86–1.06) .344</td>
</tr>
<tr>
<td>18</td>
<td>0.75 (0.55–1.02) .066</td>
<td>0.91 (0.82–1.02) .099</td>
</tr>
<tr>
<td>19</td>
<td>0.63 (0.45–0.89) .009</td>
<td>0.86 (0.75–0.98) .021</td>
</tr>
<tr>
<td>Family composition (reference = single-parent household)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-parent household</td>
<td>1.32 (1.06–1.64) .015</td>
<td>1.05 (0.96–1.15) .325</td>
</tr>
<tr>
<td>Parental communication about reproductive health (reference = no communication)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication with 1 parent</td>
<td>1.13 (0.87–1.47) .360</td>
<td>1.06 (0.95–1.18) .323</td>
</tr>
<tr>
<td>Communication with both parents</td>
<td>1.73 (1.34–2.24) &lt;.001</td>
<td>1.14 (1.04–1.26) .008</td>
</tr>
<tr>
<td>Beliefs about masculinity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less traditional beliefs</td>
<td>1.00 (0.75–1.31) .981</td>
<td>1.00 (0.91–1.10) .922</td>
</tr>
<tr>
<td>Neutral beliefs, reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More traditional beliefs</td>
<td>0.62 (0.48–0.81) &lt;.001</td>
<td>0.86 (0.77–0.96) .009</td>
</tr>
<tr>
<td>Enabling factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s education level (continuous)a</td>
<td>1.06 (1.02–1.10) .005</td>
<td>0.99 (0.98–1.01) .416</td>
</tr>
<tr>
<td>Annual family income (continuous)b</td>
<td>1.12 (1.06–1.19) &lt;.001</td>
<td>1.01 (0.99–1.04) .259</td>
</tr>
<tr>
<td>Health insurance (reference = no)</td>
<td>3.21 (2.49–4.15) &lt;.001</td>
<td>1.62 (1.40–1.87) &lt;.001</td>
</tr>
<tr>
<td>Need factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious illness or injury (reference = no)</td>
<td>1.42 (1.08–1.87) .013</td>
<td>1.13 (1.04–1.23) .006</td>
</tr>
<tr>
<td>Ever had sex (reference = no)</td>
<td>0.87 (0.70–1.08) .200</td>
<td>1.01 (0.93–1.10) .788</td>
</tr>
<tr>
<td>Comorbidity of risk behaviors (reference = ≤1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>0.82 (0.63–1.06) .134</td>
<td>0.99 (0.89–1.10) .847</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

a Data from univariate logistic regression models.

b Data from Poisson regression, log pseudolikelihood = –1471.61; pseudo R2 = 0.18; N = 1617.

c Data are adjusted RRs and 95% confidence intervals representing relationship between independent variable and physical examination in the past year while controlling for all other independent variables in this table.

d Missing data (n = 170) were replaced using sample mean and dummy for missings included in final model (P not significant).

e Missing data (n = 104) were replaced using sample mean and dummy for missings included in final model (P not significant).
while controlling for factors described in the previous multivariate analysis. For these analyses we ran separate multivariate models stratified by age (15–17 and 18–19 years), family composition (single- and 2-parent households), and masculine beliefs (less traditional, neutral, and more traditional).

Sources of parental communication on health care use were found to vary by age, family composition, and masculine beliefs (Table 4). Analyses by age found that communication about reproductive health with both parents predicted increased health care use in the last year for younger and older male adolescents, although the importance of talking with both parents together varied by age. Analyses by family composition found that, among male adolescents who live in 2-parent households, those who communicate with both parents separately are more likely to have a physical examination than male adolescents who do not communicate with either parent (1.15 [1.01–1.30]). Parental communication did not influence the use of health care among male adolescents in single-parent households. Analyses by masculine beliefs found that, among male adolescents with more traditional beliefs, those who communicated with their father only or both parents together were more likely to have a physical examination than male adolescents who did not communicate with either parent (RR [95% CI]: 1.61 [1.13–2.29] and 1.55 [1.09–2.20], respectively). As shown in Table 4, a nearly identical pattern was found for male adolescents with less traditional masculine beliefs.

**DISCUSSION**

Three modifiable factors (masculine beliefs, parent-teen communication, and insurance status) prospectively influence health care use among male adolescents in the United States. These findings can be used to inform interventions to improve adolescent male health through increased use of health care.

To our knowledge, this is the first report linking adolescents’ beliefs about masculinity and male roles to health care use behaviors. Our findings that male adolescents with more traditional masculine beliefs are less likely to get health care is consistent with research focused on adult men. Our findings demonstrate that such attitudes may hinder adolescent male use of health care and may be consistent with Courtenay’s suggestion that boys’ lack of help seeking can itself be considered a risk behavior. Within this context, additional research is needed to better understand how masculine beliefs influence adolescent male care-seeking behaviors. Programs that promote health and gender equity among boys are currently under evaluation. These programs are designed, in part, to target mythologies that suggest that care-seeking is a sign of weakness and to promote the belief that care seeking can be consistent with the male role and seen as a sign of strength. An alternative strategy that warrants investigation among male youth populations may be to promote health and target services in a manner that is more congruent with traditional male gender roles.

Parent-teen communication has long been accepted as an important contributor to adolescent health. Studies that examine parent-teen communication about sex have reported gender-specific issues (that mothers are more likely than fathers to talk with their children about sex and that mothers talk more to daughters than sons). Also, the influence of mothers has been shown to outweigh that of fathers as it relates to the sexual behaviors of their teenage sons and daughters. Our findings provide new insight into the relationship between parent-son communication about reproductive health and health care use and highlight the unique importance of father-son communication. In this study, communication with both mothers and fathers predicted increased health care use for male adolescents regardless of age and for sons with either more or less traditional beliefs.

**TABLE 4 Exploring the Relationship Between Parental Communication and Health Care Use in the Past Year According to Age, Family Composition, and Beliefs About Masculinity**

<table>
<thead>
<tr>
<th>Parental Communication About Reproductive Health Variable*</th>
<th>Communication With Mother Only</th>
<th>Communication With Father Only</th>
<th>Communication With Both Parents, Separately</th>
<th>Communication With Both Parents, Together</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI P</td>
<td>RR 95% CI P</td>
<td>RR 95% CI P</td>
<td>RR 95% CI P</td>
</tr>
<tr>
<td>All</td>
<td>1.03 0.91–1.16 .652</td>
<td>1.15 0.99–1.32 .068</td>
<td>1.15 1.03–1.29 .017</td>
<td>1.14 1.03–1.28 .014</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger</td>
<td>1.05 0.88–1.25 .576</td>
<td>1.15 0.94–1.42 .166</td>
<td>1.11 0.94–1.32 .228</td>
<td>1.20 1.03–1.39 .022</td>
</tr>
<tr>
<td>Older</td>
<td>1.02 0.87–1.19 .835</td>
<td>1.12 0.91–1.39 .291</td>
<td>1.17 1.01–1.15 .043</td>
<td>1.10 0.94–1.18 .225</td>
</tr>
<tr>
<td>Family composition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-parent household</td>
<td>1.14 0.93–1.40 .205</td>
<td>1.24 0.93–1.67 .149</td>
<td>1.14 0.89–1.46 .309</td>
<td>1.19 0.90–1.56 .217</td>
</tr>
<tr>
<td>2-parent household</td>
<td>0.96 0.82–1.11 .557</td>
<td>1.11 0.94–1.32 .205</td>
<td>1.15 1.01–1.30 .033</td>
<td>1.12 1.00–1.26 .061</td>
</tr>
<tr>
<td>Beliefs about masculinity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less traditional beliefs</td>
<td>1.11 0.80–1.54 .527</td>
<td>1.53 1.07–2.20 .020</td>
<td>1.21 0.90–1.63 .203</td>
<td>1.35 1.02–1.79 .037</td>
</tr>
<tr>
<td>Neutral beliefs</td>
<td>0.98 0.86–1.13 .807</td>
<td>0.98 0.82–1.18 .850</td>
<td>1.09 0.96–1.24 .176</td>
<td>1.07 0.94–1.21 .294</td>
</tr>
<tr>
<td>More traditional beliefs</td>
<td>1.26 0.89–1.78 .193</td>
<td>1.61 1.13–2.29 .009</td>
<td>1.36 0.93–2.00 .115</td>
<td>1.55 1.09–2.20 .014</td>
</tr>
</tbody>
</table>

The data were controlled for all other factors in Table 3.

*Reference is no communication.
masculine beliefs. For adolescent sons with either more or less traditional beliefs, talking with fathers about reproductive health issues seems to be particularly important. Isolated mother-son communication did not predict health care use in our study. Future research is needed to examine the content and quality of parent-son communication as it relates to male use of health care and to further explore parental communication within the context of single-parent households.

Consistent with existing literature, insurance plays a major role in whether male adolescents get health care. The proportion of male adolescents in our study who reported that they were uninsured (14.6%) is similar to that of more recent national samples (F. L. Sonenstein, PhD, written communication, 2006 [data from the National Survey of Family Growth]). Newacheck et al recently reported that adolescents who reside in regions outside the Northeast are more likely to be uninsured. Our study shows that regional variation in health care use persists after controlling for insurance status. Strategies to reduce adolescent male barriers to care may, thus, include extending insurance coverage to all adolescents and young adults, developing equitable insurance plans for male adolescents and young adults that are comparable to reproductive health care services available for female adolescents and young adults (e.g., family planning) and improving access to care in all of the US regions.

It is important to highlight that male adolescents who are at higher risk of health problems on the basis of reported risk-related behaviors (e.g., sexual intercourse, substance use, and truancy) are equally likely to have a physical examination in the last year when compared with lower-risk adolescents after controlling for serious illness or injury. This is unfortunate, because male adolescents engaging in risk-related behaviors may benefit the most from connections to the health care system. Strategies to identify and connect this population to care are needed and may involve collaboration with allied professionals (e.g., teachers, counselors, and community leaders) and the juvenile justice system. These strategies will need to be linked to efforts to support physicians’ delivery of high-quality adolescent clinical preventive services, such as STI/HIV testing and age-appropriate immunizations.

A major strength of this study is its prospective nature and the use of a racially and ethnically diverse national sample. This study also has several potential limitations. First, self-report measures have inherent limitations, although adolescent reports of their own health care behaviors are probably at least as accurate as those of parental report. Second, there are limitations with our main outcome variable. We are unable to determine the reason that respondents had a physical examination by their regular care provider, so we cannot distinguish acute from routine visits. Furthermore, we are unable to independently test the influence of having a regular source of care on health care use, because these variables were linked in the original survey instrument. This combined measure does decrease the risk of overestimation of adolescent male health care, because it described examinations linked to a regular source of care from examinations provided in group settings as part of sports clearance events. Third, bias based on attrition between waves is possible. The risk for bias is expected to be small, because previous analyses have shown no attrition bias in the areas of sexual or contraceptive behaviors or in any of the other the main study variables except for age (older boys were less likely to follow-up at wave 2; \( P < .04 \)). Next, the internal reliability of the masculine beliefs scale is somewhat lower than that traditionally found for scales used in behavioral research. Although this scale may not fully capture masculine beliefs, it is able to prospectively differentiate adolescent male health care use, thus demonstrating construct validity. Finally, NSAM is an older data set, but we believe our findings are still relevant given the expected stability of our main study predictor and outcome variables. NSAM remains a seminal prospective data set to examine adolescent male reproductive health. This data set provides us a unique opportunity to examine prospectively whether modifiable factors, including masculine beliefs and parental communication, within the context of an organized framework are related to adolescent male health care use.

CONCLUSIONS

Our study suggests that efforts to enhance adolescent male health through health care should include work to modify masculine stereotypes, increase mothers’ and fathers’ communication about health with their sons, and expand health insurance coverage. Specific efforts to connect male adolescents at high risk of health problems to health care are needed. Primary care providers should encourage mothers and fathers to talk with their sons about general and reproductive health and the importance of connections with health services. Whether establishing better connections between male adolescents and health care can subsequently lead to better connections between adult men and health care (and improved men’s health) is an important area of future longitudinal research.

ACKNOWLEDGMENTS

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Association Between Congenital Heart Defects and Small for Gestational Age

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. Infants with congenital heart defects may experience inhibited growth during fetal life. In a large case-control study, we addressed the hypothesis that infants with congenital heart defects are more likely to be small for gestational age than infants without congenital heart defects after controlling for selected maternal and infant characteristics.

METHODS. Using data from population-based birth defect registries, the National Birth Defects Prevention Study enrolled infants with nonsyndromic congenital heart defects (case subjects) and infants without congenital heart defects or any other birth defect (control subjects). Small for gestational age was defined as birth weight below the 10th percentile for gestational age and gender. Association between congenital heart defects and small for gestational age was examined by conditional logistic regression adjusting for maternal covariates related to fetal growth.

RESULTS. Live-born singleton infants with congenital heart defects (case subjects, n = 3395) and live-born singleton infants with no birth defect (control subjects, n = 3924) were included in this study. Case subjects had lower birth weights compared with control subjects. Small for gestational age was observed among 15.2% of case subjects and among only 7.8% of control subjects. Congenital heart defect infants were significantly more likely to be small for gestational age than control infants.

CONCLUSIONS. Infants with congenital heart defects are approximately twice as likely to be small for gestational age as control subjects. Small for gestational age status may affect clinical management decisions, therapeutic response, and prognosis of neonates with congenital heart defects. Although the etiology of growth retardation among infants with congenital heart defects is uncertain, further exploration may uncover a common pathogenesis or causal relationship between congenital heart defects and small for gestational age.
CONGENITAL HEART DEFECTS (CHDs) are the most prevalent birth defects and frequently require multiple hospitalizations and surgical procedures. Prevalence estimates range from 8 to 11 per 1000 live births.\textsuperscript{1,2} Thus, in the United States, \textasciitilde32 000 to 44 000 infants are born with a cardiac defect each year.\textsuperscript{1} Many infants will require corrective or palliative surgery and extensive hospitalizations during the first year of life.\textsuperscript{3,4} Medical and surgical outcomes are dependent on the complexity of the cardiac lesion, and other infant characteristics, such as lung development, prematurity, and birth weight.\textsuperscript{5,6} After corrective or palliative surgery, multiple studies have documented failure to grow in infants with CHDs because of increased metabolic demands and decreased caloric intake.\textsuperscript{6} The degree of preoperative growth failure has been associated with longer time on the ventilator, difficulty feeding postoperatively, a higher risk of infection, longer hospitalizations, and poor postoperative catch-up growth.\textsuperscript{5–9}

Although the association between CHDs and low birth weight or small for gestational age has been described in clinical and pathologic case series and in case-control studies, few studies have been population based and/or controlled for maternal and fetal determinants of growth.\textsuperscript{10–15} The estimated risk of small for gestational age in large population-based studies has varied by the type of cardiac defects. Published reports indicate that infants with CHDs are \textasciitilde1.8 to 3.6 times more likely to be small for gestational age than infants without CHDs.\textsuperscript{10–15}

The etiology of most nonsyndromic CHDs is unknown but likely involves a complex interaction between multiple environmental exposures and genetic susceptibilities. Similarly, the etiology of small for gestational age is complex. The temporal relationship between CHDs and small for gestational age cannot be discerned from case series or case-control studies. It is possible that both CHDs and small for gestational age occur independently but share common risk factors. For example, maternal periconceptional smoking is the leading cause of small for gestational age in developed countries.\textsuperscript{17–21} Similarly, some case-control studies provide evidence indicating that maternal periconceptional smoking increases the occurrence of CHDs,\textsuperscript{16,22–25} Elevated total maternal homocysteine levels have been shown to be associated with an increased risk of small for gestational age\textsuperscript{26} in infants. Our group has also reported a higher incidence of CHDs associated with high maternal homocysteine levels, suggesting a common pathway\textsuperscript{25,27} related to maternal nutrition. Alternatively, it is possible that small for gestational age in infants with CHDs may be attributed to abnormal fetal hemodynamics,\textsuperscript{28,29} The objective of our study was to investigate the association between CHDs and small for gestational age in a large population-based sample while controlling for multiple maternal and fetal covariates.

METHODS

Case and Control Selection

Eligible case and control subjects were born between October 1997 through December 2002 and enrolled in the National Birth Defects Prevention Study (NBDPS). Details regarding the methods of NBDPS have been published previously.\textsuperscript{30} Briefly, the NBDPS is a multicenter ongoing population-based case-control study intended to identify the etiology of \textasciitilde30 nonsyndromic birth defects, including septal, conotruncal, and obstructive heart defects. Case subjects were identified by birth defect surveillance registries in 8 states using uniform diagnostic criteria.

For the investigation reported herein, infants born with CHDs were included if they met the following criteria: (1) the infant had no known single gene disorder or chromosomal abnormality; (2) the diagnosis of a CHD occurred before the child was 1 year of age and was based on an echocardiogram, heart catheterization, surgical or autopsy report; (3) the mother spoke English or Spanish; (4) the infant was not placed for adoption or in foster care; (5) they were singleton births; and (6) they had no extracardiac anomalies. Control subjects were infants with no birth defects randomly selected from birth certificates or hospital discharge listings in the same states as case subjects. During the study period, the birth population covered by the 8 states was \textasciitilde482 000 births per year. Approximately 18\% of eligible case mothers and 21\% of control mothers refused to participate in the NBDPS study during this time period.

Classification of Cardiac Defects

Each CHD case was reviewed by 1 of 4 NBDPS case classifiers\textsuperscript{31} and described as “simple” or “associated” based on the complexity of the lesion. Cardiac defects were classified into 4 categories based on the anatomic lesion: (1) conotruncal, including transposition of the great arteries, tetralogy of Fallot, truncus arteriosus, double outlet right ventricle, malaligned ventricular septal defect, and interrupted aortic arch type B; (2) septal, including atrial, ventricular, and atrophic ventricular septal defects; (3) right-sided obstructive, including pulmonary valve stenosis, pulmonary atresia, and tricuspid atresia; and (4) left-sided obstructive, including aortic valve stenosis, hypoplastic left heart syndrome and variants, coarctation of the aorta, and interrupted aortic arch types A and C lesions. Complex CHD lesions, which included total and partial pulmonary venous connection, double inlet left ventricle, and other lesions with \textasciitilde3 cardiac defects, were excluded from this analysis.

Maternal and Infant Covariates

As part of the NBDPS, mothers of case and control subjects completed an extensive interview regarding multiple preconceptional, periconceptional, and preg-
nancy exposures. A detailed list of exposures included in these interviews has been published previously. Maternal factors collected for the NBDPS and known to be associated with small for gestational age included maternal socioeconomic status, age, race/ethnicity, gestational weight gain, prepregnancy BMI, parity, preexisting diabetes, hypertension, infections such as cytomegalovirus or rubella smoking, alcohol consumption, and use of marijuana or cocaine. Infant variables studied included infant gender and race/ethnicity.

Growth Parameters
Birth weight was obtained from the birth certificate and added to the NBDPS clinical database. Small for gestational age was defined as a birth weight less than the 10th percentile for a given gestational age and gender based on a standardized birth weight distribution of US live births. Gestational age was obtained from the clinical database; if this was missing, we used a calculated variable using expected date of delivery.

Statistical Methods
Maternal and infant characteristics measured on an interval scale were compared between CHD case and control subjects using the Mann-Whitney/Wilcoxon rank sum test. The frequency of small for gestational age was computed for normal control subjects, CHD case subjects, and each CHD subtype independently. Multiple linear regression was used to model birth weight as a function of case-control status and maternal and infant covariates. Adjusted means were computed from the fitted model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between small for gestational age and CHDs were estimated using conditional logistic regression adjusting for infant and maternal factors collected for the NBDPS and known to be associated with small for gestational age and CHDs were estimated using conditional logistic regression adjusting for infant and maternal factors and grouping on mother’s state of residence. Covariates for inclusion were determined based on results of the bivariate analyses and evidence published previously.

RESULTS
From October 1997 through December 2002, 3501 women who had live-born singleton infants with CHDs and no other congenital abnormality (case subjects) and 3953 women who had live-born singleton infants without any birth defects (control subjects) were enrolled in the NBDPS. Of these participants, 100 case subjects and 21 control subjects who had preconceptional type 1 or type 2 diabetes were excluded from the analyses. Six case and 8 control subjects were excluded from the analysis secondary to inconsistent and erroneous birth weight and gestational age measurements. The final sample consisted of 3395 case and 3924 control subjects.

In this NBDPS cohort, the vast majority (2796 (82.4%)) had a simple cardiac lesion. Septal heart defects were the most common malformation (44.4%), followed by conotruncal (22.4%), right-sided obstructive (16.8%), and left-sided obstructive (16.3%) defects.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Selected Characteristics of CHD Case and Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>CHD Case Subjects (N = 3395), n (%)</td>
</tr>
<tr>
<td>Infant race</td>
<td></td>
</tr>
<tr>
<td>White, not of Hispanic origin (ref)</td>
<td>2128 (62.7)</td>
</tr>
<tr>
<td>Black, not of Hispanic origin</td>
<td>425 (12.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>650 (19.1)</td>
</tr>
<tr>
<td>Others</td>
<td>162 (4.8)</td>
</tr>
<tr>
<td>Infant gendera</td>
<td></td>
</tr>
<tr>
<td>Male (ref)</td>
<td>1821 (53.6)</td>
</tr>
<tr>
<td>Female</td>
<td>1574 (46.4)</td>
</tr>
<tr>
<td>Gestational age, wka</td>
<td></td>
</tr>
<tr>
<td>Term or postterm (ref)</td>
<td>2807 (82.7)</td>
</tr>
<tr>
<td>Preterm</td>
<td>588 (17.3)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Primiparity (ref)</td>
<td>1349 (39.7)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>2044 (60.2)</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
</tr>
<tr>
<td>Lower than high school (ref)</td>
<td>579 (17.1)</td>
</tr>
<tr>
<td>High school</td>
<td>909 (26.8)</td>
</tr>
<tr>
<td>≥ 16 y</td>
<td>996 (29.3)</td>
</tr>
<tr>
<td>Maternal cocaine use</td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td>3371 (99.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>23 (0.7)</td>
</tr>
<tr>
<td>Hypertension during pregnancya</td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td>3022 (89.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>370 (10.9)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
</tr>
<tr>
<td>Underweight: &lt; 18.5 (ref)</td>
<td>202 (5.9)</td>
</tr>
<tr>
<td>Normal weight: 18.5 to ≤ 25</td>
<td>1712 (50.4)</td>
</tr>
<tr>
<td>Overweight: 25 to &lt; 30</td>
<td>747 (22.0)</td>
</tr>
<tr>
<td>Obese: ≥ 30</td>
<td>603 (17.8)</td>
</tr>
<tr>
<td>Smoking between B1 and T3a</td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td>2647 (78.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>747 (22.0)</td>
</tr>
<tr>
<td>Drinking between B1 and T3</td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td>2035 (59.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>1339 (39.4)</td>
</tr>
<tr>
<td>Mean prepregnancy weight (SD)a</td>
<td>68.0 (17.0)</td>
</tr>
<tr>
<td>Mean weight gain (SD)</td>
<td>13.7 (7.7)</td>
</tr>
</tbody>
</table>

B1 indicates 1 month before pregnancy, T3, last trimester of pregnancy; ref, reference.

a P < .05 after ORs and 95% CIs were adjusted for state of resident.
nancy than control subjects (13.7 vs 14.5 kg; \( P = .002 \)). Infants with CHDs were >3 times more likely to be premature than control subjects (OR: 3.16; 95% CI: 2.69–3.70) and less likely to be female (OR: 0.85; 95% CI: 0.78–0.94). The mean gestational age for case subjects was 38 weeks, and the mean gestational age for control subjects was 39 weeks. After controlling for gestational age and infant and maternal risk factors, CHD case subjects had lower mean birth weights (3039.56 g; SE: 35.8) compared with control subjects (3128.42 g; SE: 35.5; \( P < .0001 \)).

As shown in Table 2, 15.2% of case subjects compared with 7.8% of control subjects were small for gestational age (OR: 2.09; 95% CI: 1.78–2.46). The strength and direction of this association remained among those with simple or associated heart lesions. The risk of small for gestational age was also significantly higher for each heart defect subtype group compared with control subjects. The ORs ranged from 1.83 (95% CI: 1.36–2.47) for left-sided obstructive defects to 2.41 (95% CI: 1.89–3.08) for conotruncal defects.

In the general population, more premature infants are small for gestational age than term or postterm infants. Thus, we conducted a stratified analysis to determine whether the association between CHDs and small for gestational age would be similar in preterm and term/postterm infants. The adjusted ORs for small for gestational age among individual cardiac subtypes for preterm and term/postterm infants are displayed in Fig 1. Among both preterm and term infants, after controlling for maternal and infant covariates, case subjects were more likely to be small for gestational age than control subjects. Among preterm infants, those with conotruncal and septal heart defects had the highest odds ratio for small for gestational age (OR: 3.24; 95% CI: 1.65–6.37 and OR: 2.29; 95% CI: 1.39–3.79, respectively).

**DISCUSSION**

The findings of this population-based case-control study demonstrate that infants with CHDs are more likely to be small for gestational age and premature than control infants. Our findings are consistent with recent reports from other developed countries. In a British study, including participants born between 1987 and 2001, 16% of infants with CHDs, were premature compared with 17.3% in our study. Being small for gestational age is usually defined as <10% for a given gestational age, and, thus, one may expect more control infants to be small for gestational age than found in our study sample. However, we excluded twins and higher-order multiples and infants with syndromes, which may explain why only 7.8% of the control subjects were small for gestational age.

The nature of the etiologic and temporal relationships between CHDs and fetal growth remains elusive, but 2 competing hypotheses seem plausible. Some risk factors for small for gestational age may also be associated with CHDs. It remains unclear whether small for gestational age and CHDs coexist because of common underlying etiologic pathways, such as maternal smoking, or because CHDs independently affect the growth of the fetus. The critical period for CHD development is between the third and ninth weeks of gestation. Snijders et al showed that erythropoietin levels were increased significantly in small for gestational age infants secondary to fetal hypoxia. Although it is possible that altered fetal circulation because of CHDs might result in low birth weight, no consistent hemodynamic pattern with respect to oxygen saturations or hemoperfusion can explain our findings.

Clinical knowledge about the association that we found between CHDs and small for gestational age may have significant implications in both prenatal and postnatal care. Closer monitoring of fetal growth may be warranted after a prenatal diagnosis of CHD. Nutritional programs in pregnant women at risk of small for gestational age have been shown to improve infant outcomes, and mothers diagnosed with CHDs by fetal echocardiography may benefit from nutritional interventions. Postnatal clinical management of the infant with CHD and fetal growth restriction is dependant on cardiac pathology. The most common subtype of CHD is septal heart defects, which often require anticongestive

**TABLE 2 CHD Case Subjects and Subtypes With Small for Gestational Age**

<table>
<thead>
<tr>
<th>CHD</th>
<th>N</th>
<th>Small For Gestational Age, n (%)</th>
<th>Adjusted OR (95% CI)a</th>
<th>Adjusted OR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>3924</td>
<td>307 (7.82)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Total case subjects</td>
<td>3395</td>
<td>516 (15.20)</td>
<td>2.07 (1.78–2.40)</td>
<td>2.09 (1.78–2.46)</td>
</tr>
<tr>
<td>Simple heart lesion</td>
<td>2796</td>
<td>409 (14.63)</td>
<td>1.96 (1.67–2.30)</td>
<td>1.98 (1.68–2.35)</td>
</tr>
<tr>
<td>Associated heart lesion</td>
<td>599</td>
<td>107 (17.86)</td>
<td>2.54 (1.99–3.23)</td>
<td>2.55 (1.97–3.31)</td>
</tr>
<tr>
<td>Conotruncal heart defect</td>
<td>762</td>
<td>124 (16.27)</td>
<td>2.27 (1.82–2.85)</td>
<td>2.41 (1.89–3.08)</td>
</tr>
<tr>
<td>Septal heart defect</td>
<td>1509</td>
<td>240 (15.90)</td>
<td>2.14 (1.78–2.58)</td>
<td>2.06 (1.69–2.51)</td>
</tr>
<tr>
<td>Left obstructive heart defect</td>
<td>552</td>
<td>70 (12.68)</td>
<td>1.72 (1.30–2.27)</td>
<td>1.83 (1.36–2.47)</td>
</tr>
<tr>
<td>Right obstructive heart defect</td>
<td>572</td>
<td>82 (14.34)</td>
<td>1.97 (1.51–2.56)</td>
<td>2.02 (1.52–2.69)</td>
</tr>
</tbody>
</table>

a ORs and 95% CIs were adjusted for maternal hypertension during pregnancy.

b ORs and 95% CIs were adjusted for infant race, parity, maternal age at conception, education, pre-pregnancy BMI, weight gain during pregnancy, and cocaine use between 3 months before pregnancy to end of pregnancy, smoking and drinking status between 1 month before pregnancy to the end of pregnancy, maternal hypertension during pregnancy, and state of resident.
medications if there are signs of congestive heart failure. These children are typically more prone to be placed on medications if the child has concomitant growth failure. They are also more likely to be referred for surgical repair of their underlying lesion if they continue to have growth retardation in the face of adequate medical and nutritional therapy. In contrast, infants with cyanotic heart lesions require multiple palliative surgeries in infancy. If this high-risk group of infants is nutritionally deficient secondary to fetal growth restriction, this can lead to prolonged postoperative hospital stays, as well as invasive surgeries, such as gastrostomy tube placement for nutritional rehabilitation before hospital discharge.

Our findings were based on participants in the NB-DPS, which is the largest population-based case-control sample of all major cardiovascular malformations ever conducted in the United States. This study uses a structured maternal questionnaire to provide detailed information to confirm gestational age and exposure to environmental and behavioral factors. Uniform criteria for clinical confirmation of the cardiac defect and a rigorous review of abstracted medical chart data by an expert panel of clinicians also maximizes homogeneity between cases.

Limitations of our study must be considered. Sample sizes when stratified by prematurity were limited, reducing our ability to detect statistically significant differences in small for gestational age among specific cardiac phenotypes. Echocardiograms were not performed on control subjects, and thus some may have undiagnosed CHDs. We were not able to obtain length and head circumference data on the majority of NB-DPS centers; this information would be relevant in future studies, because it would provide “symmetry” data regarding the timing of intrauterine growth retardation. Symmetrical growth retardation is associated with in utero injury early in pregnancy.

Further study of the association between CHD and small for gestational age will hopefully provide insights into basic mechanisms that may lead to both outcomes. Identifying risk factors for both CHDs and small for gestational age will contribute to the evidence base required for the planning and implementation of primary prevention programs to prevent heart defects and optimize pregnancy outcomes. A greater clinical understanding of the association between CHDs and small for gestational age may have significant implications for prenatal care. Closer monitoring of fetal growth and maternal nutrition is warranted after prenatal diagnosis of CHD. These women may be candidates for nutritional monitoring and more frequent and detailed ultrasounds to determine serial fetal weights. In addition, infants with CHDs who are small for gestational age require substantial nutritional intervention postnatally to curtail growth-related problems and improve clinical outcomes in infancy and early childhood.
ACKNOWLEDGMENTS

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We thank all staff members of the Centers for Birth Defects Research and Prevention and all of the centers’ abstractors. Most of all, we thank all of the families of children who have participated in the National Birth Defects Prevention Study.

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A New Phenotypical Variant of Intrauterine Growth Restriction?

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A link between intrauterine growth restriction and major adult-onset diseases has been reported. In this study we observed a series of hitherto-unrecognized clinical features in a population of children with intrauterine growth restriction.

OBJECTIVES. A link between intrauterine growth restriction and major adult-onset diseases has been reported. In this study we observed a series of hitherto-unrecognized clinical features in a population of children with intrauterine growth restriction.

PATIENTS AND METHODS. A total of 77 Italian children (aged 9.45 ± 2.08 years) with antenatally diagnosed intrauterine growth restriction and small-for-gestational-age birth, along with their parents, were examined. The children with intrauterine growth restriction and were small for gestational age were subdivided into 2 groups (“variant” versus control subjects) according to evidence of auricle morphology deviation from normal. The following variables were determined: (1) external ear auricle geometry; (2) function of the posterior communicating arteries of the circle of Willis, as assessed by transcranial Doppler ultrasonography; (3) articular mobility, as assessed by Beighton’s 9-point scale; (4) skin softness; and (5) distortion product–evoked otoacoustic emissions.

RESULTS. Intrauterine growth restriction–variant children (n = 27) showed a significant female predominance, a lower proportion of maternal pregnancy-induced hypertension/ preeclampsia, and a higher head circumference as compared with intrauterine growth restriction control subjects. Mothers of small-for-gestational-age–variant children showed significantly different auricular geometry parameters as compared with the intrauterine growth restriction controls mothers. An excess of bilaterally nonfunctioning posterior communicating arteries was observed both in the children with the intrauterine growth restriction–variant phenotype and their mothers as compared with the control groups. Significantly increased proportions of joint hypermobility and skin softness were observed in the intrauterine growth restriction–variant children as compared with controls subjects.
with the intrauterine growth restriction–variant phenotype and their mothers showed bilateral distortion product–evoked otoacoustic emissions notches versus none in the control subjects, with an associated reduction of the area under the curve in both the intrauterine growth restriction–variant children and their mothers. No significant differences between the variant and control groups regarding the fathers were observed.

CONCLUSIONS. We propose that the observed phenotypical constellation may represent an unrecognized variant of intrauterine growth restriction.

INTRAUTERINE GROWTH RESTRICTION (IUGR) has a prevalence of 10% among all pregnancies, varying from rates of 3% to 5% among healthy mothers up to ≥25% in high-risk groups. IUGR resulting in birth weight small for gestational age (SGA) is a known risk factor for high perinatal morbidity and mortality and has been related previously to development of several of the major diseases of later life, including coronary heart disease, obesity, noninsulin dependent diabetes, hypertension, and stroke. Studies linking IUGR with long-term adverse health consequences have so far depended on crude measures of fetal growth, such as overall weight or length. Recently, fetal growth of liver and kidneys has been shown to be impaired in intrauterine growth-retarded infants, thus supporting the concept that fetal environmentally caused “programming” may increase the risk of functional defects and diseases in later life. However, no morphologic markers of impaired fetal growth that persist later in life are known to date, with the possible exceptions of fingerprints pattern abnormalities and shape of the palm or a high second-to-fourth-digit finger-length ratio in specific SGA subsets. Here, we describe a series of children with idiopathic IUGR/SGA showing previously unrecognized, phenotypical features, including auricle shape variations, bilaterally reduced or absent hemodynamic responses of the posterior communicating arteries (PCoAs) of the circle of Willis, joint hypermobility, soft skin, and bilateral subclinical cochlear dysfunction.

METHODS

Subjects
A total of 77 Italian children (boys: 32; girls: 45; gestational age at birth: 35.49 ± 2.50 weeks; age at examination: 9.45 ± 2.08 years) with antenatally diagnosed IUGR (as defined as insufficient fetal growth < 2 SD or < 3rd percentile) below the mean for gestational age and SGA birth (as defined as insufficient body size < 2 SD or < 3rd percentile) below the mean for weight and/or length in relation to gestational age and gender for the Italian population), followed up in a regular clinical program, were enrolled, along with their parents (mothers, age at examination: 40.57 ± 4.61 years, range: 35–48 years; fathers, age at examination: 42.5 ± 0.71 years, range: 37–49 years). The examined families originated from Tuscany (67 of 77 [87%]), Apulia (8 of 77 [10.4%]), and Basilicata and Sicily (1 of 77 [1.3%]) each. The percentiles for body height and weight at examination were determined on the basis of Italian cross-sectional growth charts. None of the participants had primary growth failure syndromes, congenital infections, known chromosomal aberrations, genetic syndromes, or showed specific dysmorphic features or developmental delay. None of the participants had a history of cerebrovascular disorders or preexisting systemic illness, known cochlear disease, history of environmental noise exposure, or inherited connective tissue diseases. After providing their respective histories, all of the subjects underwent a complete physical examination. Low maternal weight was defined as prepregnancy or delivery weight < 45.36 kg or BMI ≥ 19.8 kg/m², and low maternal weight gain was defined as < 0.27 kg per week. None of the mothers had a history of malnutrition and/or chronic use of alcohol or narcotics. None of the examined parents had a history of past or current smoking, hypertension, hypercholesterolemia, or diabetes mellitus. The IUGR/SGA children were subdivided into 2 groups (variant versus control subjects) according to subjective evidence of auricle morphology deviation from normal (Fig 1A), and the following variables were determined: (1) external ear auricle geometry; (2) PCoA function, as assessed by transcranial Doppler ultrasonography; (3) articular mobility; (4) skin softness; and (5) distortion product–evoked otoacoustic emissions (DPOAES). The main reason for doing a long-term clinical follow-up in our IUGR/SGA children was an arterial pressure monitoring study.

The follow-up was systematic, without previous sample selection. Our follow-up “theoretical” duration is up to age 14 years. Approval from the institutional review board and informed consent for clinical examination, instrumental studies, and photographic imaging were obtained.

External Ear Geometry
The maximum width of longest axis (LA), shortest axis (SA) of the auricle, and the distance of SA from the lowest auricle point (SA-D) were measured (Fig 1A). SA/LA and SA/SA-D ratios were used as size-independent geometric indicators of auricle shape. The SA-D and SA/LA ratios from both ears were evaluated, and the mean of the measurements was used for each individual in the analyses. Morphometric measurements of the auricle were collected with Vernier calipers to 0.01-mm accuracy by 2 operators who were unaware of the results of the other clinical and/or instrumental findings. The asymmetry index was also calculated by subtracting the average length of the right side of the trait from the
left and correcting for trait size (ie, 100 × right − left/ [right + left]/2).11

Transcranial Color-Coded Duplex Ultrasonography
Ultrasound flow-flow examination was performed with a color-duplex scanner (Philips Sonos 5500, Agilent Technologies, Hewlett-Packard, Andover, MA), using either a 3- to 11-MHz linear transducer or a 2.5-MHz 90° sector transducer head for evaluating the extracranial carotid and vertebral arteries and the intracranial basal arteries, respectively. Examination of the internal carotid (intracranial tract), vertebral artery (V4 segment), and basilar artery, as well as in the anterior (precommunicating, A1 segment), middle (main trunk, M1 segment), and posterior (precommunicating and postcommunicating, P1-P2 segments) cerebral arteries through the temporal bone window, was performed according to standard techniques14–16 (see Fig 2 for a diagram with the segments of the circle of Willis). All of the subjects showed sufficient acoustic windows. The blood flow velocity changes in the precommunicating parts (A1 and P1, respectively) of the anterior and posterior cerebral arteries were measured during common carotid artery (CCA) compression. To avoid a systemic cardiovascular reaction, compressions were applied for 3 to 5 cardiac cycles, low in the neck just proximal to the sternal head of the clavicle. The anterior communicating artery was defined as functional if blood flow was reversed in the ipsilateral A1 and enhanced in the contralateral A1 during CCA compression. The PCoA was considered to be functional if the flow velocity in the P1 was enhanced >20% during ipsilateral CCA compression. PCA was defined as fetal configuration (ie, the major stem of the PCA arising from the ipsilateral internal carotid artery instead of from the basilar artery) in case of significant decrease in peak velocity after CCA ipsilateral compression. The transcranial color-coded duplex ultrasonography was conducted by a single operator blind to further clinical or instrumental information. The methodology used was standard and sufficiently reproducible (κ = 0.93 [SE: 0.021]; range: 0.89–1.0).

Joint Hypermobility
Joint hypermobility was evaluated using the Beighton’s 9-point scale17 by clinicians blind to other clinical or instrumental information. In children, joint hypermobility was defined as the presence of ≥3 of 5 positive criteria, according to Beighton and Carter,17,18 and in their parents as a mobility score >4.19

FIGURE 1
Auricle shape in the IUGR/SGA variant and their mothers. A, Variant; B, IUGR/SGA control child; C, schematic graph; D and E, ear shape: right-to-left asymmetry in the mother of a child with the IUGR/SGA variant.

FIGURE 2
Schematic diagram of the arterial segments of the circle of Willis as identified by transcranial color-coded duplex ultrasonography.
Skin Softness
An excessive skin softness was evaluated as a subjective variable by 2 independent observers (interobserver agreement for increased skin softness: \( \kappa = 0.910 \) \( [SE: 0.025] \); range: 0.846–1.0) who were unaware of the subjects’ clinical history and findings.

Distortion Product–Evoked Otoacoustic Emissions
Otoacoustic emissions, expressing the response that the cochlea emits in the form of acoustic energy, are determined by the contractile activity of the outer hair cells and the mechanical and structural features of the basilar membrane. Otoacoustic emissions are currently used as objective indicators of cochlear pathology and used in several neonatal hearing loss screening programs.\(^{20,21}\) In the present study, cochlear function (DPOAEs) was investigated in all of the IUGR/SGA children and their parents using an ILO 292 DP Echoport OAE Analyzer 5.0 (Otodynamics Ltd, London, United Kingdom).\(^{22–24}\)

Two simultaneous pure tones were sent to each ear (\( f_2 > f_1 \) with an \( f_2/f_1 \) ratio \( = 1.22 \), sounds intensity \( = 70 \text{ dB sound pressure level} \), with a frequency range of 1–6 kHz). The degree of cochlear dysfunction was determined by calculating the area under the curve (AUC) for all of the DPOAE recordings. In case of a detectable “notch” (ie, a marked reduction in the intensity of otoacoustic emissions in the frequency response; \( \text{Fig 3} \)), its mean peak frequency was determined. All of the subjects had normal otoscopic findings and normal hearing, as preliminarily assessed using pure tone audiometry, tympanometry, stapedius reflex tests, and auditory brainstem responses.

Data Analysis
Differences in categorical and continuous variables between the 2 SGA groups were assessed using \( \chi^2 \) or Fisher’s exact tests and Student’s paired \( t \) test (Bonferroni corrected significance levels) or Wilcoxon’s test, as appropriate. AUC for DPOAEs was determined using a serial measurements algorithm. The MedCalc 8.1.1 statistical software (MedCalc Software, Mariakerke, Belgium) was used. A 2-sided \( P \) value of \(< .05\) was considered statistically significant.

RESULTS
A multiple comparison between children with the IUGR variant and controls is shown in the Table 1. The children belonging to the IUGR-variant group showed a significant female predominance (\( P = .0226 \)), a lower proportion of maternal pregnancy-induced hypertension/preeclampsia (\( P < .0001 \)), and a higher head circumference (\( P < .0001 \)), whereas no statistically significant differences were present regarding age at examination, gestational age at birth, history of maternal SGA, percentiles for height and weight at examination, birth weight, and birth length (\( P \geq .4991 \)).

The children with the IUGR variant showed a different auricular geometry, as compared with IUGR control subjects, exhibiting significantly lower \( \text{SA-D}/\text{LA} \) ratios and higher \( \text{SA}/\text{LA} \) and \( \text{SA-D} \) asymmetry indices (all \( P < .0001 \); Table 1). Likewise, their mothers showed significantly different auricular geometry parameters as compared with the mothers of IUGR control subjects (\( \text{SA-D}/\text{LA} \) ratio: \( 0.6247 \pm 0.063 \) vs \( 0.7049 \pm 0.0197 \), \( P = \)

![FIGURE 3](image-url)

DPOAEs in a child with the IUGR/SGA variant (A) and the corresponding mother (B). A notch (ie, a marked reduction in the frequency response) is evidenced (arrows) in both graphs, with a mean frequency peak at \( \sim 2.5 \text{ kHz} \) in the child and \( \sim 3.2 \text{ kHz} \) in the mother. The right-ear graph is shown for both subjects. (y-axis: sound intensity, dB SPL; x-axis: sound frequency, kHz).
TABLE 1
Comparisons of Relevant Clinical Characteristics in IUGR/SGA Children With and Without Auricle Shape Variations

<table>
<thead>
<tr>
<th>Variables</th>
<th>SGA Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and pregnancy</td>
<td></td>
</tr>
<tr>
<td>Male/female (% female)</td>
<td>6/21 (77.77)</td>
</tr>
<tr>
<td>Age at examination, mean ± SD, y</td>
<td>9.4 ± 1.65</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension/preeclampsia, n (%)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Gestational age at birth, mean ± SD, wk</td>
<td>35.05 ± 5.13</td>
</tr>
<tr>
<td>SGA mother, n (%)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Family history of SGA, n (%)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Axometry, mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1484 ± 520</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>41.0 ± 3.32</td>
</tr>
<tr>
<td>Birth head circumference, cm</td>
<td>31.83 ± 1.18</td>
</tr>
<tr>
<td>Height at examination, percentile[^d]</td>
<td>36.14 ± 27.56</td>
</tr>
<tr>
<td>Weight at examination, percentile[^d]</td>
<td>44.43 ± 35.60</td>
</tr>
<tr>
<td>External ear geometry, mean ± SD</td>
<td></td>
</tr>
<tr>
<td>SA/LA asymmetry index, %[^e]</td>
<td>3.25 ± 0.25</td>
</tr>
<tr>
<td>SA-D asymmetry index, %[^e]</td>
<td>17.99 ± 3.5</td>
</tr>
<tr>
<td>Transcranial color-coded duplex ultrasonography</td>
<td></td>
</tr>
<tr>
<td>Bilaterally nonfunctional PCoAs, n (%)[^f]</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Joint hypermobility, n (%)[^g]</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Beighton’s score[^h]</td>
<td>5 ± 0.5</td>
</tr>
<tr>
<td>Skin softness, n (%)</td>
<td>27 (100)</td>
</tr>
<tr>
<td>DPOAEs</td>
<td></td>
</tr>
<tr>
<td>Bilateral notch, n (%)</td>
<td>27 (100)</td>
</tr>
<tr>
<td>AUC, right ear, mean ± SD, dB SPL</td>
<td>35.95 ± 14.07</td>
</tr>
<tr>
<td>AUC, left ear, mean ± SD, dB SPL</td>
<td>23.90 ± 2.69</td>
</tr>
</tbody>
</table>

[^a] See Fig 1A.
[^b] 0.05 < P ≤ .01.
[^c] P < .001.
[^d] Data shown are the percentiles at examination, adjusted for age and gender.
[^e] Asymmetry index indicates \((100 \times \text{right} - \text{left}) / (\text{right} + \text{left})\).
[^f] Postcompression systolic velocity increase <20% over baseline values in the ipsilateral PCA.
[^g] Data include the presence of ≥3 of 5 positive criteria, according to Beighton et al[^g] and Carter and Wilkinson.[^g]
[^h] Values are median ± semi–interquartile range.
[^i] A notch is defined as a sharp decrease in the intensity of otocoustic emissions at middle-high frequencies.

.0040; SA/LA asymmetry index[^e]: 12.70 ± 7.52% vs 1.47 ± 0.25%, P = .0009; SA-D asymmetry index: 13.45 ± 3.09% vs 3.96 ± 0.21%, P < .0001) with the exception of the SA/LA ratio (0.5852 ± 0.0546 vs 0.5736 ± 0.016). Ear shape variation was found to be bilateral in the variant IUGR/SGA subjects, whereas it was unilateral in the unaffected variant SGA mothers. By contrast, no significant differences between the variant and control groups were observed regarding the fathers (P ≥ .45; data not shown).

Nonfunctional PCoAs showed postcompression values in the ipsilateral PCA (mean ± SD) of a 4.34% ± 5.98% increase over basal values (range: 0%–11.27%) vs functional PCoAs with a 76.96% ± 26.89% increase over baseline (range: 23.12%–119.06%). A statistically significant excess of bilaterally nonfunctioning PCoAs was observed both in the children with the IUGR variant (P < .0001) and their mothers (26 of 27 [96.3%] vs 0 of 50 [0%]; P < .0001) as compared with the control groups (Table 1). No significant differences were evidenced regarding the fathers (P ≥ .8200; data not shown).

Significantly increased proportions of joint hypermobility and skin softness were observed in the IUGR-variant children as compared with control subjects (P < .0001; Table 1). On the other hand, no significant differences were observed concerning articular mobility and skin examination for the parental groups (P ≥ .6515; data not shown), and none of the examined SGA-variant children showed abnormal skin laxity.

All of the children with the IUGR variant and their mothers showed evidence of bilateral DPOAEs notches (Fig 2) as compared with none of the control subjects (P < .0001), with an associated reduction of the AUC in both the IUGR-variant children (P < .0001; see Table 1) and their mothers (AUC right ear: 19.05 ± 18.86 dB of sound pressure level, SPL, vs 48.17 ± 13.41 dB SPL, P < .0001; AUC left ear: 15.11 ± 13.53 dB SPL vs 58.12 ± 18.77 dB SPL, P < .0001). However, the peak frequency of the notches for the variant IUGR children was signifi-
icantly lower than that of their mothers (2.63 ± 0.39 kHz vs 3.21 ± 0.27 kHz, P < .0001). No significant DPOAE differences were evidenced regarding the fathers (P ≥ .6611; data not shown). Likelihoods of random association for the described features in individual children and child-mother pairs were estimated to be ~2.25 × 10⁻⁸ and ~1.35 × 10⁻⁹, respectively.

**DISCUSSION**

Our findings suggest the presence of a previously unrecognized phenotype in a subset of IUGR/SGA children, based on the following: (1) abnormal auricle shape, related to a minor developmental defect of the helix; (2) bilaterally low hemodynamic responses of the PCoAs; (3) bilateral subclinical cochlear dysfunction; (4) excessively soft skin; and (5) joint hypermobility. In addition, the described IUGR/SGA variant was found to be associated with distinct maternal phenotypic features, including auricle shape changes, transcranial color-coded duplex ultrasonography evidence of bilaterally nonfunctional PCoAs, and subclinical bilateral cochlear dysfunction. The order of magnitude (~10⁻⁸ to 10⁻⁹) estimated for a random association of the described signs would theoretically justify a new clinical entity. Given that the follow-up was systematic, without previous subject selection, it is unlikely that selection criteria could potentially affect data interpretation. However, given that intrauterine mortality for this variant remains unknown, an inevitable selection bias could theoretically be present.

Formation of the external ear is a very complex process, and its careful examination and detailed description may prove to be of diagnostic value in specific syndromes. The auricle appears early during embryogenesis, developing from the first and second pharyngeal arches, and can be impacted by any disruptions of its development, as well as by the effects of the intrauterine environment. Although a statistical relationship between abnormal external ear geometry and IUGR/SGA had been suggested previously by our group, the present study indicates that a variant auricle shape is associated with a complex phenotype, thus identifying a previously unrecognized IUGR subset. At this stage of our study, inner ear imaging was not performed. As a consequence, cochlear malformations cannot be ruled out in this particular IUGR/SGA subgroup. However, inner ear congenital malformations are usually found in patients with syndromic sensorineural hearing loss, such as Pendred syndrome, although exceptions are known to exist. In particular, patients with complex of enlarged vestibular aqueduct, Mondini dysplasia, large vestibule, and semicircular canal dysplasia usually present with fluctuating hearing loss (93%). This was obviously not the case in our described SGA-variant phenotype, whereas the hearing “abnormality” observed in our SGA-variant subjects, that is, the presence of notches at DPOAEs, was subclinical at the time of examination.

As the pharyngeal arches develop during the fourth week, they are supplied by arteries, the aortic arches, and the distal parts of the third pair of aortic arches join with the dorsal aortae to form the internal carotid arteries, which supply the ears, orbits, and brain. The PCoAs arise from the dorsal aspect of the intracranial internal carotid artery, run caudally and medially, and, finally, join to the PCA, forming an important connection between the carotid and vertebrobasilar circulations. Therefore, the associated abnormalities of the external ear and the PCoAs could be considered as the result of an aberrant development of the mesoderm of the pharyngeal arches.

The occurrence of notches at the DPOAEs in children with the phenotypical SGA variant indicates a subclinical impairment of the outer hair cell function. The mean peak frequencies of the notch at middle-high frequencies in both children with the IUGR/SGA variant and their mothers are compatible with a subclinical dysfunction of the intermediate-basal gyrus of the cochlea. The internal ear develops in the fourth week from the surface ectoderm: the hair cells are specified from the simple epithelium of the early otic vesicle, deriving probably from the same common progenitor of the supporting cells through appropriate cell-cell contacts. Thus, the subclinical cochlear dysfunction here observed may likely reflect a primary disturbance of these mechanosensory cells.

The observed changes in skin texture, associated with increased skin softness and macroscopic changes in the stratum corneum, add to previous findings of subtle, permanent skin markers in children with a history of impaired fetal growth. In particular, a relationship among IUGR, fingerprints pattern abnormalities, shape of the palm, and hypertension had been reported previously. On the other hand, joint hypermobility, a common benign condition (10%–15% in the Western population) of unknown pathogenesis has been related previously to infantile hypertrophic pyloric stenosis, as well as to genetic disorders involving the extracellular matrix (ECM). The coexistence of joint hypermobility and skin abnormalities in SGA children with nonfunctional PCoAs suggests a possible involvement of ECM, although at this stage there is no definite proof for either a previously recognized or undescribed collagen disorder in this subgroup of SGA subjects.

The relatively spared head growth at birth shown by the SGA-variant subjects suggests a form of “primary” IUGR as opposed to the IUGR mostly “secondary” to maternal pregnancy-induced hypertension/preeclampsia of the control group. As a consequence, IUGR should be considered as an adverse effect by a fetoplacental pathology on the intrauterine growth for a fetus with a normal growth target as opposed to a preprogrammed
lower size in the “primary” (ie, variant) form described here. By contrast, the observed female prevalence and the close similarity between some of the phenotypical features of SGA-variant children and those of their mothers (ie, auricle helix change, low hemodynamical responses of the PCoAs, and subclinical cochlear dysfunction) remain unexplained at this time, while raising the possibility of inherited traits.

Considering all of these features, the phenotype of the described IUGR/SGA variant is likely the consequence of a large, developmental disturbance occurring early in embryogenesis. In addition, it should be noted that this multiple developmental disorder seems to be generally benign, although no data exist on the intrauterine mortality rate in the proposed phenotypical variant. If we consider the skin, reciprocal epithelial-mesenchymal interactions could coordinate a common developmental program, and its disturbance can determine disorders with defects in multiple organs (ie, pleiotropy). In this context, the ECM could play a primary role, containing a diversity of molecules interacting with each other, as well as with epithelial and mesenchymal cells via specific cell-surface molecules (integrins).

The precise molecular defects underlying the observed clinical phenotype are difficult to be predicted at this stage of knowledge. In IUGR complex genetic mechanisms, such as uniparental disomy or epigenetic changes seem to be involved in generating different subtypes. In our series, the absence of familial cases makes it unlikely a single gene/monogenic Mendelian inheritance model, whereas suggesting the role of more complex genetic/environmental mechanisms in determining phenotypic features. The use of new, more refined molecular investigation techniques, such as comparative genomic hybridization genomics and telomeric array, could provide interesting clues for a better understanding molecular pathogenesis of the condition described in our patients. Additional studies are also needed to explore the frequency and geographic distribution of the observed IUGR/SGA variant, as well as its possible relationships with long-term prognosis and other possible markers of fetal programming.

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Pediatrics on the Web: 10 Years of Innovation and Discovery

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The author has indicated he has no financial relationships relevant to this article to disclose.

ABSTRACT

The electronic edition of Pediatrics celebrates its 10th birthday this year. This article describes the origins and evolution of the online edition of Pediatrics, which, after launching in 1997, featured the world’s first online-only section of a medical journal. Over the proceeding 10 years the journal introduced numerous innovations, including e-mail alerts, postpublication peer review, video supplements, online classified advertisements, Web-based manuscript submission, early release, and the development of the eJournal Archive. This article also describes the use and reception of the electronic journal. Whether measured by article accesses, citation rates, or the number of manuscript submissions, the electronic edition of Pediatrics has proven to be a success. It has allowed the journal to publish a larger number of articles and reach a wider audience than would have been economically possible with a print-only publication. Yet, even as Pediatrics recreates itself online, it is clear that there is much more that can be done to fully realize the potential of the new medium to facilitate professional communication.

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Key Words
electronic journals, journalology

Abbreviations
AAP—American Academy of Pediatrics
PDF—portable document format
BMJ—British Medical Journal
JAMA—Journal of the American Medical Association
HINARI—Health InterNetwork Access to Research Initiative

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics
The electronic edition of *Pediatrics* celebrates its 10th birthday this year. At the time it was launched, this was a groundbreaking innovation. In today’s world, in which everyone over the age of 12 seems to have his or her own blog or podcast, it is amazing to think that only 10 years ago the *Electronic Pages*, introduced by Jerold Lucey, MD, and Kent Anderson, were the first and only electronic-only section of a medical journal available on the planet. So much has changed over the last decade that the editors thought it would be worthwhile to take the occasion of this anniversary to look back over the landscape traversed, catalog some of the more notable milestones in the journal’s recent history, and hazard some speculation as to what may lie in the terrain ahead.

**Origins and Milestones**

The online-only section of the journal, titled the *Electronic Pages*, debuted on January 6, 1997. The *Electronic Pages* were originally conceived of as an online-only supplement to the print journal. This electronic feature of the journal contained articles that could not be found in the print edition, and, at least initially, the print articles could not be found online. In hindsight, dividing the journal into electronic-only and print-only components seems a bit strange. However, the *Electronic Pages* were begun as an experiment. The American Academy of Pediatrics (AAP) wanted to test 2 hypotheses: (1) whether the online edition might allow the journal to publish more articles at a lesser incremental cost than printed articles (for this reason, it made sense to keep both the accounting and the online-edition entirely separate), and (2) whether the online edition could reach a wider international audience than the print edition.

Both hypotheses proved affirmative. Although each online article still incurred the associated costs of peer review, copyediting, and typesetting (electronic portable document format [PDF] files still must be typeset to facilitate desktop printing), just as with printed articles, we found that the cost of online production was more than offset by the savings in printing and postage. Over the course of the next year, the journal was able to expand the number of original research articles published by one third without an equally dramatic increase in costs. By 1998, the *Electronic Pages* were recording more than 20,000 unique visitors from more than 80 countries each month. Expressions of gratitude and interest began to pour in from readers and pediatric societies as far away as Hong Kong, Burma, and Brazil. Eighteen months after it began, the experiment was so successful that the AAP decided to expand its scope. In July 1998, the electronic edition of *Pediatrics* was expanded to include every article from the print journal. Given that the electronic journal contained more material than the print version, it was now, less than 2 years after it launched (and regardless of whether we were ready for this change), the journal of record.

More innovations were to follow. In 1999, e-mail alerts were developed and allowed readers to track published material by subject, author, keyword, or citation. One simply sets up an alert, and whenever *Pediatrics* publishes an article matching those criteria, the journal sends out an e-mail alert with a link directly to the relevant article. This alert system can even track articles published in hundreds of other top-tier medical journals. In addition, one can elect to simply receive the table of contents of each issue as it is published via e-mail. Links are embedded in the e-mail to take the reader directly to any article he or she finds interesting.

Later that same year, the journal introduced “post-publication peer review.” This feature allows readers to rapidly respond to articles that were published in the journal. Next to the online version of every article is a link that invites a response. Readers may click on that link and write a comment, which is rapidly reviewed by an editor for relevance and professionalism and then, if appropriate, posted online within 48 hours. Although the naming of the feature was criticized in the *British Medical Journal* (*BMJ*) for excessive use of the letter “P,” it was a name carefully chosen by the editors. Many journals offer similar features, which are typically referred to as “e-letters” or “rapid response.” Such terms adequately describe the medium or format of such mechanisms but not the purpose. Peer review does not does not stop with an article’s acceptance by a journal. The medium of electronic publication offered a mechanism to shorten the delay between publication and the receipt of feedback from the wider medical and scientific communities. In implementing this mechanism, *Pediatrics* wanted to make explicit the notion that post-publication responses, which include these rapid electronic comments as well as more formal letters to the editor and subsequent studies or reports on the same topic, are part of the overall continuum of peer review.

Fundamentally, online-only articles and postpublication peer review, although innovative means of expanding and expediting scientific communication, are nothing more than new and more efficient means of old forms of communication. These online-only devices are digital versions of old-fashioned articles, letters, and other written communication. The ink has been replaced with pixels and paper fiber with the liquid crystals of the modern computer screen. Other than this shift in medium, however, these articles do not appear notably different from the articles that first appeared in *Pediatrics* in 1948 (or, for that matter, in *Philosophical Transactions* in 1665). However, the World Wide Web is not confined to the limitations imposed by ink and paper. Why, the editors asked, should journal articles be so constrained? In March 2000, *Pediatrics* introduced the journal’s first article with video. The article, by Rich et al., reported on
the role of video intervention/prevention assessment in the management of asthma. The authors asked 23 children and adolescents to record video diaries of how they live with and manage disease in the context of their lives. As part of the article, Rich et al provided excerpts from these videos. In one video, a child’s mother is seen, after the child has left the room, turning off the video camera with a lit cigarette in one hand. In another, we see the dust from a nearby construction site coating the walls and windows of the child’s apartment building. In addition to making a compelling case for the use and value of video intervention/prevention assessment, the videos provide the reader with insight into the lives of young patients who are living with asthma in environments beyond their control—insight that could not be conveyed as effectively by other means.

Since these first videos appeared in 2000, Pediatrics has published numerous articles with online-only photographs, audio files, and other supplemental data. In theory, as long as data are captured in a digital format that is readable by the majority of computer users, there is no limit to the type of data that can be included in an article. (Given the rapidly decreasing cost of electronic storage space, there is no practical limit either). The publication of these data sets marks the first true departure from the print edition of the journal in terms of the article’s form—the beginning, perhaps, of the evolution of the article and the journal—to a format native to the digital environment.

Classified advertisements have long been a staple of the journal-publishing business. They have appeared in the print edition of Pediatrics since 1948. They consist largely of advertisements for vacant positions and announcements for fellowships or other career opportunities. Classified ads were part of the online edition of Pediatrics, just as they have long been, and continue to be, part of the print edition. However, to take full advantage of the rapidly developing medium of the Internet and the rapid shift in behavior of those who seek career information to electronic resources, the AAP realized that it needed a site dedicated to this purpose if it was to stay relevant to members and other readers of the journal. It was no longer sufficient for classified advertisements and announcements to merely be online. They needed to be fully searchable and enable readers to filter search results by geographic area, position description, subspecialty, and so on. In addition, those seeking employment should have a way of efficiently creating and disseminating their curriculum vitae, and these curriculum vitae should, likewise, be fully searchable by employers. Therefore, in June 2001, the AAP launched a new Web site called PedJobs, which was specifically designed to support career-oriented classified advertisements and announcements. In this point, the classified advertisements were removed from the online edition of Pediatrics, and readers interested in reading the classifieds online were directed to PedJobs. PedJobs proved to be remarkably successful and, therefore, was completely redeveloped in 2005 to provide readers with more sophisticated tools such as customized e-mail alerts. In addition, the scope of the site was expanded to encompass a number of pediatric health care professionals including nurses, nurse practitioners, and physician assistants.

In January 2004, Pediatrics launched a new feature that was to have a significant impact on both the print and online editions of the journal: Web-based manuscript submission. Although the journal’s editorial office had been tracking manuscripts for years via specialized computer software, it became possible for authors to simply go to the journal’s Web site, click on a link, and upload their manuscripts along with supporting data including figures, tables, videos, audio files, and any other electronic media. The reasons for offering this functionality were twofold: to save both time and money. Before Web-based submission, authors had to prepare multiple printed review copies of their manuscript, develop any photographic images, put electronic files on a disk, write a submission letter, and mail the whole package (at their expense) to the journal’s editorial office. With Web-based submission, authors would be able to save both time preparing manuscripts and the cost of postage (which, if the author was located outside North America, could be substantial). In addition, the journal staff spent inordinate amounts of time opening packages, reviewing materials, and then repackaging manuscripts for review, revision, and editing. Decision letters and other correspondence needed to be drafted and mailed, and all of that shipping and correspondence had to be tracked and paid for. Web-based submission would allow the journal staff to focus more time and energy on supporting the peer-review and editorial process and less time tracking mail. In addition, eliminating all of those postage costs would, we suspected, offset the cost of the new technology.

Most of our assumptions proved correct. The savings in postage costs for the journal were indeed significant enough to offset the cost of the new system. Also, as the journal staff became more familiar with the technology, we began to see some efficiencies emerge. However, any time savings gained from the technology were quickly redirected to managing a side effect of the new system for which we were largely unprepared: a rapidly increasing volume of submissions. Although we suspected, on the basis of anecdotal reports from other journals that had implemented similar technology, that the new service would result in a modest increase in submissions, we were totally unprepared for what followed. Over the next 24 months, the rate of manuscript submissions to Pediatrics rose by a staggering 65%. The editors, who initially suspected this sudden increase would be a temporary anomaly, were eventually forced to become more
selective as a result of a growing backlog of manuscripts. The journal’s acceptance rate plunged from 28% to less than 20%. Even with this reduction of the acceptance rate, the size of issues has nearly doubled over the last year. Although this is a nice problem to have, it does come with certain economic consequences: we are still printing more than half of the articles we accept, and paper and postage rates have risen considerably in recent years. In addition, readers have complained about the decreasing portability of the print issues. Although one might take a slender journal issue along on a plane ride, one thinks twice about packing an object that resembles the local telephone book. To save the journal’s bank-book and the backs of our readers (to say nothing of the planet’s forests), we are making efforts to publish more articles online only and to become even more selective in accepting articles. This last part is exceeding difficult because the field of pediatrics is quite healthy, which leads to a cornucopia of interesting research, reports, and commentary arriving from around the world via our Web site on a daily basis.

To further expedite the dissemination of scientific information, Pediatrics introduced a feature called “early release” in October 2004. The term refers to articles that are published online in advance of the issue in which they ultimately appear. For example, an article might be published in the early-release section of the journal’s Web site in January. That same article will eventually appear in the February or March issue of the print and/or online editions of Pediatrics. As we work on copyediting, typesetting, proofreading, and electronically preparing each article for publication, it is inevitable that some articles are completed before others. Why not, we asked, publish the articles that are completed early? If an article is ready to be published 3 weeks before the issue in which it is scheduled to appear, why not simply publish it in advance on our Web site? Because there was no technical reason that this could not be done and we could find no editorial argument against it, we set up an early-release section in the online journal and began publishing these articles. At first, we limited the early release of articles to twice per month, primarily to keep the schedule simple for the journalists who report on articles published in the journal. After 1 year, we adjusted the schedule to allow for weekly releases. Thus far, reporters and readers both seem to be able to keep up.

As these various features and functions were developed, they were added to the journal’s Web site and placed wherever we thought they would best fit. The Web site was designed in 1996 before anyone knew much about Web design. There was no such thing as “user-centric design” because no one had any idea how people would end up using journal sites. As it turned out, we did some things well from the outset by keeping the journal’s homepage very simple (Google would shortly prove how useful a simple, functional Web site could be). However, over the years, as new features were added, the site became increasingly cluttered and difficult to navigate. In addition, we were not sure which features were most useful or how to best display them. To remedy this deficiency of information, we spent a year researching how readers of Pediatrics interact with the journal, both in print and online. We conducted a series of focus-group sessions, sent out surveys, conducted interviews, and closely studied our usage statistics. After analyzing these data, we sat down with a designer and developed a new design, which would be closely synchronized with a new print design that was being developed simultaneously. Both designs, print and online, were launched in January 2006. The online design aimed to make navigation more intuitive, make the journal’s features more accessible, and bring the journal’s content front and center. The reception of both designs by readers has been overwhelmingly positive.

We have received a few excellent suggestions for additional improvements (such as ways of making tables more readable) and are assessing the feasibility of implementing these ideas.

January 2007 witnessed the official release of the latest, and one of the most important, milestones in the journal’s online history: the Pediatrics eJournal Archive. Readers who have happened to look under the “past issues” tab on the journal’s Web site recently, or looked closely at the date range on search results generated by the journal’s search engine, may have noticed that there is suddenly a lot more to look at—more than 100 000 pages more. Over the past 3 years, in partnership with Google and Stanford University’s HighWire Press, we have collected, organized, scanned, and digitized every issue of Pediatrics ever published, back to volume 1 issue 1. All of these issues have been converted into PDF files and separated into articles. Readers now have access to every article ever published in Pediatrics, from 1948 until the present. In addition, we have keyed in every title, author, keyword, and abstract and processed the full text of every article with sophisticated optical character-recognition software to enable search queries across the journal’s entire publication history. In the months to follow, we will be adding every nonarticle page of the journal ever published, including advertisements, classified advertising, special announcements, the journal’s masthead (which lists the editorial-board membership), and anything else published in the journal that was not, strictly speaking, considered editorial content.

Several years ago, Kent Anderson, who was at one time the managing editor of Pediatrics (and, later, director of medical journals at the AAP) before departing for the New England Journal of Medicine, argued that publishers needed to develop what he called “useful archives.” He defined a useful archive as one that is designed primarily for readers of today, providing access to both
new and older material to researchers, clinicians, and other readers from wherever they choose to work. *Pediatrics* now has such archive. We hope today’s readers find this new eJournal Archive as useful as those in generations to come.

**HIGHWIRE PRESS**

The journal and the AAP have been very fortunate in selecting technology partners, and several of them have been instrumental in the development of the online journal. Foremost among these partners has been HighWire Press. HighWire is a division of Stanford University’s library system and operates as a cross between a Silicon Valley start-up and a university think tank. Launched in 1995, HighWire hosts the Web sites of many of the most highly regarded scientific and medical journals in the world, including *Journal of Biological Chemistry*, *Science*, *New England Journal of Medicine*, *Journal of the American Medical Association* (*JAMA*), *Proceedings of the National Academy of Sciences*, the *BMJ*, *Blood*, *Journal of Clinical Oncology*, *Circulation*, *Chest*, and *Radiology*, among hundreds of others. *Pediatrics*, *Pediatrics in Review*, *NeoReviews*, *AAP Grand Rounds*, *AAP News*, *AAP Policy*, and the *Red Book* are all hosted by HighWire. HighWire is an innovation-focused not-for-profit organization, the mission of which is to support the development of scholarly communication by providing technology solutions for (primarily) not-for-profit publishers such as professional societies and university presses.

Nearly all of the technology on the journal’s Web site was developed by HighWire. In some cases, HighWire developed the technology directly for *Pediatrics*. In other cases, technology was developed initially for other publishers and then was later adapted for *Pediatrics*. In still other cases, the AAP, in consultation with other organizations and HighWire, co-developed mutually applicable innovations. There is a remarkable spirit of collegiality and cooperation among the not-for-profit organizations whose publications are hosted by HighWire and who meet twice annually to discuss ideas, share data from publishing experiments, and debate the issues that impact the rapidly changing scholarly publishing landscape. It is this spirit that makes possible large-scale innovations such as “reciprocal toll-free reference linking.” This rather inelegant term refers to the very elegant ability of a reader to be able to follow a hyperlink from the reference list of any journal article hosted by HighWire to any other cited article hosted by HighWire, without any subscription barriers. In other words, if one is reading a *Pediatrics* article, and that article cites an article published in *JAMA*, one can simply click on the hyperlink in the reference list and be taken instantly to the *JAMA* article, even if that reader does not have a subscription to *JAMA*, and vice versa. This scale of barrier-free linking between journals from different publishers is unique in the publishing world.\(^\text{11}\) As *Pediatrics* enters the second decade of partnership with HighWire Press, we aim to continue this tradition of collegiality and innovation and work to create the journal of the future while bringing the research of today to more people than ever before.

**ACCESSING THE ELECTRONIC JOURNAL**

By the opening years of the current century, nearly all of the world’s peer-reviewed scientific and medical journals had developed online editions. As the spindles of the World Wide Web extended into the far corners of the globe at a breathtaking rate, more people found themselves with access to high-quality, peer-reviewed health care information than at any point in history. With the old barriers to information eliminated (eg, the costs of printing, shipping, storage, and retrieval), the AAP explored ways to provide access for anyone interested in reading the journal, anywhere in the world, regardless of financial resources. To this end, the AAP, along with dozens of other medical organizations, partnered with the World Health Organization’s Health InterNetwork Access to Research Initiative (HINARI). Through HINARI, people at institutions in ~120 developing nations around the world can access *Pediatrics* at little or no cost.

We have also installed software on the journal’s Web site that recognizes from where in the world a reader is accessing the Internet. For those readers in the 60 poorest nations in the world, there is no need for registration with HINARI—they are simply provided full access at no cost and with no registration.\(^\text{12,13}\)

In addition, the AAP realizes that the Internet has not reached everywhere. There are still parts of the world in which Internet access is unavailable or available unreliably or at such low speeds that browsing the journal is impractical. To reach these areas, the AAP partnered with the Satellife Network. Satellite editors identify relevant articles from *Pediatrics* among other journals and e-mail text-only files to individuals known to have Internet connectivity. These individuals then print out multiple copies of these e-mails and deliver them to even more remote regions. Therefore, at least some level of relevant, timely health care information is able to reach even the most remote regions of the globe.\(^\text{12}\)

Finally, the AAP decided to maximize access to *Pediatrics* even for those fortunate enough to live in more developed economies. Since 1997, all online-only articles have been freely available the moment they are published, as are all AAP policy documents and any articles that the AAP or the editors think may have broad public or interdisciplinary appeal. All together, nearly half of every issue of *Pediatrics* is available without a subscription on the day it is published. After 12 months, 100% of each issue is made freely available online. By adopting this publication model, *Pediatrics* is able to provide the high-quality peer-reviewed information it pub-
lishes to the widest possible audience while remaining financially stable and self-sufficient.

USAGE AND CITATION

The question of whether the online edition of Pediatrics would be used was put to rest long ago. Usage, as measured in terms of article downloads, has also been growing steadily each year. Over the period of 1999–2005 (the only years for which complete usage data were available as of the writing of this article), usage climbed from 1.1 million to over 11.5 million annual article accesses (see Fig 1). Article accesses are probably the best indicator of usage for a journal site. Other indicators such as “hits” or “page views” reveal total Web-site usage, including use of the home page, tables of contents, help pages, search pages, subscription-ordering pages, etc. If the purpose of the journal Web site is to provide readers with information of interest to them, and that information comes largely in the form of articles, then measuring the number of times those articles are viewed by readers should be a journal’s primary yardstick. We want to measure how many times the reader succeeds in finding information of value to him or her. If one were measuring hits, a search that did not result in finding relevant information would be counted among one’s statistics. By measuring article accesses, we track the instances when readers actually view an article or abstract and filter out for separate analysis the times when they fail to do so.

One obvious reason that the usage is going up year after year is simply that there is more to look at each year. At the end of each year, the articles published in the preceding 12 months remain on the site. So, each year the volume of articles in the archive grows. Although the usage for any 1 article decays over time, starting with peak usage in the months immediately after publication and then steadily tapering off, it never reaches zero. This is the “long-tail” effect noted by Chris Anderson in his famous Wired Magazine article. As more and more articles are added to the archive or “tail,” overall usage rises. It will be interesting to look at the impact on usage attributable to our eJournal archive. By this time next year, we should have data that describe the effect of adding 50 years of content to the site at once.

In addition to more articles being read online, we are able to tell, from looking at the number of IP addresses from which the site was accessed, that more people are visiting the journal each year. In January 1998 we recorded traffic from 25 460 different IP addresses. In January 2006 traffic from 338 991 IP addresses, representing readers from over 130 countries, was recorded. These IP addresses are registered all over the world, from Argentina to Zimbabwe and Switzerland to Swaziland.

We are frequently asked whether online-only articles are read as frequently as those articles that appear both in print and online. That is a difficult question to answer. From 1999–2003, online-only articles were accessed more often online than those articles that also appeared in print (see Fig 2). This is not surprising, however, given that there is no other way to access these articles. Even those people who prefer to read from the printed edition of the journal must access online-only articles online, if only to print them out on their desktop printers. What is surprising is that in 2004 online accesses of print-and-online articles were approximately equal to those of online-only articles, and then in 2005 the trend reversed, with online-only articles being accessed less than print-and-online articles. One possible explanation for this trend is that more people are relying exclusively on the online edition of the journal. Readers at universities, for example, may be relying exclusively on the online subscription to the journal provided by their university and not reading from print at all. Similarly, those access-

**FIGURE 1**

Article accesses: 1999–2005. Article access is defined as an instance in which a user downloads the article abstract or the full-text HTML or PDF version of the article.
ing the journal through HINARI or any of the open-access initiatives supported by the journal are likely reading exclusively online. Also, because there are typically more print-and-online articles in each issue than online-only articles, it stands to reason that overall accesses for the category would be higher.

Although more readers may be relying exclusively on the online edition of Pediatrics, it should be noted that those who do receive the print edition of the journal still prefer to do much of their reading in print. As mentioned above, in preparation for redesigning both the print and online editions of Pediatrics, we undertook studies to better understand how readers interacted with the journal and the constellation of other professional resources they regularly consulted.15,16 Because AAP members receive both the print and online editions of the journal as a benefit of membership, we studied the ways in which AAP members used both formats. Far and away, the most cited purpose for reading Pediatrics was current awareness. Other prominent reasons cited were treatment, diagnosis, and teaching. In a series of focus-group sessions and interviews, we heard members repeatedly tell us that they prefer the print edition for keeping current, because it is more convenient and portable. It simply arrives in their mailboxes and can be read anywhere. However, even those who receive the print edition reported increased usage of the online edition for purposes such as research or preparation for teaching. Although the print edition is very convenient for reading current articles, the online edition is more useful for conducting searches or for finding older material.

In addition to online usage reports and surveys of readers, another key indicator that we track regularly are citations. Overall citations to Pediatrics have risen steadily since launching the online edition. In 1997, the first year in which the online edition was available, the journal’s impact factor jumped nearly 1 point, from 2.748 the year before to 3.466. (The impact factor is calculated by taking the total number of citations to a journal in the current year and then dividing by the number of articles published during the previous 2 years). Since then, the impact factor has continued to rise steadily, to 4.272 in 2005, the most recent year for which there are available citation data.

In addition, total citations to the journal have risen dramatically. In 1997, there were 16,800 citations to the journal. By 2005, this number nearly doubled to 31,633, which almost accounts for more citations than the next 2 most-cited journals in the field combined. More important than absolute numbers, Pediatrics has risen from third to first in the field of pediatrics as measured by impact factor, which means that the rise in impact factor has been an increase relative to other publications. It is difficult to ascribe this improvement directly to the presence of the online edition, although we do speculate that having a strong Web presence increases the likelihood of being read and, hence, cited. We also know that having a Web-based submission system embedded in one’s Web site leads to more submissions and, therefore, the ability to be more selective. Although nearly every other journal in the field now has an online edition and Web-based manuscript submission, Pediatrics may have benefited from a first-mover effect.

Periodically we have looked at the citation rates of individual articles to compare how online-only articles are cited relative to print and online articles.17 Our most recent delve into the citation data was 1 year ago. We found that citations to online-only articles continue to lag print-and-online articles by a significant margin, although they are growing at a quicker rate. In 2003–2004, the last period for which we have mature data.
(one needs to allow 1 to 2 years after an article’s publication for citations to accrue), citations to online-only articles increased by 15%, from 1.20 citations per article in 2002 to 1.41 citations per article in 2004. Citations to print-and-online articles increased by 7% during this period, from 3.63 to 3.89 citations per article. So, although there continues to be a notable gap 10 years after launch, citations to online-only articles are increasing at a faster rate of growth than print-and-online articles.

**PEDIATRICS IN CONTEXT: THE ELECTRONIC PUBLISHING LANDSCAPE**

In the decade since *Pediatrics* launched its online edition, nearly every peer-reviewed medical and scientific journal in the world has followed suit. HighWire Press recently launched the 1000th journal on its hosting platform. Large publishers such as Elsevier and the newly merged Wiley-Blackwell host even more titles on their respective platforms, and nearly every major university press now publishes their journals on the World Wide Web. As Schriger et al noted in their excellent survey of the online functionality of medical journals published in the January 2007 issue of *Pediatrics*, today “there are many Web-only journals but very few print-only journals.” This is a seismic shift from 10 years ago, when the reverse was true.

Schriger et al reported some other interesting findings that bear repeating here. *Pediatrics* continues to lead in terms of online-only publication. Among prominent medical journals, *Pediatrics* publishes the largest number of online-only articles. This will undoubtedly change at some point in the future, because there is a growing number of online-only journals (including the AAP’s *NeoReviews*). In addition, weekly journals such as *Circulation* and *New England Journal of Medicine* have doubled and tripled, respectively, their output of online-only articles over the last few years. In addition to online-only articles, Schriger et al examined online-only supplemental material that is included alongside articles that appear both in print and online (such as the *Pediatrics* video article described above). They note that, although such supplemental material is still relatively sparse, its presence increased by more than threefold during the period surveyed. In 2003 only 2% of articles had such supplemental material, but by 2005 they accompanied 7% of surveyed journal articles.

A third finding by Schriger et al that is relevant here was that rapid response (or postpublication peer review) has not been widely adopted among medical journals. Only 12% of the journals surveyed offer such a feature, and among the journals that do offer a rapid-response mechanism, reader participation has been mostly dismal. Among the 12% of journals with a rapid-response feature (including *Pediatrics*), 82% of articles received no reader responses—with a few notable exceptions. Chief among the exceptions is the *BMJ*, which boasts an average of 6 responses per article on the 80% of their articles that receive postings. As Schriger et al do not offer a compelling explanation for this extraordinary reader-response rate (nor have I been able to locate one elsewhere), a case study of the *BMJ*’s rapid-response feature might yield information relevant to other journals.

The most interesting finding reported by Schriger et al was a negative one. They reported that there is “little evidence of journals using the Web to provide readers an interactive experience with the data or with each other.” This finding can be easily confirmed by a tour of journal Web sites. The only interactive feature that one is able to find (and that only in a minority of titles, as discussed above) is rapid response, which, with a few exceptions, has not been embraced enthusiastically by readers. Nowhere are there other functions that allow readers to interact with either published data or each other. Although other spheres of human endeavor have developed robust interactive Web sites that have revolutionized such activities as dating, news reporting, selling that old box of memorabilia found in the attic, and sharing vacation pictures, journal sites have been very slow to develop and integrate interactive forms of communication. On the one hand, this is puzzling given that medicine is such a collaborative discipline and physicians have been quick to adopt new diagnostic and therapeutic technologies. On the other hand, perhaps it is precisely because the practice of medicine is so collaborative that physicians have not seen the need for additional communication channels. However, it is only a matter of time before a generation that was reared on interactive, multimedia Web sites will graduate from medical school and expect this sort of functionality as a matter of course. If scientific and medical journals do not adapt to these expectations, they will quickly find themselves in the position of scrip toriums after the introduction of Gutenberg’s printing press.

**CONCLUSIONS**

Ten years ago, *Pediatrics* launched an online edition as a modest experiment. It is clear now that it is no longer an experiment but, rather, a transition to a new paradigm of professional communication on par with—or perhaps even greater than—the transition from scrip toriums to the printing press that took place 550 years ago. It is interesting that printed materials before the year 1501 are referred to as “incunabulum” (singular) or “incunabula” (plural), which is a borrowing from Latin and means “swaddling clothes.” It connotes the idea that printed matter was, during this time, in its infancy or early period. Taking a long view, we have only begun the transition to online journals and are clearly in our incunabula period. Over the last 10 years we have essentially replicated the printed journal in the electronic format. And although a number of online-only features...
have been introduced, we have only begun to truly reinvent the journal in a form native to the digital medium. Features such as video supplements have added something to the article that cannot be replicated in print, and postpublication peer review has created an infrastructure for rapid interactivity that would not be possible off-line. However, with these exceptions, the online journal is still largely a simulacrum of the print edition.

There are some good reasons for this. The print edition of the journal is very successful and continues to be heavily used: 92% of AAP members have indicated they still wish to receive the print edition. For those members and other subscribers who continue to receive the print edition, the large majority of reading still takes place in print. This is not unique to Pediatrics. Most medical journals have continued to maintain print editions despite having developed Web sites. Print is still easier to read and causes less eye strain than all but the best and brightest monitors. It is more portable in some ways than the electronic edition. One can read the electronic edition from any computer, but the print edition can be read easily on a plane, on the couch, or at the breakfast table. Laptops are still somewhat cumbersome, and one must still worry about spilling coffee or other breakfast table detritus on them. The print edition is automatic: it simply shows up in one’s mailbox. One does not have to go online, log-in, perform a search, download an article, or even press a “print” button. One simply opens the journal and starts reading. In addition, one can write on a print copy or highlight notable passages. The print edition will likely continue to be more convenient for many readers until a new device is invented that replicates these attributes in electronic form—a digital paper that can be written on, easily shoved in one’s briefcase, automatically download one’s reading materials, and is resistant to coffee and other professional hazards.

While we wait for such a device to be developed by the technical wizards of our day, there is still a great deal that can be done to improve and expand electronic journals using current technologies. Functionality can be developed to allow readers to better interact with data. Data sets could be placed online with tools that facilitate data modeling and analysis. The use of audio and video can be greatly expanded. Above all, means of enabling and encouraging more reader-to-reader communication can be expanded. The online medium opens the possibility for journals to become far more interactive and to engage professionals to a degree that simply was not possible in print. Given this potential, the next 10 years are shaping up to be just as interesting as the last 10. Pediatrics has every intention of continuing to evolve, experiment, and lead this electronic transition, ensuring that the journal is as relevant to the readers of tomorrow as it is to those of today.

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REFERENCES
Inflammatory Markers and Mediators in Tracheal Fluid of Premature Infants Treated With Inhaled Nitric Oxide

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ABSTRACT

OBJECTIVE. We compared serial measurements of inflammatory mediators and markers in infants treated with inhaled nitric oxide or placebo to assess the effects of inhaled nitric oxide therapy on lung inflammation during bronchopulmonary dysplasia. We investigated relationships between respiratory severity scores and airway concentrations of inflammatory markers/mediators.

METHODS. As part of the Nitric Oxide (to Prevent) Chronic Lung Disease trial, a subset of 99 infants (52 placebo-treated infants and 47 inhaled nitric oxide-treated infants; well matched at baseline) had tracheal aspirate fluid collected at baseline, at 2 to 4 days, and then weekly while still intubated during study gas treatment (minimum of 24 days). Fluid was assessed for interleukin-1β, interleukin-8, transforming growth factor-β, N-acetylglucosaminidase, 8-epi-prostaglandin F2α, and hyaluronan. Results were normalized to total protein and secretory component of immunoglobulin A.

RESULTS. At baseline, there was substantial variability of each measured substance and no correlation between tracheal aspirate fluid levels of any substance and respiratory severity scores. Inhaled nitric oxide administration did not result in any time-matched significant change for any of the analytes, compared with the placebo-treated group. There was no correlation between any of the measured markers/mediators and respiratory severity scores throughout the 24 days of study gas administration. In the posthoc analysis of data for inhaled nitric oxide-treated infants, there was a difference at baseline in 8-epi-prostaglandin F2α levels for infants who did (n = 21) and did not (n = 26) develop bronchopulmonary dysplasia at postmenstrual age of 36 weeks.

CONCLUSIONS. Inhaled nitric oxide, as administered in this study, seemed to be safe. Its use was not associated with any increase in airway inflammatory substances.
Of the >4 million births in the United States each year, premature births account for 12.3%; very low birth weight infants account for 1.4%. Although the survival rate for these premature newborns has improved, morbidity and long-term complications persist. Approximately 10,000 to 15,000 of these infants develop bronchopulmonary dysplasia (BPD) of prematurity each year in the United States, with mortality rates varying from 5% to 30%. Therapy to prevent or to ameliorate BPD should reduce the duration of positive pressure ventilation and elevated fraction of inspired oxygen (FiO₂) and reduce overall pulmonary morbidity.

One recently completed, randomized, blinded, multicenter, placebo-controlled trial of inhaled nitric oxide (iNO), the Nitric Oxide (to Prevent) Chronic Lung Disease (NO-CLD) trial, tested whether iNO administered between 7 and 21 days of age to infants with birth weights of 500 to 1250 g would be efficacious and safe for prevention or amelioration of BPD. The results demonstrated significant reductions in total BPD and in the more severe variants of BPD, as assessed at postmenstrual ages of 36, 40, and 44 weeks. There was no increase in the incidence of the common morbidities of prematurity in the infants treated with iNO, compared with those treated with placebo.

A second goal of the NO-CLD clinical trial was to determine the safety of iNO, as used in the trial. The impact of iNO administered for a clinically meaningful time into already inflamed, immurely developed lungs is uncertain. Persistence of elevated tracheal aspirate fluid (TAF) concentrations of the innate proinflammatory substances interleukin-1β (IL-1β) and interleukin-8 (IL-8) at 1 week of age has been associated with increased risk of BPD. The concentration of the extracellular matrix component and cell migration-promoting substance hyaluronan has been shown to be altered by respiratory distress syndrome of prematurity and by inflammation-associated lung injury. How iNO administration affects the presence of these substances has not been evaluated.

NO can have both proinflammatory and antiinflammatory effects. In the presence of elevated FiO₂, NO is converted to NO₂, peroxynitrite, and other oxides of nitrogen, which may initiate or exacerbate pulmonary inflammation. iNO may also modulate the pulmonary inflammatory response by downregulating the production of inflammatory cytokines and by decreasing lung neutrophil accumulation. Hyperoxia and elevated NO levels have been shown to induce cell death in in vitro lung fibroblast cultures. Because iNO is coadministered with high FiO₂ into an environment with preexisting inflammation when given to infants at risk for BPD, it is important to evaluate the specific effects of the dose and duration of treatment used in the NO-CLD study on lung inflammation.

Another form of lung injury results from cell membrane oxidation by reactive oxygen species. A marker of membrane oxidative injury, 8-epi-prostaglandin F₂α (8-epi-PGF₂α), mediates neonatal pulmonary hypertension in animal models and is associated with pulmonary hypertension in human newborns. The effects of iNO on 8-epi-PGF₂α production or presence in the airway are unknown. Assessing changes in 8-epi-PGF₂α if any, with iNO administration could provide insight into the mechanism of action of iNO in this clinical setting.

The potent cytokine transforming growth factor-β (TGF-β), which is derived from alveolar macrophages, regulates fibroblast activity, reduces surfactant production, and has been found to be increased in TAF of infants developing BPD. Active TGF-β also has been implicated in the development of pulmonary fibrosis in adults. Fibrosis and airway simplification are pathologic hallmarks of fully established BPD. Therefore, the effects of iNO administration on active TGF-β could offer insights into its mechanisms of action. Our objectives in this study were (1) to determine the relationship between inflammatory markers/mediators and disease severity in premature infants at 7 to 21 days; (2) to investigate the effect of iNO on the inflammatory profile, to assess both safety and the potential mechanisms of NO in lung disease; and, (3) for the subset of infants who received iNO and from whom serial TAF samples were obtained, to identify whether the response to iNO was predictable from baseline TAF data.

METHODS

Summary of Parent Clinical Trial

The results reported in the present study were obtained from a subset of infants enrolled in the placebo-controlled NO-CLD trial. The study enrolled infants with birth weights of 500 to 1250 g who were between 7 and 21 days of age and required ventilatory support. Treated infants received decreasing concentrations of iNO, beginning at 7 to 21 days of age and 20 ppm, for a minimal duration of 24 days. The respiratory severity score was used as an index of respiratory support. The respiratory severity score is calculated as mean airway pressure × FiO₂.

Infants who received iNO (n = 294) demonstrated a 43.9% rate of survival without BPD at postmenstrual age of 36 weeks, compared with 36.8% for the 288 infants in the placebo group (P = .042). There was no difference in mortality rates. Benefit was sustained at 40 and 44 weeks. There was no increase in the incidence of any of the common complications of prematurity, including intracranial injury, for the iNO-treated infants.

The TAF samples from which the current results were derived were collected from 99 of the 582 infants enrolled. Serial samples were collected routinely from infants enrolled in the study at the Children’s Hospital of Philadelphia, at the Hospital of the University of Penn-
sylvania, at Westchester Medical Center (Valhalla, NY), and at Children’s Mercy Hospitals and Clinics (Kansas City, MO). Of the 99 infants for whom serial TAF samples were obtained, 52 infants had been assigned randomly to placebo gas treatment and 47 to iNO treatment. Informed parental permission was obtained specifically for the collection of samples, in addition to permission for enrollment in the study. No parent who gave permission for the primary study declined permission for the TAF sampling.

**TAF Collection and Processing**

TAF was collected as described previously by our group,\(^{19,20}\) by using saline lavage, at baseline, at 24 to 48 hours, at 4 days, and then weekly during study gas treatment (minimum of 24 days). Aspirated samples were placed in sterile tubes and centrifuged at 500 × g for 10 minutes, and the supernatant was frozen immediately at −70°C. Aliquots of the supernatant and the cell pellet were shipped frozen, with overnight express delivery, to Philadelphia. The aliquots were thawed and centrifuged at 27 000 × g for isolation of the surfactant fraction. Results of the surfactant function studies are being reported separately.\(^{21}\) Assays for TGF-β, hyaluronan, N-acetylglucosaminidase (NAG), and total protein were performed in Philadelphia; assays for IL-1β, IL-8, 8-epi-PGF\(_{2α}\), and the secretory component of Immunoglobulin A (IgA) were performed in Kansas City. To account for dilution of epithelial lining fluid during collection, results were normalized to total protein and secretory component of IgA levels, both measured in the same sample (Fig 1).

**Assays for IL-1β and IL-8**

IL-1β and IL-8 (acute proinflammatory cytokines) were assayed by using commercial enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN). These assays use a quantitative sandwich ELISA technique, with assay sensitivities of <1 pg/mL and <3.5 pg/mL, respectively and intraassay coefficients of variation of 2.4% and 4.6%, respectively.

**Assay for TGF-β**

Active TGF-β content was assayed by using the mink lung epithelial cell (MLEC) line, according to the protocol described by Abe et al.\(^{22}\) The MLEC line is a TGF-β-responsive cell line that is stably transfected with the human plasminogen activator inhibitor promoter (a TGF-β-responsive gene) fused to a luciferase reporter gene. MLECs were plated in a 96-well plate at 1.8 × 10\(^4\) cells per well, allowed to attach for 3 hours, and then cultured overnight with 30 μL of TAF supernatant or 40 to 1200 pg/mL TGF-β standard. MLEC extracts were lysed the next day and assayed for luciferase activity by using the luciferase assay system (Promega, Madison, WI). Recombinant human TGF-β was purchased from Sigma (St Louis, MO).

**Assay for NAG**

TAF supernatant and cell pellets were assayed for NAG activity as an index of macrophage content. The NAG assay measures the spectrophotometric release of p-nitrophenol from a conjugated NAG substrate and is based on the method described by Nitta et al.\(^{23}\) In a 96-well plate, 20 μL of TAF supernatant or cell pellet (diluted 1:10) or 25 to 400 μU of β-nitro-acyetylglucosaminidase standard (Sigma) was incubated with 10 μL of Triton X-100 and 20 μL of substrate (15 mmol/L p-nitrophenyl-N-acetyl-β-glucosaminidase; Sigma) for 30 minutes at 37°C, to allow for product formation. The reaction was stopped with the addition of 200 μL of 0.2 mol/L Na\(_2\)CO\(_3\) to each well. The change in absorbance at 450 nm of each well was measured, and NAG activity in the samples was calculated from the standard curve.

**Assay for 8-Epi-PGF\(_{2α}\)**

The non-cyclooxygenase-derived prostaglandin 8-epi-PGF\(_{2α}\), a biomarker of lipid oxidative injury, was assayed by using a commercial ELISA kit (Assay Designs, Ann Arbor, MI). The direct competitive ELISA technique measures both free and esterified isoprostane after alkaline hydrolysis of phospholipid-coupled 8-epi-PGF\(_{2α}\). The assay sensitivity is <40 pg/mL, and the intraassay coefficient of variation is 11.3%.

**Assay for Hyaluronan**

Hyaluronan was measured by using a competitive ELISA-like method, as published previously by Lokeshwar et al.\(^{24}\) and by Maeda et al.\(^{25}\) Hyaluronic acid (ICN Biochemicals, Aurora, OH) at 0.2 mg/mL was coated on microtiter plates for binding to a biotinylated hyaluronic acid-binding peptide (bHABP) (Seikagaku, Tokyo, Japan). Samples and standards were digested with protease overnight at 37°C, to remove any potential interfering proteins. The next day, samples were diluted...
either 1:2 or 1:4 in phosphate-buffered saline, and 60 μL of sample or standard was incubated with 60 μL of bHABP for 1 hour at 37°C. Serial dilutions of hyaluronic acid standards (Healon; Pharmacia and Upjohn, Kalama-zoo, MI), ranging from 0 to 3000 ng/mL, were included; 100 μL of samples or standards were transferred to hyaluronic acid-coated plates and allowed to react for 1 hour at 37°C. Binding to bHABP was detected with the addition of streptavidin-biotin complex (Vectastain; Vector Laboratories, Burlingame, CA), followed by the ad-dition of α-phenylenediamine (Sigma) for colorimetric analysis. The absorbance of each well was scanned at 405 nm, and hyaluronic acid content was normalized to TAF protein content and expressed as nanograms of hyaluronic acid per milligram of protein.

Total Cell Number Determination
For determination of total cell number in TAF cell pel-
ets, the CyQuant cell proliferation assay kit (Invitrogen, Carlsbad, CA) was used to assay DNA content, according to manufacturer’s instructions. In a 96-well plate, cells were lysed with a 1× CyQuant-GR cell lysis buffer and incubated for 5 minutes with a proprietary fluorescent dye that binds to nucleic acids. DNA standards ranged from 0 to 1000 ng/mL. The fluorescence of each well was measured by using a microplate reader with an excitation wavelength of 485 nm and an emission wave-length of 535 nm. Conversion of DNA to cell number used a value of 6.5 pg of DNA per human diploid cell. The total cell count was obtained for each sample, to investigate the possibility of iNO-associated increase or decrease in airway inflammatory cell content.

Normalization of Analytes
Assays were normalized with 2 methods, to account for the inevitable variations in dilution during the collection process. Concentrations of the soluble secretory compo-nent of IgA and of total protein measured in the same sample served to normalize each TAF sample. The soluble secretory component of IgA was measured by using an established 96-well ELISA technique.26 Polyclonal rabbit antihuman secretory component served as a pri-mary antibody, with horseradish peroxidase-conjugated rabbit antihuman immunoglobulin (Dako, Glostrup, Denmark) as a secondary antibody. Quantification was performed against a standard curve from 2.34 ng/mL to 300 ng/mL, with purified human colostrum. Total pro-tein levels in the TAF supernatant were determined by using the bicinchoninic acid reagent (BioRad, Hercules, CA).

Statistical Analyses
On the basis of TAF measurements in a phase 2 study,20 we anticipated a wide range of values at baseline. A prospective power analysis indicated that a change in the mean equal to the SD (standardized event ratio of 1.0), tested at an α of .05 (2-tailed) and a β of 90%, would require 21 patients per group. A standardized effect size of 0.5 with the same assumptions would require a sam-ple size of 63 patients per group. Given the anticipated rate of patient accrual at the 3 study sites committed to collecting TAF samples, we sought to enroll a minimum of 50 to 60 patients for each arm of the main trial for the TAF analysis.

For nonparametric data comparison (eg, the normal-ized TAF concentrations at each time point for each substance of interest), the Mann-Whitney test was used. Data are expressed as box plots demonstrating the me-dian, 25th and 75th percentiles as the limits of the box, and 5th and 95th percentiles as the error bars. For con-tinuous and normally distributed data (eg, severity score, birth weight, and gestational age), the unequal t test was used, with correction for multiple comparisons. Categorical data (eg, gender and outcome) were evalu-atated with the χ² test or Fisher’s exact test. For the posthoc hypothesis-generating analysis, we did not ad-just for multiple comparisons.

RESULTS
The 99 infants had a total of 519 TAF samples collected and analyzed. Each analyte was assayed in duplicate in each sample, and the results were averaged.

The 47 iNO-treated infants and the 52 placebo-treated infants were well matched according to birth weight, gestational age, and postnatal age at the time of study entry (Table 1). In parallel with the overall study, there was a trend toward greater rates of survival without BPD for the iNO-treated infants (Table 1). The 99 patients were also representative of the infants in the 2 treatment arms of the parent study (Table 2). Of the 99 infants in the subset, 31 were treated in Philadelphia, 13 at Westchester Medical Center, and 55 at Children’s Mercy Hospital. There were 4 deaths among the 99 infants, 2 in each randomized group. Because infants were extubated typically to continuous positive airway pressure as the trial progressed, the number of samples obtained diminished at the later data collection times.

There were 64 infants (33 placebo-treated infants and 31 iNO-treated infants) who were still intubated and had sample collections at days 9 to 12; the total number at the day 23 to 26 collection time was 28 (17 placebo-treated infants and 11 iNO-treated infants).

At study entry, before treatment, there was substan-tial variability in each of the substances assessed (Figs 2–8). In no case was there a significant difference be-tween the infants subsequently treated with iNO and those treated with placebo. There was no correlation between any of the substances measured and the respi-ratory severity score at baseline (data not shown).

iNO administration resulted in no significant changes, compared with the placebo-treated group, over the pe-riod of time assessed for any of the markers (Figs 2–8).
Data are shown as normalized to total protein. The same statistical results were obtained if the results were normalized to soluble secretory component of IgA (data not shown). In addition, there were no differences in the concentrations of markers, or in the total cell counts, when they were assessed separately for infants entered early (7–14 days) or later (15–21 days) (data not shown). Posthoc analysis showed that clinical benefit was limited to early-entry infants.4 There were no correlations between any of the substances measured and

### TABLE 1: Baseline Data for the Subset of Infants With Serial TAF Collection

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 52)</th>
<th>iNO (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, mean ± SD (median), g</td>
<td>732 ± 148 (706)</td>
<td>758 ± 165 (733)</td>
</tr>
<tr>
<td>Gestational age, mean ± SD (median), wk</td>
<td>25.7 ± 1.6 (25.3)</td>
<td>25.5 ± 1.4 (25.0)</td>
</tr>
<tr>
<td>Age at lavage, mean ± SD (median), d</td>
<td>15.7 ± 4.5 (16.0)</td>
<td>15.5 ± 4.5 (15.0)</td>
</tr>
<tr>
<td>Respiratory severity score, mean ± SD (median)</td>
<td>4.1 ± 2.3 (3.4)</td>
<td>4.1 ± 2.6 (3.3)</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (non-Hispanic)</td>
<td>40.4</td>
<td>44.7</td>
</tr>
<tr>
<td>Black</td>
<td>40.4</td>
<td>48.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Asian</td>
<td>3.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Gender, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59.6</td>
<td>53.3</td>
</tr>
<tr>
<td>Female</td>
<td>40.4</td>
<td></td>
</tr>
<tr>
<td>Alive without BPD at PMA of 36 wk, n (%)</td>
<td>16 (30.8)</td>
<td>21 (44.7)</td>
</tr>
</tbody>
</table>

PMA indicates postmenstrual age.

### TABLE 2: Parent Study Baseline and Outcome Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 288)</th>
<th>iNO (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, mean ± SD, g</td>
<td>759 ± 155</td>
<td>766 ± 161</td>
</tr>
<tr>
<td>Gestational age, mean ± SD, wk</td>
<td>26 ± 1.5</td>
<td>26 ± 1.5</td>
</tr>
<tr>
<td>Age at lavage, median (interquartile range), d</td>
<td>16 (13–19)</td>
<td>16 (12–19)</td>
</tr>
<tr>
<td>Respiratory severity score, median</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Alive without BPD at 36 wk, %</td>
<td>36.9</td>
<td>43.9a</td>
</tr>
<tr>
<td>Death by 36 wk, n (%)</td>
<td>18 (6.2)</td>
<td>16 (5.4)</td>
</tr>
</tbody>
</table>

a P = .042.

### FIGURE 2
IL-1β levels versus time on the study gas for the 2 groups. No significant differences were noted. Data are presented in a whisker plot; the horizontal line within each box represents the median, the upper and lower limits of the box are 75th and 25th percentiles, respectively, and the error bars represent the 5th and 95th percentiles. The plus signs represent the means. The numbers of infants from whom samples were collected were as follows: baseline: placebo, 45; iNO, 47; day 9 to 12: placebo, 33; iNO, 31; day 23 to 26: placebo, 17; iNO, 11.

### FIGURE 3
IL-8 levels versus time on the study gas for the 2 groups. Data are expressed as described for Fig 2.

### FIGURE 4
Active TGF-β levels versus time on the study gas for the 2 groups. Data are expressed as described for Fig 2.
respiratory severity scores measured throughout the first 3 weeks after initiation of the study gas.

One posthoc analysis limited to the 47 infants treated with iNO was performed. Of those 47 infants, 21 (44.7%) had a favorable outcome (survival without BPD at 36 weeks) and 26 demonstrated either BPD or death ($n = 2$) at $\geq36$ weeks. Infants treated with iNO, when divided according to this primary outcome at postmenstrual age of 36 weeks, did not differ in any important demographic characteristic (Table 3). At baseline, the iNO-treated infants who had improved outcomes had higher normalized 8-epi-PGF$_{2\alpha}$ levels in TAF than did the infants with unfavorable outcomes ($P = .017$) (Table 4). At day 4 of treatment, this difference no longer existed (data not shown).

**DISCUSSION**

**Overall Results**

The current results were obtained from a representative subset of patients enrolled in a multicenter, double-blind, randomized trial of iNO (the NO-CLD study) designed to reduce the incidence or severity of BPD. iNO administration was associated with fewer infants devel-

### TABLE 3 Data for 47 Patients Treated With iNO

<table>
<thead>
<tr>
<th>No BPD</th>
<th>BPD/Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Body weight, mean ± SD, g</td>
<td>773 ± 168</td>
</tr>
<tr>
<td>Gestational age, mean ± SD, wk</td>
<td>25.3 ± 1</td>
</tr>
<tr>
<td>Age at enrollment, mean ± SD, d</td>
<td>15.4 ± 4.9</td>
</tr>
<tr>
<td>Respiratory severity score at enrollment, mean ± SD</td>
<td>3.15 ± 1.96</td>
</tr>
<tr>
<td>Ethnicity, n</td>
<td></td>
</tr>
<tr>
<td>White (non-Hispanic)</td>
<td>9</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td>Gender, n</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
</tbody>
</table>

There were no statistically significant differences between the 2 groups of iNO-treated infants.
Injury, 8-epi-PGF2 during lung injury, and one marker of lung oxidative stress, hyaluronan, an extracellular matrix component that is altered in levels of NAG, a marker for macrophages in airways. We also measured hyaluronan levels also is consistent with the finding of no increase in NAG levels and no change in proinflammatory cytokine levels.

Hyaluronan
Hyaluronan, a component of the extracellular matrix, helps stimulate inflammation and fibrosis after lung injury and has been associated with increased lung water content in adult animals. The hydrodynamic properties of hyaluronan support pulmonary cell migration; increased hyaluronan likely promotes pulmonary macrophage aggregation. We found no change in TAF hyaluronan levels with iNO treatment. The lack of change in hyaluronan levels also is consistent with the finding of no increase in NAG levels and no change in proinflammatory cytokine levels.

TGF-β
TGF-β is a fibrogenic cytokine thought to play a crucial role in lung parenchymal remodeling, particularly that which results in enlarged air spaces. It has been associated with prolonged oxygen therapy after BPD. In the present study, active TGF-β was identified in the TAF but there was no significant change with iNO administration.

8-Epi-PGF2α
The 8-isoprostanes (such as 8-epi-PGF2α), a family of non-cyclooxygenase-derived prostaglandins, are generated through direct oxidation of membrane phospholipids. These substances serve as markers for pulmonary oxidative injury and may themselves contribute to pulmonary hypertension. No difference in TAF levels for control and treated patients was found at baseline or at any treatment time.

Reproducibility of Assays
Each of the assays was performed in duplicate or triplicate, and the results were averaged. In addition, we sought to make sure that the shipment of samples and controls were processed by the same laboratory technician. This was done to improve the reproducibility of the data.

Proinflammatory Cytokines
In the lung, IL-8 is generated both from alveolar macrophages and from epithelial cells, fibroblasts, microvascular epithelium, and apparently smooth muscle cells. Both IL-1β and IL-8 participate in the recruitment of inflammatory leukocytes to the pulmonary interstitium and air space. One previous report demonstrated the abundant expression of IL-8 mRNA in infants who progressed to develop BPD. The lack of change in IL-1β, IL-8, and TGF-β levels in both groups during study gas administration is consistent with no significant change in levels of NAG, a marker for macrophages in airways. There was no correlation between NAG levels and total cell counts in the placebo-treated and iNO-treated groups.

Table 4: Baseline Values for Infants Treated With iNO

<table>
<thead>
<tr>
<th></th>
<th>No BPD (n = 21)</th>
<th>BPD at 36 wk (n = 26)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β, ng/mg protein</td>
<td>611 (117–758)</td>
<td>461 (54–585)</td>
<td>.4</td>
</tr>
<tr>
<td>IL-8, ng/mg protein</td>
<td>6733 (7275–9932)</td>
<td>8070 (3800–16 185)</td>
<td>.5</td>
</tr>
<tr>
<td>TGF-β, ng/mg protein</td>
<td>2075 (1090–5735)</td>
<td>1364 (820–4195)</td>
<td>.4</td>
</tr>
<tr>
<td>Hyaluronan, ng/mg protein</td>
<td>27 157 (16 359–46 276)</td>
<td>17 724 (6876–32 311)</td>
<td>.1</td>
</tr>
<tr>
<td>NAG, U/mg protein</td>
<td>32 (21–50)</td>
<td>34 (19–49)</td>
<td>.9</td>
</tr>
<tr>
<td>8-epi-PGF2α, ng/mg protein</td>
<td>2071 (434–23 140)</td>
<td>407 (195–2252)</td>
<td>.017</td>
</tr>
</tbody>
</table>

* Mann-Whitney test.

To our knowledge, these results are derived from the largest number of preterm patients at high risk for developing BPD reported to date. Most previously published studies reported serial results, without separate control and intervention groups. An important characteristic of our data set is that collection started at a minimum of 7 days of age and a median of 15 to 16 days and continued in many cases through the next 3 weeks. The results included no samples obtained at birth but only those collected after a minimum of 7 days, presumably after the mechanisms for developing BPD were already activated. In addition, given the inherent limitations of assaying substances in epithelial lining fluid, we normalized the results both according to total protein and according to the soluble secretory component of IgA. It is unclear which denominator is preferable for this population, because infants developing BPD have characteristics of our data set is that collection started at a minimum of 7 days of age and a median of 15 to 16 days and continued in many cases through the next 3 weeks. The results included no samples obtained at birth but only those collected after a minimum of 7 days, presumably after the mechanisms for developing BPD were already activated. In addition, given the inherent limitations of assaying substances in epithelial lining fluid, we normalized the results both according to total protein and according to the soluble secretory component of IgA. It is unclear which denominator is preferable for this population, because infants developing BPD have...
the necessary second thaw/refreeze cycles did not alter measurements. We limited the number of thaw/refreeze cycles to 1 for 8-epi-PGF\textsubscript{2\alpha}, which is known to be sensitive to this process. All aliquots for measurement of the analytes were treated identically, so that any effects would be shared equally between samples from iNO-treated and placebo-treated infants. In a separate evaluation of 3 thaw/refreeze cycles for IL-1β, we found no effect on the results of the assay (data not shown).

Limitations of the Study
TAF data may not represent in a predictable manner concentrations of inflammatory cells or their products in the pulmonary interstitial or vascular spaces. However, they do correlate with epithelial lining fluid measurements,\textsuperscript{12,13} and the use of either total protein or soluble secretory component of IgA provides a reasonable way of normalizing the data.\textsuperscript{24} No evidence of exacerbation of inflammation or oxidative injury was found with iNO administration.

Receptors for IL-1β and IL-8 were not assayed, and the antiinflammatory cytokine IL-10 was not measured. Others have used IL-1/IL-10 and IL-8/IL-10 ratios as a way of expressing lung inflammatory status.\textsuperscript{15} Other vasoactive mediators that might have been affected by iNO (for example, endothelin-1) were not included in the panel of substances measured.\textsuperscript{36} Given the limited amount of TAF obtained at each time point, we were unable to perform all biologically plausible assays.

Infants needed to remain intubated for serial TAF collections to occur. As infants improved, many were treated with nasal continuous positive pressure ventilation systems and eventually with supplemental oxygen delivery through nasal cannulae. Our results were limited in that only the more severely affected infants, who needed prolonged support with endotracheal tube-delivered positive pressure ventilation, were available for serial sampling. However, the numbers of dropouts were similar for the 2 groups during the sampling times reported here. There was no evident trend, even in the full data set for infants who had baseline, day 4, and then serial weekly collections.

Posthoc Analysis
In the parent study, the number needed to treat to produce 1 less infant with BPD was 14 for the overall study and 5 for the early enrollment group.\textsuperscript{4} Because of the cost and complexity of iNO administration for many days, it is crucial to identify clinical or laboratory markers predicting benefit with iNO treatment.

In the posthoc analysis, we sought to identify from within the panel of markers used for this study whether ≥1 of the substances measured at baseline (mean of 16 days of age) would predict a favorable response to iNO. Baseline TAF 8-epi-PGF\textsubscript{2\alpha} levels were higher for the iNO-treated infants who responded favorably to iNO.

One speculation from this hypothesis-generating activity is that NO may produce a more favorable response if introduced into a pulmonary environment that includes factors contributing to elevated pulmonary vascular resistance. However, no decrease in severity score was noted for the 21 infants between baseline and 4 days of treatment. A decrease in severity score might have been expected if a decrease in pulmonary vascular resistance, with concomitant improvement in ventilation perfusion matching and improved arterial oxygen tension and saturation, had occurred. Alternatively, the elevated 8-epi-PGF\textsubscript{2\alpha} levels at baseline might indicate an environment of increased oxidative injury, a specific situation in which iNO would be beneficial.

CONCLUSIONS
Our findings of no identifiable significant change in the panel of proinflammatory or lung injury markers and mediators used for this study suggest that the administration of iNO in the dose and duration used here was safe. No iNO-associated evidence of an increase in lung inflammation or injury was identified. This suggests that, if the iNO-associated clinical improvements result from changes in the proinflammatory milieu of the lung, then the mechanism must be an indirect one. In the subpopulation of infants who received iNO, only 8-epi-PGF\textsubscript{2\alpha} was identified as possibly associated with infants who progressed to BPD, compared with those who did not. Additional work differentiating the iNO-treated favorable- and unfavorable-outcome groups is underway.

ACKNOWLEDGMENTS
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We thank the NO-CLD investigators, nurses, residents, fellows, staff physicians, and respiratory therapists who made this work possible. We thank Cheri Castor in Kansas City and Theresa McDevitt in Philadelphia for overseeing the processing of the samples. We thank Mary S. Bailey for help with manuscript preparation and Christopher Norberg, MS, and Steve Simon, PhD, for help with data management. We thank INO Therapeutics for supplying study gas and equipment for the parent trial.

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Do All Infants With Apparent Life-Threatening Events Need to Be Admitted?

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. The goal was to identify criteria that would allow low-risk infants presenting with an apparent life-threatening event to be discharged safely from the emergency department.

METHODS. We completed data forms prospectively on all previously healthy patients <12 months of age presenting to the emergency department of an urban tertiary care children’s hospital with an apparent life-threatening event over a 3-year period. These patients were then observed for subsequent events, significant interventions, or final diagnoses that would have mandated their admission (eg, sepsis).

RESULTS. In our population of 59 infants, all 8 children who met the aforementioned outcome measures, thus requiring admission, either had experienced multiple apparent life-threatening events before presentation or were in their first month of life. In our study group, the high-risk criteria of age of <1 year and multiple apparent life-threatening events yielded a negative predictive value of 100% to identify the need for hospital admission.

CONCLUSIONS. Our study suggests that >30-day-old infants who have experienced a single apparent life-threatening event may be discharged safely from the hospital, which would decrease admissions by 38%.
A n apparent life-threatening event (ALTE) is defined as “an episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid, but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging.” It is unclear, however, whether an ALTE is a predictor of subsequent death, sudden infant death syndrome (SIDS), or some other serious disorder in infants. Therefore, the question of whether infants presenting with an ALTE require hospital admission for a thorough diagnostic evaluation remains controversial. Hoffman et al suggested that infant apnea was a risk factor for SIDS. Steinschneider, Kelly et al, and Burchfield and Rawlings thought that infants who presented with ALTEs were at high risk for subsequent ALTEs and/or death resulting from SIDS. Others suggested that ALTEs may indicate underlying sepsis, pertussis, physical abuse, arrhythmias, metabolic diseases, seizures, or even cardiac tamponade. The SIDS rate for infants with ALTEs who required cardiopulmonary resuscitation was found to be 10% in one study, and it increased to 28% with multiple ALTEs. On the basis of these studies, it became common practice to view infants presenting with an ALTE as being at high risk, to admit them to the hospital for a diagnostic evaluation, and to consider discharge with home apnea/bradycardia monitoring.

In contrast, Hodgman et al found that infants with ALTEs were not at increased risk for subsequent ALTEs. Southall et al studied 2-channel cardiorespiratory recordings for infants who died as a result of SIDS, and they found that SIDS could not be predicted on the basis of the presence of apnea or “abnormal” cardiorespiratory events. More recently, the Collaborative Home Infant Monitoring Evaluation Study found that infants with ALTEs had no more episodes of apnea than did control subjects and that serious cardiorespiratory events did not occur during the peak incidence of SIDS at 2 to 4 months of age. These studies cast doubt on the idea that ALTEs are precursors to SIDS or other serious disorders in infants. These conflicting results highlight the question of how infants with ALTEs should be treated when they present to the emergency department (ED).

Many well-written review articles on the topic of ALTEs exist, and consideration of inpatient admission is recommended strongly by some authors. However, no prospective study has established that ALTEs recur more frequently in the days immediately after an ALTE or that these infants require hospital admission. Few practitioners would question the need for admission of an infant who looks unwell or for whom a diagnosis requiring admission is made in the ED. However, when a child demonstrates normal physical examination results after a suspected ALTE at home, there is a paucity of literature data to support the psychosocial and economic burden of a hospital admission. Therefore, we attempted to determine criteria that would allow risk stratification in the ED of patients with ALTEs, into a high-risk group of patients who required admission and a low-risk group of patients who could be discharged safely if reliable caretakers and follow-up care were ensured. Although a larger validation set will be required to substantiate this in the future, our goal was to create a set of high-risk criteria for patients with ALTEs, with a negative predictive value of >90%, that could determine the need for hospital admission.

**METHODS**

This study was a prospective observational analysis of consecutive patients with ALTEs who presented to the ED between July 2002 and April 2005. This study was approved by the institutional review board. The National Institutes of Health statement included in the introduction was used to define ALTEs for the purposes of this study.

Our hospital is a tertiary-care, freestanding, academic, pediatric facility with a dedicated ED (annual census: 60 000). Of all infants with ALTEs who present to our ED, most are admitted to the hospital, although some are not. The purpose of this study was to develop criteria that might predict whether admission was required. In determining which patients with ALTEs required admission, 2 primary questions were addressed, as follows. The first involved predictive criteria. What potential patient characteristics could be used to predict the risk of serious sequelae in infants with ALTEs? These were tested against outcome criteria to determine whether they predicted accurately the need for admission. To stratify risk, we analyzed factors assumed or debated in the literature to increase the risk of SIDS, including (1) family history of SIDS, (2) patient history of moderate prematurity (gestational age between 30 weeks and 37 weeks), (3) previous ALTEs, (4) patient age, (5) presence of upper respiratory infection symptoms, (6) child’s color and tone during the ALTE, (7) duration of the ALTE, as estimated by observers, (8) interventions required, (9) appearance of the child in the ED, (10) suspicion of child abuse, and (11) multiple ALTEs within 24 hours.

The second question involved outcome criteria. What outcomes would be considered to mandate admission? We considered any of the following factors to require admission: (1) subsequent events requiring resuscitation during hospitalization, (2) any subsequent ALTEs and an identifiable pathologic condition that was treated during hospitalization, (3) a diagnosis made after admission that would have put the patient at risk with discharge and would normally necessitate admission if identified in the ED (eg, child abuse or serious neonatal bacterial infection), or (4) development of a life-threatening condition.
Infants <12 months of age were included if they had a convincing history of an ALTE, as determined by the attending physician in the ED. Infants were excluded for a history of extreme prematurity (estimated gestational age of <30 weeks was chosen because of the high risk of persistence of apnea of prematurity for infants with estimated gestational ages of 24–28 weeks\textsuperscript{17}, uncorrected cardiac disease, known seizure disorder, significant developmental delay, or chronic lung disease requiring treatment. Patients under the care of a neonatologist or pulmonologist because of previous ALTEs were also excluded. All charts were also reviewed by the principle investigator to ensure that the child met the definition of an ALTE and did not meet any exclusion criteria. If a child had an episode of apnea attributable to a clearly discernible disease diagnosed by the ED (ie, pertussis), these were not labeled as ALTEs, and the infants were not included. We included both well- and ill-appearing children. Institutional review board-certified personnel were present 7 days per week, 24 hours per day, to collect a consecutive sample of patients. No family refused consent.

Because this study was purely observational, no modifications were made to the patients’ treatment or disposition because of the study. In the ED, the treating physician completed a form documenting the patient characteristics described above. Studies were performed and patients were admitted or discharged at the discretion of the attending physician. Discharged patients were contacted by telephone at 24 to 72 hours, and admitted patients were observed for additional episodes, results of testing, and final diagnosis during their hospital stay. Attempts were also made to contact all patients at 1 week, to obtain outcome data. Regardless of whether patients were actually admitted to the hospital, all patients were categorized as either hospitalization required (HR) or hospitalization not required (HNR), on the basis of the outcome criteria discussed above. Briefly, patients who required resuscitation during hospitalization, experienced subsequent events attributable to a condition identified during hospitalization, or were diagnosed as having a condition that would have put the patient at risk of acute deterioration if he or she had been discharged were classified as HR. Admitted patients who were discharged without an imminently life-threatening diagnosis and experienced either no events or minor, self-resolved events during hospitalization were classified as HNR. Patients discharged from the ED were contacted at 24 to 72 hours and, if well and without subsequent events, were also placed in the HNR category.

Odds ratios (ORs) for the need for hospitalization were calculated by using univariate analyses. Multivariate analysis was not performed because of the small number of patients who ultimately required hospitalization in each subset. Significance was tested by using Fisher’s exact tests. In addition, we attempted to develop criteria that would predict with nearly 100% negative predictive value that a child would not require hospitalization. The sample size goal was to enroll sufficient patients to provide a negative predictive value with the lower end of the 95% confidence interval (CI) at 90%. The sensitivity, specificity, and predictive values of these pooled criteria were calculated with CIs.

**RESULTS**

Sixty-four patients were enrolled, and 59 were included in the final analysis. Of the 5 eliminated, 1 did not meet the definition of an ALTE, 2 met exclusion criteria, and 1 was discharged from the ED and subsequently could not be reached; 1 was well without subsequent events when seen 45 hours into the hospital stay, but all subsequent records were lost and the treating physician could not be contacted. Of the 59 patients in the final analysis, 55 were actually admitted to the hospital, and 4 were discharged from the ED.

In our analysis, 8 (14%) of the 59 patients were placed in the HR category. These 8 patients were all admitted. Two required PICU transfer, 3 had multiple significant apneic episodes while hospitalized, 1 developed an oxygen requirement, and 2 required treatment for significant infectious or neurologic conditions. More information on the patients who required hospital admission is listed in Table 1. The remaining 51 patients did not experience an event or receive a diagnosis that

<table>
<thead>
<tr>
<th>Patient Age, wk</th>
<th>High-Risk Criteria</th>
<th>Reason for Admission/Hospital Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Age</td>
<td>Multiple apnea/desaturation episodes with GERD, oxygen requirement</td>
</tr>
<tr>
<td>1</td>
<td>Multiple ALTEs, age</td>
<td>Became hypoxemic, oxygen requirement</td>
</tr>
<tr>
<td>1</td>
<td>Multiple ALTEs, age</td>
<td>Seizure, suspected nonaccidental trauma</td>
</tr>
<tr>
<td>3</td>
<td>Multiple ALTEs, age</td>
<td>Intubated because of apnea</td>
</tr>
<tr>
<td>4</td>
<td>Multiple ALTEs, age</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>7.5</td>
<td>Multiple ALTEs</td>
<td>Multiple apnea/desaturation episodes with GERD</td>
</tr>
<tr>
<td>8</td>
<td>Multiple ALTEs</td>
<td>PICU for apnea, encephalitis</td>
</tr>
<tr>
<td>8</td>
<td>Multiple ALTEs</td>
<td>Multiple apnea/desaturation episodes with GERD</td>
</tr>
</tbody>
</table>

GERD indicates gastroesophageal reflux disease.
would have required hospitalization and thus were placed in the HNR category. Four of the HNR patients were discharged from the ED and subsequently contacted by telephone, and 47 were admitted.

The most common unifying features of the 8 HR patients were a history of multiple ALTEs within 24 hours of admission (7 of 8 patients) and age of \( \leq 1 \) month (5 of 8 patients). Prematurity (gestational age of \(< 37 \) weeks) was also common (3 of 8 patients). When the HR and HNR groups were compared, a history of multiple ALTEs and prematurity proved to be significantly different. An intergroup comparison of the symptoms studied is listed in Table 2.

Because a history of multiple ALTEs and age of \( \leq 1 \) month (defined as 30 days) were the most common features noted among the HR infants, we evaluated the utility of using either of these features as a criterion for admission. Admitting all patients with ALTEs who were \(< 1 \) month of age and/or had a history of multiple ALTEs would provide a sensitivity and negative predictive value of 100% to identify patients who require admission, according to our aforementioned outcome criteria. Because an adverse outcome was a rare event in our population, the CI for the sensitivity was large; however, the CI of the negative predictive value was 90% to 100%. Tables 3 and 4 contain the data and the sensitivity, specificity, and predictive values for this tool in identifying infants who require admission.

**DISCUSSION**

Our study shows that only 14% of the patients who presented to our ED with a diagnosis of ALTE had a condition or subsequent event necessitating hospitalization. The high-risk criteria (multiple ALTEs within 24 hours and age of \( \leq 1 \) month) identified each of those patients with a negative predictive value of 100%, with a CI lower limit of 90%. Therefore, the possibility of being able to discharge safely a subset of well-appearing, low-risk patients with ALTEs exists, if the results of this pilot study are borne out in a larger, multicenter population of patients with ALTEs. In our small group of 59 infants, 26 (44%) who did not meet high-risk criteria could have been discharged safely from the ED.

Several additional patient characteristics were found to be predictive of subsequent events with calculation of ORs, most notably prematurity (OR: 14) and blue discoloration of the face during the ALTE (OR: 4). These were not included in our high-risk criteria, and all premature or cyanotic patients in our study population who required hospitalization also met the high-risk criteria. However, prudence suggests that prematurity should play a role in physician decision-making. Similarly, we did not include ill appearance in our criteria. Five patients looked ill at presentation, and all of those infants did not include ill appearance in our criteria. Five patients looked ill at presentation, and all of those infants met the high-risk criteria regardless of appearance. Nonetheless, our personal practice continues to be that a child should be well-appearing and have follow-up care ensured to be discharged. No child in this study was admitted for social reasons or suspicion of nonaccidental injuries; however, these factors may be considerations for certain infants with apnea.

Previous studies suggested a higher incidence of SIDS for patients with a family history\(^1\) and higher rates of subsequent events for children requiring resuscitation or experiencing multiple events at home\(^2\) and those with prolonged apnea and normal muscle tone during the event.\(^3\) Our study was not powered specifically to assess this, but we found no association between the degrees of resuscitation perceived necessary by the parents or the muscle tone during the event and the need for hospitalization. Although it was not the focus of this study, because it would not affect an ED physician’s decision to admit a patient in the short term, we attempted to obtain long-term follow-up data on the patients included. One third of the patients were contacted successfully at 3

---

**TABLE 2** Comparability of Patients With ALTEs Requiring Hospitalization and Not Requiring Hospitalization

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>HR (n = 8)</th>
<th>HNR (n = 51)</th>
<th>P</th>
<th>OR for Requiring Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, wk</td>
<td></td>
<td></td>
<td></td>
<td>.149</td>
<td></td>
</tr>
<tr>
<td>Age of (&lt; 1 ) mo</td>
<td>21</td>
<td>62.5</td>
<td>35.3</td>
<td>.127</td>
<td>3.3</td>
</tr>
<tr>
<td>Multiple ALTEs, %</td>
<td>14</td>
<td>87.5</td>
<td>13.5</td>
<td>.001(^a)</td>
<td>4</td>
</tr>
<tr>
<td>Prematurity, %</td>
<td>6</td>
<td>37.5</td>
<td>3.9</td>
<td>.009(^b)</td>
<td>14</td>
</tr>
<tr>
<td>Male, %</td>
<td>35</td>
<td>62.5</td>
<td>56.9</td>
<td>.765</td>
<td>1.3</td>
</tr>
<tr>
<td>Previous ALTE, %</td>
<td>8</td>
<td>12.5</td>
<td>11.8</td>
<td>.952</td>
<td>1.1</td>
</tr>
<tr>
<td>URI symptoms, %</td>
<td>23</td>
<td>37.5</td>
<td>35.3</td>
<td>.904</td>
<td>1</td>
</tr>
<tr>
<td>Turned blue, %</td>
<td>41</td>
<td>87.5</td>
<td>64.7</td>
<td>.198</td>
<td>4.2</td>
</tr>
<tr>
<td>Tone normal, %</td>
<td>17</td>
<td>37.5</td>
<td>23.6</td>
<td>.405</td>
<td>1.1</td>
</tr>
<tr>
<td>Duration of (&gt; 1 ) min, %</td>
<td>29</td>
<td>25</td>
<td>54.9</td>
<td>.134</td>
<td>0.27</td>
</tr>
<tr>
<td>Awake previously, %</td>
<td>44</td>
<td>75</td>
<td>72.5</td>
<td>.08</td>
<td>1.13</td>
</tr>
<tr>
<td>Stimulated, %</td>
<td>39</td>
<td>75</td>
<td>60.8</td>
<td>.445</td>
<td>1.9</td>
</tr>
<tr>
<td>Given CPR, %</td>
<td>7</td>
<td>12.5</td>
<td>11.8</td>
<td>.952</td>
<td>1.07</td>
</tr>
</tbody>
</table>

URI indicates upper respiratory infection; CPR, cardiopulmonary resuscitation.

\(^a\) Fisher’s exact test, \(P = .001\).

\(^b\) Fisher’s exact test, \(P = .015\).
months. Of those, 2 HNR patients experienced subsequent nonfatal ALTEs (one 3 weeks after discharge and one 6 weeks after discharge), and 1 HNR patient developed possible cardiomyopathy 3 months after admission.

Because the vast majority of our patients fared well throughout their admissions, the number requiring hospitalization was low, which yielded a large CI for the sensitivity of our criteria. However, this does support the rarity of subsequent events and life-threatening conditions for otherwise asymptomatic ALTE patients and the use of a negative predictive value to assess the utility of our work. Ideally, a larger validation set could be tested in a future multicenter study, to confirm our findings. Clearly, the specificity is unacceptably low to be useful; however, our goal was to ensure that all high-risk children are admitted, and we are willing to accept a low specificity to maintain adequate sensitivity and negative predictive value. The 1 patient who was lost to follow-up monitoring after being discharged from the ED presents an additional limitation. Although this child’s outcome is not known, there is no record of a return visit to our ED or any complaint or legal action initiated within 2 years after the child’s discharge.

CONCLUSIONS
Our study showed that only 14% of infants presenting with an ALTE to the ED had a subsequent clinical course that would have required hospitalization for diagnosis or protection from acute deterioration. All of these cases were predicted because the infants had multiple ALTEs before the ED visit and/or they were <30 days of age. We speculate that most infants who do not meet these high-risk criteria can be discharged safely from the ED.

REFERENCES
Cost-effectiveness and Potential Impact of Rotavirus Vaccination in the United States

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. In February 2006, a safe, efficacious, orally administered pentavalent human-bovine reassortant rotavirus vaccine was licensed and recommended for routine immunization of all children in the United States. We assessed the health and economic impacts of a national rotavirus immunization program in the United States.

METHODS. Monte Carlo cost-effectiveness analyses, from health care and societal perspectives, of vaccination of a hypothetical US birth cohort of 4 010 000 children monitored from birth to 59 months of age were performed. We compared the disease and economic burden of rotavirus infection in an unvaccinated cohort of children with one vaccinated at 2, 4, and 6 months with pentavalent human-bovine reassortant rotavirus vaccine.

RESULTS. A routine rotavirus immunization program would prevent 13 deaths, 44 000 hospitalizations, 137 000 emergency department visits, 256 000 office visits, and 1 100 000 episodes requiring only home care for children <5 years of age in the United States. Assuming costs of administration of $10, the break-even price per dose of vaccine was $42 from the societal perspective and $12 from the health care perspective. From the societal perspective, at the manufacturer’s price of $62.50 per dose, vaccination would cost $138 per case averted, $3024 per serious case averted, and $197 190 per life-year saved, at a total cost of $515 million to the health care system and $216 million to society. Key variables influencing the results were parental workdays lost, costs of hospitalization, emergency department visits, and child care.

CONCLUSIONS. Despite a higher burden of serious rotavirus disease than estimated previously, routine rotavirus vaccination would unlikely be cost-saving in the United States at present. Nonetheless, rotavirus vaccination may still be considered a cost-effective intervention.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Key Words
rotavirus vaccines, cost-benefit analysis, United States

Abbreviations
PRV—pentavalent human-bovine reassortant rotavirus vaccine
RRV-TV—tetravalent rhesus-human reassortant rotavirus vaccine
ICD-9-CM—International Classification of Diseases, Ninth Revision, Clinical Modification
DTaP—diphtheria-tetanus-acellular pertussis
CDC—Centers for Disease Control and Prevention

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RotaVirus is the most common cause of severe gastroenteritis among children <5 years of age in the United States. In 1998, a tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) (RotaShield; Wyeth Laboratories, Collegeville, PA) was licensed and recommended for inclusion in the US schedule for routine childhood immunizations. In October 1999, after >500,000 children had received ≥1 dose,1 the vaccine was withdrawn after reports of cases of intussusception among recent vaccinees.2

Since 1999, 2 new oral rotavirus vaccines with different biological properties have been developed. Large clinical trials with 60,000 to 70,000 children have demonstrated these vaccines to be highly efficacious and without evidence of vaccine-associated intussusception or other serious adverse events.3,4 In February 2006, the US Food and Drug Administration licensed a pentavalent human-bovine reassortant rotavirus vaccine (PRV) (RotaTeq; Merck, Whitehouse Station, NJ)5 and the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) recommended this vaccine for routine immunization of infants in the United States.

The Advisory Committee on Immunization Practices requires cost-effectiveness analyses to make recommendations for new vaccines. Our previous cost-effectiveness study of vaccination with the discontinued RRV-TV demonstrated that, each year, a rotavirus vaccination program would prevent 39% of all episodes of rotavirus gastroenteritis, including 67% of hospitalizations, 59% of emergency department visits, and 55% of physician visits. In 1996 US dollars and at $20 per dose, the program was projected to cost $107 million to the health care system but overall would result in savings of $296 million to society.6 That study is now outdated in several key aspects. First, it was based on vaccine efficacy data for the discontinued RRV-TV vaccine, and newer vaccines have different biological properties. Second, modern modeling techniques allow for better assessment of data uncertainty, such as the natural variation of disease incidence from year to year. Third, many data elements, such as vaccine coverage, likely vaccine price, and the burden and cost of rotavirus disease, have changed in the past 10 years, as have health care utilization patterns.6 Finally, no calculation of the costs of possible adverse effects of rotavirus, such as intussusception, was included previously. We present updated estimates of the disease burden of rotavirus in the United States, estimate the impact of vaccination, and perform a cost-effectiveness analysis by using recent data on the newly licensed and recommended PRV.

METHODS

Overview
We built a probabilistic (Monte Carlo) model by using spreadsheet-based software (@Risk 4.5.4; Palisade, Newfield, NY) to calculate the cost-effectiveness of fully vaccinating a cohort of 4,010,000 children against rotavirus. We used cumulative probability distributions to describe the total annual number of cases of rotavirus disease for children 0 to 59 months of age. To estimate the risk of rotavirus gastroenteritis requiring medical care (hospitalization, emergency department visit, hospital outpatient visit, or physician office visit), we used the following general formula:

number of rotavirus-related gastroenteritis episodes for each outcome = annual number of episodes of gastroenteritis (all causes) for that outcome × probability that episode is attributable to rotavirus.

We also used probability distributions to describe the medical and nonmedical costs of each episode of rotavirus gastroenteritis and to estimate vaccine efficacy.

We used the following formula for cost-effectiveness:

(cost of vaccination program − costs saved because of outcomes averted)/number outcomes prevented by vaccination program.

We calculated the cost-effectiveness ratio per life-year saved, per case (any disease) averted, and per serious case (hospitalization, emergency department visit, or death) averted, from both a health care payer perspective (medical costs borne primarily by health plans) and a societal perspective (medical and nonmedical costs). We discounted costs at 3% per year. All costs were inflated to 2004 equivalent values, by using the medical component of the consumer price index.7

To estimate the actual impact of a mature vaccine program on disease burden, we calculated the total national reduction in cost and number of episodes in any 1 year by using current national vaccine coverage estimates. With the assumption of a static population, the annual number of any one outcome among all children <59 months of age equals the cumulative number of that outcome a birth cohort experiences from 0 to 59 months.

Estimates of Disease Burden of Rotavirus

Rotavirus Gastroenteritis Requiring Medical Care
To obtain annual national weighted estimates of the mean total number of gastroenteritis episodes requiring care among children up to 59 months of age, we applied International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for gastroenteritis of determined cause (bacterial: codes 001-005.9, excluding code 003.2, and codes 008-008.5; parasitic: codes 006-007.9, excluding codes 006.3-006.6; viral: codes 008.6-008.8) and of undetermined cause (infectious: codes 009.0-009.3; noninfectious: codes 558.9 and 787.91) to data from the National Health Care Survey (National Center for Health Statistics, CDC)8 for each year from 2000 through 2003.
1993 to 2002. A SE was calculated from the survey data by using methods described elsewhere, allowing each annual estimate to be described as a normal distribution. Our source for data on hospitalizations was the National Hospital Discharge Survey, that for emergency department and hospital outpatient visits was the National Hospital Ambulatory Medical Care Survey, and that for physician office visits was the National Ambulatory Medical Care Survey (Appendix 1). We extracted the records with the relevant codes in the first 15 positions for hospitalizations and the first 5 positions for outpatient visits.

To estimate the number of rotavirus events requiring medical care, we multiplied each distribution of diarrhea outcomes (hospitalization, emergency department visit, hospital outpatient visit, or physician office visit) in any 1 year by a second likelihood distribution that the outcome was attributable to rotavirus. For hospitalizations, we built a probability distribution by using rotavirus-related data from the largest prospective study of gastroenteritis-related hospitalizations conducted over 8 years (Table 1 and Appendices 1 and 2). No data exist on the proportion of emergency department visits attributable to rotavirus in the United States, although data from Canada suggest a proportion of 40%. Evidence from vaccine trials indicated that the reduction in emergency department visits for all gastroenteritis in a population vaccinated against rotavirus was more than the reduction in outpatient settings but less than that in hospitalizations (P. Heaton, MD, written communication, 2005). Therefore, we assumed that a median of 28% of gastroenteritis-associated emergency department visits would be attributable to rotavirus. For outpatient and physician office visits for gastroenteritis, no longitudinal data on the rotavirus proportion were available; therefore, we determined a distribution by using averages from published studies in the United States and abroad (Table 1 and Appendices 1 and 2).

The resulting estimated numbers of rotavirus-related outcomes were then standardized to the population <5 years of age in that year, to give the number of outcomes in the birth cohort of 4,010,000 over a period of 5 years. Analyses of the age distributions of rotavirus illness requiring hospitalization, outpatient visit, or no medical care were similar in several studies; therefore, we applied an age distribution for rotavirus hospitalizations to estimate the number of outcomes requiring medical care that this birth cohort would experience at each of the following ages: <3 months, 3 to 5 months, 6 to 23 months, 24 to 35 months, 36 to 47 months, and 48 to 59 months (Fig 1).

**Rotavirus-Related Deaths**

We used estimates of 20 to 40 rotavirus-related deaths among children <5 years of age in the United States from 2 studies. In those studies, risk of death was higher at earlier ages than risk of milder outcomes; therefore, we divided the risk of death between age groups according a distribution derived from one of those studies (Fig 1 and Table 1).

**Rotavirus Gastroenteritis Not Requiring Medical Care**

We assumed a uniform distribution of the overall incidence of rotavirus gastroenteritis in children <5 years of age, by using data from 2 longitudinal studies on the risk of a rotavirus gastroenteritis episode in the first 5 years of life. We distributed the risk in each age group as for episodes requiring health care (Fig 1). We applied these age-specific risks to the US birth cohort, to give us the total number of rotavirus episodes experienced each year by children <5 years of age. To calculate the number of children in each age group who experienced rotavirus-related gastroenteritis that did not require medical care, we subtracted the estimated numbers of deaths and episodes requiring health care from the total number of rotavirus gastroenteritis episodes (Table 1).

### Table 1: Probability Distributions of Estimates of Risk of Rotavirus Disease in Children 0 to 59 Months of Age Without Rotavirus Vaccination Program

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proportion Rotavirus Positive, Median (5th to 95th Percentile), %</th>
<th>Probability Distribution</th>
<th>Cumulative Individual Risk of Event by Age of 59 mo Median</th>
<th>Equivalent Cumulative No. of Events by Age of 59 mo in US Population, Median (5th to 95th Percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any rotavirus gastroenteritis</td>
<td>Uniform</td>
<td>0.75</td>
<td>0.65–0.85b</td>
<td>3 010 500 (2 609 100–3 411 900)b</td>
</tr>
<tr>
<td>Death</td>
<td>Uniform</td>
<td>7.7 × 10^-6</td>
<td>7.8 × 10^-6 to 1.0 × 10^-6b</td>
<td>30 (21–39)b</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Derivedb</td>
<td>0.0167</td>
<td>0.0118–0.0229</td>
<td>67 033 (47 365–91 921)</td>
</tr>
<tr>
<td>Emergency department</td>
<td>Derivedd</td>
<td>0.0533</td>
<td>0.0359–0.0725b</td>
<td>213 946 (144 103–291 015)b</td>
</tr>
<tr>
<td>Hospital outpatient visit</td>
<td>Derivedd</td>
<td>0.0092</td>
<td>0.0042–0.0181</td>
<td>36 929 (16 859–72 653)</td>
</tr>
<tr>
<td>Office visit</td>
<td>Derivedd</td>
<td>0.0965</td>
<td>0.0499–0.1684</td>
<td>387 351 (200 299–675 958)</td>
</tr>
<tr>
<td>No medical care required</td>
<td>Residuald</td>
<td>0.5685</td>
<td>0.4513–0.6778</td>
<td>2 280 594 (1 811 518–2 720 689)</td>
</tr>
</tbody>
</table>

- Cumulative number of events in the US birth cohort monitored from birth to 5 years of age, based on a birth cohort of 4 014 000 on July 1, 2004. The cumulative number of events in the birth cohort is equal to the number of events in each year for all children <59 months of age, with the assumption of constant cohort size. The range is 5th to 95th percentile unless otherwise noted.
- Range is minimum to maximum.
- Derived distributions were created from distribution of rotavirus positivity (second column multiplied by the distribution of annual frequency of diarrhea in each health care setting). See Appendix 2 for details of fitted distributions.
- Residual distribution was calculated by subtracting the risk of death and events requiring medical care from the risk of rotavirus diarrhea of any severity in any 1 year.
Costs of Disease

Direct Medical Costs

The MarketScan database (Thomson Medstat, Ann Arbor, MI) includes >500 million claim records on inpatient and outpatient health care services from 45 large employers, health plans, and public organizations and from almost 100 different payers. We extracted gross payments (reimbursements) to providers for patient visits in the 4 years of 2000 to 2003 and fitted probability distributions to each sample of costs. To extract costs of hospitalization, we applied the specific rotavirus ICD-9-CM code (code 008.61) in any of the first 15 discharge diagnoses for inpatient services, because this code is highly specific for rotavirus-confirmed infection²⁴ and >25% of all gastroenteritis hospitalizations in the database listed this code, which suggests that these were representative of all rotavirus hospitalizations. For costs of outpatient services (ie, emergency department visit, hospital outpatient visit, or physician office visit), we used the same diarrhea-specific ICD-9-CM codes as applied to extract data from the National Health Care Survey. We chose outpatient visits for gastroenteritis attributable to any cause because the few rotavirus-coded outpatient events might have represented a bias toward more severely ill patients. We added the cost of drugs to the cost of outpatient hospital and office visits, because these were recorded separately (Table 2 and Appendix 3). Median costs of hospitalization and outpatient visits were consistent with previously published data.⁵,²⁵–²⁷

Nonmedical Costs

Loss of earnings per day of missed work for parents of children with gastroenteritis and lifetime productivity loss attributable to death were calculated from published tables with Bureau of Labor statistics adjusted for weekends and holidays.²⁸ Published estimates for workdays lost for gastroenteritis seen in a physician office vary from 0.71 days to 2 days.²⁷,²⁹–³¹ We chose a midpoint of 1.3 days of missed work for rotavirus disease seen in an outpatient clinic, 10 days for every child death, 2 days for hospitalization and emergency department visits, and 1 day for episodes not requiring medical care. Our estimate of work lost for episodes requiring home care is consistent with one study of gastroenteritis in day care²⁹ and with data for simple otitis media, which would require a comparable level and duration of home care.³² For additional costs to a family for special foods, diapers, travel, and child care, we used the average costs and SDs of these items (adjusted to 2004 dollars) reported in an outpatient study,²⁷ and we created normal distributions for these costs (Table 2). These were consistent with costs incurred at home for the same items in 2 studies of hospitalized children.³³,³⁴

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Costs of Episode of Rotavirus Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probability Distribution</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Medical costs³²</td>
<td></td>
</tr>
<tr>
<td>Hospitalization (2-d duration)</td>
<td>Logarithmic-logistic</td>
</tr>
<tr>
<td>Emergency department visit</td>
<td>Logarithmic-normal</td>
</tr>
<tr>
<td>Hospital outpatient visit</td>
<td>Logarithmic-logistic</td>
</tr>
<tr>
<td>Physician office visit</td>
<td>Logarithmic-logistic</td>
</tr>
<tr>
<td>Medication</td>
<td>Logarithmic-normal</td>
</tr>
<tr>
<td>Nonmedical costs</td>
<td></td>
</tr>
<tr>
<td>Forgone earnings of parent (per day)</td>
<td>Fixed</td>
</tr>
<tr>
<td>Travel (health care episodes and death)</td>
<td>Normal</td>
</tr>
<tr>
<td>Extra diapers (all episodes except death)</td>
<td>Normal</td>
</tr>
<tr>
<td>Special food and oral rehydration solution (all episodes except death)</td>
<td>Normal</td>
</tr>
<tr>
<td>Child care costs (all episodes)</td>
<td>Uniform</td>
</tr>
<tr>
<td>Lifetime productivity loss of child death</td>
<td>Fixed</td>
</tr>
</tbody>
</table>

Costs are given in 2004 US dollars.
³² Includes costs of drugs prescribed at the point of care except for office and hospital outpatient visits, where costs of medications are a separate cost.

FIGURE 1
Cumulative probability of rotavirus illness and death among children 0 to 59 months of age. * Derived from ref 20. † Derived from ref 22.
Cost of Program
The current manufacturer’s list price for PRV is $62.50 per dose (excluding tax). We calculated the cost-effectiveness ratios for a range of costs associated with a complete vaccination course ($0 to $300). The cost of a full vaccination course included the cost of 3 doses of vaccine and an assumed cost of administration of $10 per dose.\(^{3,2,35}\) Although the large clinical trial of PRV did not demonstrate any association with intussusception,\(^{3}\) a very low risk of intussusception attributable to the vaccine remains possible. Moreover, in the early phase of vaccine introduction, anxiety regarding possible intussusception might result in more-aggressive diagnostic evaluations among vaccinees with adverse reactions. Lastly, administration of the first dose of PRV was associated with mild gastroenteritis and vomiting in some recipients (P. Heaton, MD, written communication, 2005), which could result in an extra outpatient visit. We used inpatient records to estimate that diagnosis and treatment of intussusception with the specific ICD9-CM code (code 560.0) cost $4263 (Appendix 3). At a hypothetical rate of 1 vaccine-associated intussusception case per 50,000 vaccinees, this added $0.10 to the total cost of vaccination per child. By using outpatient costs for diagnosis of true intussusception as a proxy, we estimated $227 for evaluation of an adverse reaction to rule out intussusception (Appendix 3). To cover the cost of 1 extra outpatient diagnostic evaluation per 1500 vaccinees, $0.15 was added to the total cost per vaccinee. This rate of postvaccine adverse reactions is consistent with the rate of reports of nonserious gastrointestinal adverse events associated with administration of the withdrawn RRV-TV vaccine.\(^{36}\) No costs associated with parent travel or workdays lost were included, because we assumed that the vaccine would be administered with scheduled vaccinations (diphtheria-tetanus-acellular pertussis [DTaP] vaccine) at 2, 4, and 6 months of age.

Vaccine Efficacy
We derived our estimates of vaccine efficacy from data from a large clinical trial of PRV (Table 3).\(^{3}\) The few data available from the vaccine trial on the efficacy of an incomplete rotavirus vaccination course suggested that 1 or 2 doses might have ≥1 half the efficacy of 3 doses (P. Heaton, MD, written communication, 2005). We assumed that children 0 to 2 months of age (unvaccinated) would have no protection, those 3 to 5 months of age (1 or 2 doses) would have half the protection, and children ≥6 months of age (3 doses) would benefit from the full vaccine efficacy.

Sensitivity Analysis
We used “tornado graphs,” which the software constructed through stepwise regression procedures, to investigate the relative importance of the input distributions (Appendix 4). Because caregivers’ loss of earnings accounts for >40% of all costs of rotavirus disease and published data on workdays lost are sparse, we examined the impact on our final results of increasing and decreasing the workdays lost by 50%, rather than including a range in the model.


table

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vaccine Efficacy Estimates, %</th>
<th>This Study, Median (Minimum to Maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRV, Median (95% Confidence Interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate gastroenteritis</td>
<td>71 (63–78)(^{3})</td>
<td>65 (55–75)</td>
</tr>
<tr>
<td>Death</td>
<td>No data</td>
<td>90 (80–98)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>96 (91–98)</td>
<td>90 (80–98)</td>
</tr>
<tr>
<td>Emergency department visit</td>
<td>93 (88–96)</td>
<td>90 (75–95)</td>
</tr>
<tr>
<td>Office visit</td>
<td>86 (74–93)</td>
<td>85 (70–90)(^{4})</td>
</tr>
</tbody>
</table>

\(^{a}\) Minimum and maximum values were used for triangular distribution. Although triangular distributions generally over-represent higher values, the efficacy data from the trial show a distribution shift to higher values (ie, to the right).

\(^{b}\) Derived from data presented to the Rotavirus Working Group of the Advisory Committee of Immunization Practices (P. Heaton, MD, written communication, 2005). Vaccine efficacy against episodes of rotavirus disease not requiring care was assumed to be the same.

\(^{c}\) Same estimates used for outpatient hospital visits.

Estimate of Burden Reduction During Program
In 2003, the US National Immunization Survey found that, by 3 months of age, >89% of children had received ≥1 dose of DTaP vaccine; by 6 months, 98% had received ≥1 dose of DTaP vaccine, whereas 71% had received all 3 doses.\(^{37}\) We calculated the reduction of disease burden and cost in the US birth cohort with 95% of children having received ≥1 dose by 3 months of age, with 70% of children >6 months of age with receipt of 3 doses of rotavirus vaccine and the remaining 25% of children >6 months of age with receipt of only 1 or 2 doses.

RESULTS
Rotavirus vaccination of every child in the US birth cohort would prevent 63% of all cases and 79% of all serious cases (hospitalizations, emergency department visits, and deaths) of rotavirus disease. These estimates are of reduction in all rotavirus episodes from birth and therefore are lower than clinical trial efficacy estimates that measure effects only after vaccination. From the health care perspective, the break-even total cost of rotavirus vaccination (where net savings are as likely as net costs) is $66 per vaccinee (~$12 per dose, assuming an administration cost of $10 per dose). Rotavirus vaccination likely would be cost-saving from the health care perspective at less than $12 per dose and very probably (ie, >95% likely) would be cost-saving at less than $33 per vaccinee ($1 per dose). Vaccination would be unlikely to be cost-saving at more than $12 per dose and would incur net costs at more than $143 per vaccinee (~$38 per dose). Similarly, from the societal perspective, rotavirus vaccination very probably would be cost-sav-
ing at a total cost of less than $107 per vaccinee (ie, 5th percentile, $26 per dose) and likely would be cost-saving at up to $156 per vaccinee (ie, break-even point, $42 per dose). The vaccine would be increasingly likely to be cost-saving with prices increasing from $156, and a vaccination program would incur a net cost from the societal perspective at more than $238 per vaccinee (ie, 95th percentile, $69 per dose) (Fig 2).

At the current manufacturer’s price of $62.50 per dose ($217.50 per child, including administration costs of $10 per dose), vaccination would result in a net overall cost to the health care system, with a median cost-effectiveness ratio of $336 per case prevented (5th to 95th percentile: $165 to $436), $3024 per serious case prevented (5th to 95th percentile: $1498 to $4460), and $470 729 per life-year saved (5th to 95th percentile: $218 710 to $738 949). Vaccination would also likely incur net costs from the societal perspective, with a median cost-effectiveness ratio of $138 per case prevented (5th to 95th percentile: $44 to $247), $2636 per serious case prevented (5th to 95th percentile: $1108 to $4043), and $197 190 per life-year saved (5th to 95th percentile: $67 298 to $406 933) (Figs 2 and 3).

In the United States, rotavirus infections result in 30 deaths, 67 000 hospitalizations, 213 000 emergency department visits, 37 000 hospital outpatient visits, 387 000 physician visits, and 2 281 000 cases of gastroenteritis not requiring medical care in children <5 years of age, at a total cost of $319 million to the health care system and $893 million to society. Assuming current vaccine coverage for DTaP vaccine, rotavirus vaccination would prevent 1 530 000 cases (51%) of any rotavirus gastroenteritis, 13 deaths (44%), 44 000 rotavirus-related hospitalizations (66%), 137 000 emergency department visits (64%), 22 000 hospital outpatient visits (60%), and 233 000 office visits (60%). At a vaccine price of $62.50 per dose, a vaccination program would incur more medical costs than savings and would have a net cost of $515 million from the health care perspective. However, a program would save $299 million in nonmedical costs and overall, from the societal perspective, would incur a net cost of $216 million (Table 4).

At a total cost of $217.50 per vaccinee, the costs of hospitalizations, emergency department visits, and extra child care were the most important variables in our model (Appendix 4). Varying the number of parental days lost also had a strong influence on the results; a 50% increase in the number of workdays lost increased the best-estimate, break-even, total cost per vaccinee from the societal perspective from $156 to $187, whereas a 50% decrease in days decreased this cost to $123 per child vaccinated (Fig 4).

DISCUSSION

We estimate that, in the United States every year, 3 million children <5 years of age develop rotavirus disease, of whom ~700 000 seek health care; 280 000 of those become seriously ill (emergency department visit, hospitalization, or death). The total cost to society is $893 million, of which $319 million are to the health care system. At current coverage for the DTaP vaccine, a rotavirus vaccine program would prevent 51% of all cases of rotavirus disease and 64% of serious cases but would not be cost-saving from the health care perspective and would be unlikely to be cost-saving from the societal perspective unless the price of the vaccine were...

---

**FIGURE 2**

Cost-effectiveness ratios of rotavirus vaccination per case averted from 2 perspectives, according to total cost (2004 US dollars) per child of complete vaccination (3 doses). A, Health care perspective (medical costs); B, societal perspective (medical and nonmedical costs). The solid lines represent medians, and the dashed lines represent 5th and 95th percentiles. The arrows indicate a total cost of $217 per vaccine recipient, representing the Merck list price of $62.50 per dose plus $10 fee per administration. Cost savings are shown in parentheses.
$42 or less (assuming administration costs of $10 per dose). At $217.50 per vaccinee ($62.50 per dose), a vaccine program would incur a net cost of $336 per case averted from the health care perspective and $138 per case from the societal perspective. If the vaccine was associated with low rates of adverse events, including intussusception (undetected in the prelicensure trials), then such events would have a negligible effect on the cost-effectiveness of vaccination.

Our results differ from previous cost-effectiveness analyses for rotavirus in several respects. First, and consistent with several recent studies,9,38 our updated dis-

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Vaccine Program</th>
<th>With Vaccine Program</th>
<th>Prevented</th>
<th>Reduction, %</th>
</tr>
</thead>
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<tr>
<td>Events, n(^b)</td>
<td>2,280,594</td>
<td>1,186,873</td>
<td>1,093,721</td>
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<td>Office visits</td>
<td>387,351</td>
<td>154,059</td>
<td>233,292</td>
<td>60</td>
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<td>Hospital outpatient visits</td>
<td>36,929</td>
<td>14,687</td>
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<tr>
<td>Emergency department visits</td>
<td>213,846</td>
<td>77,186</td>
<td>136,660</td>
<td>64</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>67,033</td>
<td>22,962</td>
<td>44,071</td>
<td>66</td>
</tr>
<tr>
<td>Deaths</td>
<td>30</td>
<td>17</td>
<td>13</td>
<td>44</td>
</tr>
<tr>
<td>Total events</td>
<td>3,010,500</td>
<td>1,480,401</td>
<td>1,530,099</td>
<td>51</td>
</tr>
<tr>
<td>Costs, $ (thousands)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office visits</td>
<td>32,925</td>
<td>13,095</td>
<td>19,830</td>
<td>60</td>
</tr>
<tr>
<td>Hospital outpatient visits</td>
<td>15,907</td>
<td>6,327</td>
<td>9,580</td>
<td>60</td>
</tr>
<tr>
<td>Emergency department visits</td>
<td>71,030</td>
<td>25,626</td>
<td>45,404</td>
<td>64</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>198,551</td>
<td>68,012</td>
<td>130,539</td>
<td>66</td>
</tr>
<tr>
<td>Deaths (hospitalization cost)</td>
<td>88</td>
<td>41</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>Vaccine administration</td>
<td>0</td>
<td>99,347</td>
<td>−99,347</td>
<td></td>
</tr>
<tr>
<td>Cost of vaccine ($62.50 per dose)</td>
<td>0</td>
<td>620,915</td>
<td>−620,915</td>
<td></td>
</tr>
<tr>
<td>Total medical costs</td>
<td>318,501</td>
<td>833,363</td>
<td>−514,862</td>
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</tr>
<tr>
<td>Nonmedical costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost earnings</td>
<td>400,541</td>
<td>189,591</td>
<td>210,950</td>
<td>53</td>
</tr>
<tr>
<td>Other nonmedical costs</td>
<td>138,807</td>
<td>66,252</td>
<td>72,555</td>
<td>52</td>
</tr>
<tr>
<td>Lifetime productivity loss per child death</td>
<td>35,033</td>
<td>19,525</td>
<td>15,508</td>
<td>44</td>
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<tr>
<td>Total nonmedical costs</td>
<td>574,381</td>
<td>275,368</td>
<td>299,013</td>
<td>52</td>
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<tr>
<td>Total costs</td>
<td>892,882</td>
<td>1,108,751</td>
<td>−215,849</td>
<td></td>
</tr>
</tbody>
</table>

Costs are given in 2004 US dollars.
\(^a\) Assuming 70% coverage for 3 doses.
\(^b\) Cumulative number of events in the US birth cohort monitored from birth to 5 years of age, based on a birth cohort of 4,014,000 on July 1, 2004.48
\(^c\) Costs incurred.
ease burden estimates suggest that rates of hospitalizations and emergency department visits for rotavirus are not declining and, even corrected for a smaller birth cohort, might have been underestimated in the previous cost-effectiveness analysis. Because these serious events account for 90% of rotavirus health care costs, our analysis suggests that the impact of a rotavirus vaccine on health care systems may be larger than estimated previously. Second, our calculated overall costs of rotavirus disease to society are lower than the previous estimate of approximately $1 billion in 1996 dollars. This is in large part attributable to our more-conservative estimates of workdays lost, which is biased away from the case for vaccination. In particular, we used 1 workday lost for a case requiring only home care, whereas the previous analysis assumed 3.4 workdays lost whether medical care was required or not. Our results are consequently less favorable from the societal perspective, with a break-even cost of approximately $42 per vaccine dose, compared with $65 extrapolated from the previous analysis ($51 per dose in 1996 dollars, converted to 2004 dollars by using the medical care consumer price index2). However, with an extra 50% of workdays lost included in our model, the break-even cost moved to $52 per dose, below the current list price of $62.50. The CDC Vaccines for Children Fund provides free vaccines for eligible children and recently negotiated a price of $52 per dose of rotavirus vaccine.39 If the Vaccines for Children Fund purchased ~50% of the rotavirus vaccine supply, then this would lower the cost of vaccination of $217 per vaccinee by approximately $15, although this would have little effect on the overall conclusions (Figs 2 and 3).

Our study has several limitations in the estimation of disease burden and costs. Data from clinical trials indicated a 63% reduction in all diarrhea hospitalizations among children vaccinated against rotavirus; although the decrease was measured only among children <18 months of age, who have a relatively high incidence of rotavirus, this suggests that the true impact of a rotavirus vaccine could be substantially greater from the health care perspective than we report. Our model does not account specifically for nosocomially acquired rotavirus gastroenteritis, because no reliable data exist on the rate and cost of either treatment of these episodes or outbreak control. An unknown number of cases of nosocomial rotavirus diarrhea would have been included in the analysis, because they would have been coded as gastroenteritis at discharge.

We did not account for rotavirus disease in adults40 or for any effect of herd immunity. We might have overestimated the average value of a lost workday, because women are more often care providers but in general have lower salaries than men. Also, some evidence suggests that costs of hospitalization for rotavirus disease among vaccinated children may be lower than those among unvaccinated children.41,42 We did not use quality-adjusted life-years in our analysis because no data exist on the psychological costs of gastroenteritis of relatively short duration among young infants and parents. Future willingness-to-pay studies may better estimate the true value that parents attach to the prevention of rotavirus disease and to a risk-free vaccine. Extra costs may be incurred if pediatricians administer the vaccine in a separate visit and not concomitantly with DTaP vaccine. Program vaccine effectiveness may be lower than trial efficacy because of suboptimal vaccine storage and administration and any shift in circulating rotavirus strains to those not included in the vaccine. However, vaccine effectiveness may be higher if 1 or 2 doses provide strong protection. Although data are sparse from recent clinical trials of PRV, 1 dose of Rotashield was shown to be 89% effective against severe disease.43 The MarketScan database may under-represent poorer segments of society that are more at risk of severe, and therefore costly, rotavirus disease44 but also may be less likely to seek care for less severe episodes.

CONCLUSIONS

A mature rotavirus immunization program would prevent almost two thirds of all serious rotavirus disease but, at the current manufacturer’s list price, would almost certainly result in net costs to the health care system and would be unlikely to be cost-saving from the societal perspective. Newer vaccines have been introduced without being considered cost-saving initially, either from the health care perspective (eg, varicella32 and hepatitis B45 vaccines) or from the societal perspective (eg, pneumococcal conjugate vaccine36). Because few children die as a result of rotavirus disease in the United
States, the vaccine is currently a very expensive child-
hood vaccine for preventing death, even in comparison
with recently introduced vaccines ($197 000 per life-
year saved from the societal perspective, compared with
$80 000 per life-year saved for pneumococcal conjugate
coccal vaccine$46 and $121 000 per life-year saved for meningococcal vaccine$47). However, rotavirus vaccination may
still be a cost-effective intervention. Although compari-
sion of cases of different disease should be performed
with care, the costs per case of rotavirus averted ($138)
and per serious case averted ($263) are comparable to the
cost-effectiveness of pneumococcal conjugate vac-
teritis during eight years of study. J Clin Microbiol. 1983;
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nal study in hospitals, emergency departments, pediatric prac-
tices and child care centers during the winter rotavirus
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rotavirus diarrhea in the United States: surveillance and esti-
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78–82
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associated with rotavirus infection among children in New
808–814
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RC, Glass RI. Cost of diarrhea-associated hospitalizations and
outpatient visits in an insured population of young children in
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Pickering LK. Costs associated with office visits for diarrhea in
*J Paediatr Child Health.* 1997;33:157–160
44. Newman RD, Grupp-Phelan J, Shay DK, Davis RL. Perinatal risk factors for infant hospitalization with viral gastroenteritis. *Pediatrics.* 1999;103(1). Available at: www.pediatrics.org/cgi/content/full/103/1/e3
## APPENDIX 1. ESTIMATION OF PROPORTION OF GASTROENTERITIS EVENTS ATTRIBUTABLE TO ROTAVIRUS FOR EACH HEALTH CARE OUTCOME

### TABLE A1  Number of Cases of Gastroenteritis Among Children <5 Years of Age With Different Health Care Outcomes per Year (1993–2002)

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospitalization (NHDS)</th>
<th>Emergency Department (NHAMCS)</th>
<th>Hospital Outpatient (NHAMCS)</th>
<th>Physician Office (NAMCS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (No. of Cases)</td>
<td>SE</td>
<td>Mean (No. of Cases)</td>
<td>SE</td>
</tr>
<tr>
<td>1993</td>
<td>170 906</td>
<td>20 100</td>
<td>810 694</td>
<td>97 339</td>
</tr>
<tr>
<td>1994</td>
<td>189 815</td>
<td>22 600</td>
<td>843 033</td>
<td>92 320</td>
</tr>
<tr>
<td>1995</td>
<td>188 084</td>
<td>20 000</td>
<td>738 680</td>
<td>93 534</td>
</tr>
<tr>
<td>1996</td>
<td>184 684</td>
<td>18 200</td>
<td>908 600</td>
<td>138 137</td>
</tr>
<tr>
<td>1997</td>
<td>193 743</td>
<td>21 000</td>
<td>705 844</td>
<td>108 325</td>
</tr>
<tr>
<td>1998</td>
<td>171 126</td>
<td>20 000</td>
<td>630 046</td>
<td>87 445</td>
</tr>
<tr>
<td>1999</td>
<td>203 691</td>
<td>20 100</td>
<td>667 461</td>
<td>100 278</td>
</tr>
<tr>
<td>2000</td>
<td>171 984</td>
<td>20 800</td>
<td>627 951</td>
<td>80 625</td>
</tr>
<tr>
<td>2001</td>
<td>198 892</td>
<td>21 300</td>
<td>819 317</td>
<td>96 697</td>
</tr>
<tr>
<td>2002</td>
<td>167 625</td>
<td>19 200</td>
<td>749 745</td>
<td>154 553</td>
</tr>
</tbody>
</table>

NHDS indicates National Hospital Discharge Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey; NAMCS, National Ambulatory Medical Care Survey.

### TABLE A2  Values Used to Determine Distribution of Rotavirus Positivity Rates per Health Care Outcome

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>Data Source</th>
<th>Proportion of Outcome Positive for Rotavirus, %</th>
<th>Fitted Distribution</th>
<th>Proportion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Annual data from 1 prospective study over 8 y10</td>
<td>39, 44, 30, 39, 30, 38, 34, 29</td>
<td>β general</td>
<td>36</td>
</tr>
<tr>
<td>Emergency department visit</td>
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<td></td>
<td>Uniform</td>
<td>28</td>
</tr>
<tr>
<td>Physician Office</td>
<td>Six separate studies11-16</td>
<td>12, 17, 22, 16, 29, 21</td>
<td>β general</td>
<td>20</td>
</tr>
</tbody>
</table>

* Range is minimum to maximum.
APPENDIX 2. DISTRIBUTIONS OF PERCENT OF GASTROENTERITIS-RELATED MEDICAL VISITS ATTRIBUTABLE TO ROTAVIRUS

FIGURE A1
Distribution of percentage of gastroenteritis hospitalizations attributable to rotavirus, based on data from Brandt et al.\(^{10}\) (fitted curve and actual data). Fitted curve is drawn using the following $\beta$ functional form: $f(x) = \frac{(x - \alpha_1)(1 - x)\alpha_2}{\beta(\alpha_1, \alpha_2)}$, where $\beta(\alpha_1, \alpha_2) = \int_0^1 t^{\alpha_1 - 1}(1 - t)^{\alpha_2 - 1}dt$ where $\alpha_1 = 30.7253$, $\alpha_2 = 55.7225$, and range $0 \leq x \leq 1$. Descriptive statistics, as percent gastroenteritis hospitalizations attributable to rotavirus (fitted curve, actual data): minimum (0%, n/a); maximum (100%, n/a); mean (35.54%, 35.54%); mode (35.2%, 30.17%); median (35.4%, 36.30%); standard deviation (5.12%, 5.11%); variance (0.26%, 0.27%). Goodness-of-fit statistic (value, $P$ value): $\chi^2 (0, 1.00)$.

FIGURE A2
Distribution of percentage of gastroenteritis outpatient and non–emergency department visits attributable to rotavirus, based on data from various sources.\(^{11-16}\) (fitted curve and actual data). Fitted curve is drawn using the $\beta$ functional form (for form, see Figure A1 footnote), where $\alpha_1 = 10.6792$, $\alpha_2 = 44.0728$, and range $0 \leq x \leq 1$. Descriptive statistics, as percent of gastroenteritis outpatient and non–emergency department visits attributable to rotavirus (fitted curve, actual data): minimum (0%, n/a); maximum (100%, n/a); mean (19.51%, 19.5%); mode (18.35%, 15.83%); median (19.13%, 19.0%); standard deviation (5.31%, 5.89%); variance (0.28%, 0.29%). Goodness-of-fit statistic (value, $P$ value): $\chi^2 (0, 1.00)$. 
## APPENDIX 3. COSTS OF GASTROENTERITIS AND INTUSSUSCEPTION


<table>
<thead>
<tr>
<th>Place of Service</th>
<th>Year</th>
<th>Costs, $</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
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<tr>
<td><strong>Inpatient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>2000</td>
<td>3836</td>
<td>3082</td>
<td>6120</td>
<td>221</td>
</tr>
<tr>
<td>Hospital</td>
<td>2001</td>
<td>3654</td>
<td>2882</td>
<td>3023</td>
<td>306</td>
</tr>
<tr>
<td>Hospital</td>
<td>2002</td>
<td>3354</td>
<td>2763</td>
<td>2440</td>
<td>307</td>
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<tr>
<td>Hospital</td>
<td>2003</td>
<td>3446</td>
<td>2756</td>
<td>2682</td>
<td>500</td>
</tr>
<tr>
<td>Hospital</td>
<td>2000–2003</td>
<td>3537</td>
<td>2865</td>
<td>3516</td>
<td>1334</td>
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<td><strong>Outpatient</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>2000–2003</td>
<td>1031</td>
<td>702</td>
<td>914</td>
<td>163</td>
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<tr>
<td>Office</td>
<td>2000–2003</td>
<td>68</td>
<td>58</td>
<td>45</td>
<td>277</td>
</tr>
<tr>
<td>Outpatient hospital</td>
<td>2000–2003</td>
<td>808</td>
<td>567</td>
<td>902</td>
<td>375</td>
</tr>
<tr>
<td>All settings</td>
<td>2000–2003</td>
<td>601</td>
<td>245</td>
<td>833</td>
<td>815</td>
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</table>

Values are given in 2004 US dollars.


<table>
<thead>
<tr>
<th>Place of Service</th>
<th>Year</th>
<th>Costs, $</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>2000</td>
<td>4898</td>
<td>2968</td>
<td>11 909</td>
<td>990</td>
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<tr>
<td>Hospital</td>
<td>2001</td>
<td>7663</td>
<td>2836</td>
<td>44 828</td>
<td>1261</td>
</tr>
<tr>
<td>Hospital</td>
<td>2002</td>
<td>5597</td>
<td>2611</td>
<td>26 774</td>
<td>1306</td>
</tr>
<tr>
<td>Hospital</td>
<td>2003</td>
<td>4486</td>
<td>2667</td>
<td>12 881</td>
<td>1903</td>
</tr>
<tr>
<td>Hospital</td>
<td>2000–2003</td>
<td>5560</td>
<td>2751</td>
<td>26 836</td>
<td>5460</td>
</tr>
<tr>
<td><strong>Outpatient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>2000–2003</td>
<td>467</td>
<td>310</td>
<td>549</td>
<td>10 975</td>
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<tr>
<td>Office</td>
<td>2000–2003</td>
<td>74</td>
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<td>63</td>
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<td>Outpatient hospital</td>
<td>2000–2003</td>
<td>357</td>
<td>190</td>
<td>600</td>
<td>16 563</td>
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<tr>
<td>All settings</td>
<td>2000–2003</td>
<td>140</td>
<td>64</td>
<td>297</td>
<td>137 241</td>
</tr>
</tbody>
</table>

See “Methods” for codes used. Values are given in 2004 US dollars.

### Table A5 Costs of Intussusception Events Coded With ICD-9-CM Code 560.00 (2000–2003)

<table>
<thead>
<tr>
<th>Place of Service</th>
<th>Year</th>
<th>Costs, $</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impatient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>2000</td>
<td>12 458</td>
<td>3395</td>
<td>27 688</td>
<td>33</td>
</tr>
<tr>
<td>Hospital</td>
<td>2001</td>
<td>19 254</td>
<td>6790</td>
<td>35 723</td>
<td>22</td>
</tr>
<tr>
<td>Hospital</td>
<td>2002</td>
<td>7861</td>
<td>7367</td>
<td>5660</td>
<td>19</td>
</tr>
<tr>
<td>Hospital</td>
<td>2003</td>
<td>6558</td>
<td>3747</td>
<td>6976</td>
<td>37</td>
</tr>
<tr>
<td>Hospital Outpatient</td>
<td>2000–2003</td>
<td>11 051</td>
<td>4263</td>
<td>22 592</td>
<td>111</td>
</tr>
<tr>
<td>Office</td>
<td>2000–2003</td>
<td>99</td>
<td>65</td>
<td>110</td>
<td>43</td>
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<tr>
<td>Outpatient hospital</td>
<td>2000–2003</td>
<td>723</td>
<td>310</td>
<td>1332</td>
<td>81</td>
</tr>
<tr>
<td>All settings</td>
<td>2000–2003</td>
<td>899</td>
<td>227</td>
<td>1539</td>
<td>156</td>
</tr>
</tbody>
</table>

Values are given in 2004 US dollars.
APPENDIX 4. SENSITIVITY ANALYSIS

FIGURE A3
Tornado graph, demonstrating relative importance of model inputs at US $100 and $217 per vaccine recipient. It should be noted that no distribution was included for days off work; therefore, this input was not included but varied separately. ER indicates emergency department; ORT, oral rehydration therapy.
ARTICLE

Parental Knowledge About Antibiotic Use: Results of a Cluster-Randomized, Multicommunity Intervention

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. The goal was to determine the impact of a community-wide educational intervention on parental misconceptions likely contributing to pediatric antibiotic overprescribing.

METHODS. We conducted a cluster-randomized trial of a 3-year, community-wide, educational intervention directed at parents of children <6 years of age in 16 Massachusetts communities to improve parental antibiotic knowledge and attitudes and to decrease unnecessary prescribing. Parents in 8 intervention communities were mailed educational newsletters and exposed to educational materials during visits to local pediatric providers, pharmacies, and child care centers. We compared responses from mailed surveys in 2000 (before the intervention) and 2003 (after the intervention) for parents in intervention and control communities. Analyses were performed on the individual level, clustered according to community.

RESULTS. There were 1106 (46%) and 2071 (40%) respondents to the 2000 and 2003 surveys, respectively. Between 2000 and 2003, the proportion of parents who answered ≥7 of 10 knowledge questions correctly increased significantly in both intervention (from 52% to 64%) and control (from 54% to 61%) communities. We did not detect a significant intervention impact on knowledge regarding appropriate antibiotic use in the population overall. In a subanalysis, we did observe a significant intervention effect among parents of Medicaid-insured children, who began with lower baseline knowledge scores.

CONCLUSIONS. Although knowledge regarding appropriate use of antibiotics is improving without additional targeted intervention among more socially advantaged populations, parents of Medicaid-insured children may benefit from educational interventions to promote judicious antibiotic use. These findings may have implications for other health education campaigns.

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doi:10.1542/peds.2006-2600

Key Words
antibiotic use, parent education, randomized, prospective trial

Abbreviations
OR—odds ratio
CI—confidence interval

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HIGH RATES OF antibiotic use by young children have contributed to the increase in antibiotic-resistant infections in the community.\(^1\) Among *Streptococcus pneumoniae*, the most common bacterial cause of otitis media, meningitis, and pneumonia in young children, 20% to 33% of isolates are no longer susceptible to penicillin\(^4\)–\(^7\) and 14% to 20% are not susceptible to ≥3 antibiotic classes.\(^5\)\(^6\) A substantial portion of prescribed antibiotics is considered nonessential,\(^8\)–\(^10\) and such prescribing has been attributed partially to parental pressure (real or perceived) on physicians for antibiotic prescriptions.\(^11\)\(^12\) One half of pediatric providers report frequent parental pressure to prescribe antibiotics that are not indicated.\(^11\)–\(^13\) In one survey, one third of physicians reported recently providing an unnecessary antibiotic in response to parental demand.\(^13\) Although education of pediatric providers is needed to reduce perceived parental pressure when none is intended,\(^14\)\(^15\) parental education remains necessary to reduce widespread misconceptions about the nature of respiratory tract illnesses and the benefits of antibiotic treatment.

Several studies have revealed widespread misconceptions among parents about the treatment of common pediatric respiratory illnesses.\(^12\)\(^16\)–\(^18\) We surveyed parents to evaluate baseline knowledge of antibiotics\(^19\) before initiation of an educational intervention as part of a cluster-randomized trial in 16 Massachusetts communities to reduce unnecessary prescribing of antibiotics for young children.\(^20\) That survey, conducted in 2000, found widespread misconceptions, including a majority of parents thinking that antibiotics are needed to treat green nasal discharge, uncomplicated cough illness, and “bronchitis,” despite the fact that these illnesses are almost always caused by viruses and resolve without therapy. It also found significantly less knowledge about antibiotic indications among parents of Medicaid-insured children, compared with commercially insured children. Previous randomized trials of educational interventions to promote antibiotic knowledge assessed the impact of education on antibiotic prescribing rates\(^21\)–\(^23\) or parental satisfaction\(^24\) but not parental knowledge. One nonrandomized, community-level study found a significant improvement in parental knowledge after a 1997 educational intervention in Wisconsin.\(^25\) We sought to measure whether a cluster-randomized, multicommunity, educational intervention regarding judicious antibiotic use improved parental knowledge of antibiotic indications for young children.

We report the results of a follow-up survey conducted in 2003 in the same 16 communities. Our cluster-randomized, controlled intervention involved parent and physician educational campaigns to reduce unnecessary antibiotic use in 8 of 16 communities.\(^20\) The cluster-randomized, controlled design enabled us to assess the impact of the community-level educational intervention on parental misconceptions and to describe the secular trends in parental knowledge related to respiratory tract infections and antibiotic use. Our analysis included assessment of the impact on the population overall and particularly among Medicaid-insured families, whose baseline knowledge regarding these topics was lower.

**METHODS**

**Study Design**

The 16 Massachusetts communities were selected for the trial on the basis of geographic separation, evidence that few children crossed community boundaries to seek pediatric care, and diversity of size and demographic characteristics based on US Census data.\(^26\) Communities were dichotomized into small and large towns, paired according to a composite of percentage of Medicaid and percentage of racial minority residents (based on US Census 1990 data), and randomized in pairs to intervention or control status by using a computer routine (SAS Institute, Cary, NC).

Eight of the 16 Massachusetts communities received an educational intervention (REACH Mass) to increase knowledge of antibiotic use and to reduce unnecessary prescribing. The intervention occurred through 3 successive cold and flu seasons, from September 2000 through March 2003. Parental education in the intervention communities included 6 mailed newsletters highlighting misconceptions regarding upper respiratory illness, appropriate use of analgesics and antibiotics, and the approach of initial observation without antibiotics (“watchful waiting”) for mild ear infections in low-risk patients.\(^24\) Parents were also exposed to educational materials (stickers, posters, pamphlets, and fact sheets) in waiting rooms of local pediatric providers, pharmacies, and child care centers in intervention communities.

Similar to the preintervention parent survey in 2000,\(^19\) we mailed postintervention surveys in 2003 to randomly selected households with children <6 years of age who were insured by 4 collaborating health plans, namely, Harvard Pilgrim Health Care, Blue Cross Blue Shield of Massachusetts, Tufts Health Plan, and Mass Health (the Massachusetts Medicaid program). Addresses were limited to the zip code areas of 16 Massachusetts communities.

The number of mailings was increased in 2003 on the basis of the response rate for the preintervention survey,\(^19\) with the goal of achieving 100 respondents per community. Health plan enrollment files were sampled randomly to select addresses for ~200 commercially insured patients and 150 Medicaid-insured patients from each community. Medicaid-insured families were oversampled to allow for specific assessment of this subpopulation and to account for a lower expected response rate. In this repeated cross-sectional design, no attempt was made to survey (or to exclude from surveying) the same individuals in the 2 time periods or to ensure that re-
spondents had been exposed to intervention activities or materials. In May 2003, 5580 surveys were mailed, accompanied by a letter that described the research study and offered a children’s book as an incentive to participate. Respondent identity was not recorded, and response to the survey was assumed to imply consent to participate. In June and July 2003, 2 additional survey mailings were sent to nonresponders. The study was conducted with approval of the institutional review board of Harvard Pilgrim Health Care.

Survey Instrument, Outcome Measures, and Analysis

Identical survey items were used in 2000 and 2003, with many adapted from 2 previously published studies. Questions were targeted for a seventh-grade reading level but included some medical language in specific questions assessing how respondents interpret medical terminology commonly used in public settings (eg, virus, bacteria, and antibiotics). Eight of 10 knowledge questions focused on the role of antibiotics for specific childhood upper respiratory illnesses, and 2 focused on the difference between viral and bacterial infections. Respondents were instructed to answer the questions by assuming that the child had the described symptoms for 3 to 5 days. Acceptable responses were adapted from the Centers for Disease Control and Prevention/American Academy of Pediatrics principles for judicious antibiotic use.

Three additional items were used to assess the proclivity of parents to demand antibiotics. We calculated the percentages of correct responses to each of the 10 antibiotic knowledge questions and the percentages of affirmative responses to the 3 antibiotic demand questions in 2000 and 2003, stratified by intervention and control communities. Differences within each question were evaluated with χ² tests. We evaluated the proportion of parents with a high level of antibiotic knowledge by using an a priori threshold-based knowledge score of ≥7 of 10 questions correct. We also assessed the proportion of parents with a tendency to demand antibiotics by using a threshold of ≥1 of 3 questions answered affirmatively. Secular trends in threshold-based scores were evaluated by using 2-sample tests of binomial proportions. Because these thresholds were selected arbitrarily, we also performed an evaluation of the change in mean scores after the intervention. Finally, we performed the single subanalysis of parents of Medicaid-insured children (versus commercially insured children) as the postintervention correlate to the previously published baseline data on parental antibiotic knowledge.

To test the impact of the educational intervention on parental knowledge and demand beyond secular trends, we conducted multivariate analyses of individual responses, accounting for clustering within communities and adjusting for baseline parental knowledge in each community. We also assessed additional parent (age, race, employment, and education) and child (age, Medicaid status, and group child care participation) variables as potential confounders. Models were restricted to parent responders. The impact of the intervention was determined by using mixed-effects regression models (GLIMMIX macro and PROC MIXED in SAS, version 8.2; SAS Institute, Cary, NC). Stratified analyses were performed to assess different educational effects among parents of Medicaid-insured versus commercially insured children.

RESULTS

Response Rates

Of 5580 surveys mailed in 2003, 452 were excluded (266 for incorrect address, 128 for child age outside the intended age range, and 58 for nonparent respondent). Of the remaining 5128 surveys, 2071 (40%) were returned, similar to the 46% response rate in 2000 (n = 1106). Response rates were similar in control (median: 37%; range: 31%–43%) and intervention (median: 40%; range: 24%–44%) communities. Overall, Medicaid enrollees had a lower response rate, compared with commercial plan enrollees (25% vs 50% in 2003; P < .01). The majority of respondents were white mothers, 31 to 40 years of age, who had received some college education (Table 1). No substantial demographic differences were seen between respondents from control and intervention communities in either 2000 or 2003. Parents of Medicaid-insured children were, on average, more likely to be younger, to be nonwhite, and to have less formal education.

Secular Trends

Although large proportions of incorrect responses persisted for certain questions between the 2000 and 2003 surveys, there were several questions for which the proportions of correct responses increased substantially in control communities, which suggested secular trends toward improved knowledge without intervention (Table 2). For example, 18% in 2000 knew that green nasal discharge was not an antibiotic indication, compared with 31% in 2003 (P < .001). Substantial improvements in the percentage correct were seen for items on middle ear fluid (41% in 2000 vs 50% in 2003; P < .001) and the general question of whether antibiotics were needed for colds and flu (66% in 2000 vs 77% in 2003; P < .001). In control communities, the mean number of knowledge items answered correctly increased from 6.2 to 6.7 (P < .001), and the proportion with correct answers to ≥7 items increased from 54% in 2000 to 61% in 2003 (P < .01) (Table 3). Despite these improvements, we noted that most parents still thought that antibiotics were indicated for middle ear fluid and runny nose/green nasal discharge. There was less improvement in knowledge regarding bronchitis and whether colds are caused by viruses or bacteria. As in 2000, the majority of
Parents knew whether antibiotics should be prescribed for sore throat, strep throat, and ear infections (Table 2). Parents of Medicaid-insured children had significantly lower antibiotic knowledge, compared with parents of commercially insured children, on the basis of the mean number of items answered correctly and the proportion answering \[7/10\] items correctly at baseline \((P < .001)\) (Table 3). Furthermore, there was no increase in antibiotic knowledge between 2000 and 2003 among parents of Medicaid-insured children in control communities \((42\% \text{ answered } 7/10\text{ correct responses in 2000, compared with } 43\% \text{ in 2003})\). Conversely, parents of commercially insured children in control communities had higher knowledge scores in 2003, compared with 2000 \((58\% \text{ with } 7/10\text{ correct responses in 2000, compared with } 64\% \text{ in 2003; } P < .0001)\). However, as noted above, control communities also showed significantly higher knowledge scores in 2003, compared with 2000 \((54\% \text{ with } 7/10\text{ correct responses in 2000, compared with } 61\% \text{ in 2003})\). When controlling for baseline knowledge scores and additional parent and child characteristics in multivariate models that accounted for community clustering, we found no overall intervention effect (Table 4).

There was also no intervention effect on mean knowledge scores of intervention communities when compared with control communities \((\text{mean score improvement: } 0.1 \text{ questions; 95\% confidence interval [CI]: } -0.2 \text{ to } 0.4 \text{ questions})\) in similar multivariate models. In general, parents who were college graduates, were older, were white, were nonworking, or had a commercially insured child who was \(\geq 12\) months of age were significantly more likely to answer \(\geq 7\) of the 10 questions correctly. There was no intervention effect for items designed to measure proclivity to demand antibiotics.

### TABLE 1 Characteristics of Parent Respondents in 2000 and 2003, According to Randomization Arm and Child’s Insurance Status

<table>
<thead>
<tr>
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<th>Study Year and Randomization Arm</th>
<th>Insurance Status*</th>
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<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
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<tr>
<td>No.</td>
<td>534</td>
<td>537</td>
</tr>
<tr>
<td>Parent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother, %</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>Age, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;30\text{y})</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>(31-40\text{y})</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>(&gt;40\text{y})</td>
<td>10</td>
<td>16b</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>90</td>
<td>86</td>
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<tr>
<td>Black</td>
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<td>1</td>
</tr>
<tr>
<td>Hispanic</td>
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<td>4b</td>
</tr>
<tr>
<td>Other</td>
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<td>8</td>
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<tr>
<td>Education, %</td>
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<td></td>
</tr>
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<td>Less than high school</td>
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<td>4</td>
</tr>
<tr>
<td>College graduate</td>
<td>47</td>
<td>39b</td>
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<tr>
<td>High school graduate, some college</td>
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<td>57b</td>
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<tr>
<td>Employed, %</td>
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<td>66b</td>
</tr>
<tr>
<td>Child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>3.3 ± 1.6</td>
<td>3.3 ± 1.6</td>
</tr>
<tr>
<td>Female, %</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>In child care, %</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Healthy self-report, %c</td>
<td>86</td>
<td>91b</td>
</tr>
<tr>
<td>Medicaid-insured, %</td>
<td>27</td>
<td>25</td>
</tr>
</tbody>
</table>

* Medicaid and non-Medicaid categories include children from both intervention and control communities in both survey years.

\(b P < .05\), comparing intervention and control groups within survey year.

\(c\) Parent respondent reported child as having very good or excellent health.

### Intervention Impact

A total of 171 respondents (17\%) recalled the REACH intervention by name as a source of information regarding antibiotic use, among those surveyed in intervention communities in 2003. At baseline, there was no difference in the proportions of parents answering \(\geq 7\) of 10 questions correctly between control and intervention communities (Table 3). Among intervention communities, we found significantly higher knowledge scores in 2003, compared with 2000 (52\% with \(\geq 7\) of 10 correct responses in 2000, compared with 64\% in 2003; \(P < .0001\)). However, as noted above, control communities also showed significantly higher knowledge scores in 2003, compared with 2000 (54\% with \(\geq 7\) of 10 correct responses in 2000, compared with 61\% in 2003; \(P < .01\)). When controlling for baseline knowledge scores and additional parent and child characteristics in multivariate models that accounted for community clustering, we found no overall intervention effect (Table 4). There was also no intervention effect on mean knowledge scores of intervention communities when compared with control communities (mean score improvement: 0.1 questions; 95\% confidence interval [CI]: −0.2 to 0.4 questions) in similar multivariate models. In general, parents who were college graduates, were older, were white, were nonworking, or had a commercially insured child who was \(\geq 12\) months of age were significantly more likely to answer \(\geq 7\) of the 10 questions correctly. There was no intervention effect for items designed to measure proclivity to demand antibiotics.
Medicaid Subanalysis: Secular Trend and Intervention Impact

In contrast to the lack of an overall intervention effect, the data showed a significant intervention impact among parents of Medicaid-insured children. In intervention communities, the proportion of parents of Medicaid-insured children who met this threshold did not change in control communities (42% and 43% in 2001 and 2003, respectively). The mean number of correct responses increased from 5.6 questions to 6.3 questions in intervention communities (P = .001) and from 5.5 questions to 5.9 questions in control communities (not significant). In adjusted models accounting for community clustering (Table 4), exposure to the educational intervention increased the proportion of parents of Medicaid-insured children who had a high degree of antibiotic knowledge (adjusted odds ratio [OR]: 2.2; 95% CI: 1.1–4.5; P = .03), although there was no significant intervention effect when mean knowledge scores were evaluated in the same population (mean score improvement: 0.3 points; 95% CI: −0.3 to 0.9 points; P = .3).

After finding the selective impact of our intervention among parents of Medicaid-insured children, we sought to identify demographic or educational explanatory variables for which Medicaid insurance coverage could be a surrogate. Parents of Medicaid-insured children were

---

**TABLE 2** Responses to Parent Survey Questions

<table>
<thead>
<tr>
<th>Acceptable/Affirmative Responsesa</th>
<th>Proportion With Acceptable/Affirmative Response, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total knowledge</td>
<td></td>
</tr>
<tr>
<td>1. How often are antibiotics needed for middle ear fluid?</td>
<td>Sometimes or almost never</td>
</tr>
<tr>
<td>2. How often are antibiotics needed for deep cough or bronchitis?</td>
<td>Almost never</td>
</tr>
<tr>
<td>3. How often are antibiotics needed for colds or flu?</td>
<td>Almost never</td>
</tr>
<tr>
<td>4. How often are antibiotics needed for runny nose or green nasal drainage?</td>
<td>Almost never</td>
</tr>
<tr>
<td>5. How often are antibiotics needed for sore throat?</td>
<td>Sometimes or almost never</td>
</tr>
<tr>
<td>6. How often are antibiotics needed for strep throat?</td>
<td>Almost always</td>
</tr>
<tr>
<td>7. How often are antibiotics needed for ear infection?</td>
<td>Sometimes or almost always</td>
</tr>
<tr>
<td>8. If my child does not receive an antibiotic for cold, cough, and flu symptoms, he/she will be sick for a longer time.</td>
<td>Disagree or strongly disagree</td>
</tr>
<tr>
<td>9. Are antibiotics helpful in treating bacterial infections, viral infection, or both?</td>
<td>Bacterial</td>
</tr>
<tr>
<td>10. Are most cold, cough, and flu illnesses caused by bacteria or viruses?</td>
<td>Viruses</td>
</tr>
</tbody>
</table>

**Demand questions**

1. If I expect an antibiotic, I am less satisfied with the doctor visit if I do not receive one.
2. I would rather give my child an antibiotic that may not be needed than wait to see if he/she gets better without it.
3. If a doctor does not prescribe an antibiotic when I think one is needed, I will take my child to another doctor.

Response rates for individual questions ranged from 96% to 99%.

a Acceptable responses for total knowledge; affirmative responses for demand questions.

---

**TABLE 3** Scores Measuring Antibiotic Knowledge in 2000 and 2003

<table>
<thead>
<tr>
<th>Proportion With ≥7 of 10 Knowledge Questions Correct, %</th>
<th>Crude OR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>34</td>
</tr>
<tr>
<td>Non-Medicaid</td>
<td>58</td>
</tr>
</tbody>
</table>

Analyses were restricted to respondents with a sufficient number of answered questions for score calculation.

a Controlling only for survey year and community intervention/control status.

b P < .05.
more likely to be younger, to be nonwhite, to be less educated, to be a stay-at-home parent, and to have an older child, compared with parents of commercially insured children. Accounting for these additional predictors in the multivariate model for the total cohort reduced the magnitude of the negative association of Medicaid insurance with higher knowledge scores by approximately one half (unadjusted OR: 0.4; 95% CI: 0.3–0.5; adjusted OR: 0.7; 95% CI: 0.6–0.8).

DISCUSSION

We found that a 3-year, multifaceted, educational intervention that targeted parents, physicians, pharmacies, and large group child care centers did not improve overall community-level parental knowledge about antibiotics beyond the noted secular trend. However, there was a significant selective intervention effect in increasing the proportion of parents of Medicaid-insured children with a high level of antibiotic knowledge.

The lack of an overall intervention effect might be attributable to concurrent national and regional efforts to increase knowledge about antibiotic prescribing for children by the Centers for Disease Control and Prevention, professional medical organizations, and state-based coalitions. During the intervention phase, the National Committee for Quality Assurance released drafts of 2 Health Plan Employer Data and Information Set measures focusing on appropriate antibiotic prescribing for children with upper respiratory infection and pharyngitis. These performance measures were adopted formally for health plan reporting in 2004. Private organizations also have served as clearinghouses for information on antibiotic resistance. Complementing these efforts, or perhaps of greater importance, has been the attention of the lay press given to the issue of antibiotic resistance, often framed in dramatic terms, such as the emergence of “superbugs.” The significant increase in knowledge regarding antibiotic indications between the survey years among the control communities supports this explanation.

Despite the lack of an overall effect in these communities, the intervention had a significant impact on parents of Medicaid-insured children. Fewer parents of Medicaid-insured children had a high level of antibiotic knowledge at baseline, and there was evidence of a much smaller secular trend of increased knowledge among those respondents. The lower baseline percentage of parents of Medicaid-insured children with high antibiotic knowledge levels and the lack of secular improvement over time may be indicative of limited access to health-related information from other sources. These results highlight the possible additional benefit of focusing health education resources on Medicaid-insured families even in the presence of more global public health campaigns. Our direct-to-consumer mailings might have provided some Medicaid families with their first exposure to information related to antibiotic indications and clarification of common parental misconceptions, compared with other families, who might have received these messages through other channels. In addition, the larger proportion of parents of Medicaid-insured children who had a low level of antibiotic knowledge at baseline might have enhanced our ability to produce and to detect a significant intervention impact.

Medicaid insurance is a surrogate for other socioeconomic variables that may explain lower antibiotic knowledge. Although Medicaid insurance remained significant after adjustment for potential confounders such as parental age, education, and nonwhite race, we did not measure other important variables (such as literacy or income) that might explain the residual association of lower knowledge scores with Medicaid insurance. Future work in this area is important, because public health education should be targeted to those most likely to benefit. Although the source of health insurance per se

### TABLE 4 Multivariate Models Evaluating Parental Knowledge of Antibiotics

<table>
<thead>
<tr>
<th>Knowledge (≥7 of 10 items correct)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cohort</td>
</tr>
<tr>
<td>Year of survey (2003 vs 2000) among control communities</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Parent characteristics</td>
<td></td>
</tr>
<tr>
<td>Age of &gt;30 y</td>
<td>1.5 (1.2–1.8)</td>
</tr>
<tr>
<td>White race</td>
<td>1.8 (1.4–2.3)</td>
</tr>
<tr>
<td>College graduate</td>
<td>2.1 (1.8–2.6)</td>
</tr>
<tr>
<td>Employed</td>
<td>0.8 (0.7–1.0)</td>
</tr>
<tr>
<td>Child characteristics</td>
<td></td>
</tr>
<tr>
<td>Age of ≥12 mo</td>
<td>1.7 (1.2–2.4)</td>
</tr>
<tr>
<td>Group child care</td>
<td>1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>Medicaid-insured</td>
<td>0.7 (0.6–0.8)</td>
</tr>
<tr>
<td>Intervention effect*</td>
<td>1.2 (0.8–1.7)</td>
</tr>
</tbody>
</table>

The knowledge outcome was based on answering ≥7 of 10 survey questions correctly. The model was limited to parent responders. NA indicates not applicable.

* The effect was measured as an interaction term between intervention/control status and time.
is not an attribute that affects health-related knowledge directly, it may be an administratively simple way to identify a population more likely to benefit from targeted educational campaigns. It was not possible for us to identify whether a specific component of the educational intervention (parent mailings, Web site, or pharmacy/child care/clinic materials) was responsible for improvements in antibiotic knowledge or whether the multifaceted approach was needed.

Despite improvements in parental knowledge, frequent misconceptions related to antibiotics persist. In 2003, 30% of parents still thought that antibiotics treated viral illnesses, 70% thought that antibiotics were needed for green nasal discharge, and 90% thought that antibiotics were needed for cough illnesses. It is possible that such misconceptions will continue to diminish over time, although we think that additional concerted efforts to reduce misconceptions will continue to be necessary, particularly for less-advantaged populations. Reducing antibiotic-related misconceptions may improve a component of antibiotic overprescribing. A parent’s request for information or reassurance about the natural history of an illness is often perceived by physicians as pressure for antibiotics. Increased understanding of the uses and misuses of antibiotics may improve physician-parent discussions and prevent unnecessary prescribing. In fact, the frequency of antibiotic prescribing is declining.

Studies evaluating US antibiotic use for children demonstrated a 40% decline in antibiotic prescriptions per 1000 children per year, which likely reflects information reaching prescribers and parents through a number of complementary channels.

There are several limitations to this study. Survey respondents (40% of those receiving mailings) might be more likely than others to be concerned about antibiotic overprescribing. In addition, the lower response rate for parents of Medicaid-insured children might have limited the representativeness of our sample; use of lower-literacy questions, a multilanguage questionnaire, or a small financial incentive might have increased the response rate to that seen for parents of commercially insured children. Although similarly low response rates for mailed surveys have been reported for Medicaid populations, we acknowledge that our findings are based on a minority (25%) of respondents and might not reflect improvement in antibiotic knowledge throughout the Medicaid population. Nevertheless, because this was a randomized trial and response rates were similar among intervention and control communities, we would not expect any differential bias in the determination of intervention effects.

A second explanation for the lack of an overall intervention effect might be our cross-sectional survey design. Because we did not collect identifiers from the parents surveyed, our analysis was not based on survey responses from the same parents before and after the intervention. This meant that we could report only community-level changes, rather than improvements on an individual level. If there was substantial flux into or out of our intervention communities, then the postintervention survey might reflect respondents who were not in the community at the time of the REACH intervention. Families of the youngest children would not have received the entire 3-year intervention. Nevertheless, the goal of this community-level campaign was to change antibiotic-related knowledge and attitudes of whole communities. The analysis reported here, although conservative, is most consistent with that goal.

In addition, when interpreting the intervention effect in improving knowledge among parents of Medicaid-insured children, we cannot comment on the actual clinical impact of a 17% increase in parents with high antibiotic knowledge levels or a twofold increase in the odds of answering 7 of 10 antibiotic-related questions correctly. Whether this increase in knowledge translates to shorter physician visits or decreased inappropriate antibiotic use will need to be studied further.

CONCLUSIONS
We report both a significant secular trend toward increased knowledge of appropriate antibiotic use among parents of young children in multiple communities and a substantial effect of a concerted educational campaign in increasing knowledge of antibiotic indications among Medicaid-insured families. Had we conducted this study in the absence of control communities, we would have concluded that the intervention had a large, successful, community-wide impact on knowledge across the study period. Instead, multivariate models accounting for baseline knowledge and secular trends revealed no significant effect of the intervention on knowledge scores over and above secular changes in similar control communities. Such community-wide education campaigns to improve health-related knowledge may still be useful for other health issues for which fewer alternative sources of information exist. Even in the context of ongoing public education, this trial supports targeted intervention for families of Medicaid-insured children, who may not receive messages distributed through other channels. Strategies for delivering key public health messages must be adjusted to reach the diverse populations within a single community effectively.

ACKNOWLEDGMENTS
This work was supported by the US Agency for Healthcare Research and Quality (grant HS 10247).

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Reduction of Frequent Otitis Media and Pressure-Equalizing Tube Insertions in Children After Introduction of Pneumococcal Conjugate Vaccine

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Departments of Pediatrics, Preventive Medicine, Biostatistics, and Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; Department of Pediatrics and Strong Children’s Research Center, University of Rochester School of Medicine and Dentistry, Rochester, New York; National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

The authors have indicated they have no financial relationships related to this article to disclose.

ABSTRACT

OBJECTIVE. *Streptococcus pneumoniae* is an important cause of otitis media in children. In this study we estimated the effect of routine childhood immunization with heptavalent pneumococcal conjugate vaccine on frequent otitis media (3 episodes in 6 months or 4 episodes in 1 year) and pressure-equalizing tube insertions.

PATIENTS AND METHODS. The study population included all children who were enrolled at birth in TennCare or selected upstate New York commercial insurance plans as of July 1998 and continuously followed until 5 years old, loss of health plan enrollment, study outcome, or end of the study. We compared the risk of developing frequent otitis media or having pressure-equalizing tube insertion for 4 birth cohorts (1998–1999, 1999–2000, 2000–2001, and 2001–2002) by using Cox regression analysis. We used data from the National Immunization Survey to estimate the heptavalent pneumococcal conjugate vaccine uptake for children in these 4 birth cohorts in Tennessee and New York.


CONCLUSIONS. After heptavalent pneumococcal conjugate vaccine introduction, children were less likely to develop frequent otitis media or have pressure-equalizing tube insertions.
Patients and Methods

Sources of Data

TennCare is Tennessee’s managed care program that includes the Medicaid population and other low-income children. Each enrollee selects from 1 of 7 managed care organizations. During the study period, it included 50% of children born in Tennessee and all state children who were enrolled in Medicaid, with a high proportion of children from racial and ethnic minority groups and low-income families. The upstate New York database contains data from 3 commercial insurance managed care organizations, which together provided coverage for nearly 70% of children in the Rochester, New York, region.

Because of incomplete PCV7 vaccination information

in these administrative databases, data from the National Immunization Surveys conducted in 2001–2004 were used to estimate PCV7 vaccination coverage among children born between February 1998 and May 2003. This survey is designed to measure vaccination coverage in a nationally representative sample of US children aged 19 to 35 months. The National Immunization Survey used random-digit dialing to identify households with age-appropriate children and followed these telephone interviews with mailed surveys to the children’s vaccination providers. Only provider-verified vaccination histories are included in the analysis.

Study Population

We identified children born between July 1 and June 30, 1998–1999, 1999–2000, 2000–2001, and 2001–2002, and enrolled within 30 days of birth in TennCare or in commercial insurance plans of upstate New York. These birth cohorts were continuously followed until age 5, loss of enrollment, death, study outcome, or end of the surveillance period (June 30, 2004). For each birth cohort, we estimated the cumulative proportion of children who developed frequent otitis media or had PETs inserted.

Birth cohorts were defined by using a July to June year for 2 reasons. Although PCV7 was licensed in the United States in February 2000, coverage of PCV7 by most health insurance companies did not begin at that time. The routine administration of PCV7 began in the summer of 2000, when the American Academy of Pediatrics and the Advisory Committee on Immunization Practices published recommendations and the Vaccines for Children Program began to cover PCV7. A survey of primary health care providers in Tennessee and upstate New York confirmed that routine administration of PCV7 began after the summer of 2000 in these regions. Another reason for a July to June year was that each year includes 1 winter respiratory virus season as compared with a calendar year, which may include 0, 1, or 2 winter respiratory viral seasons.

Institutional review boards of Vanderbilt University, the State of Tennessee, University of Rochester, and the Centers for Disease Control and Prevention approved this study.

Study Outcomes

We identified 2 outcomes in cohort children: development of frequent otitis media and PET insertions. We identified all hospitalizations, emergency department visits, and outpatient visits for otitis media by International Classification of Diseases, Ninth Revision (ICD-9) codes (ICD-9 381.0–381.4, 382.x). An episode of otitis media was the first such visit or a visit at least 21 days after a previous otitis media visit to distinguish reinfections from relapses or persistent infections. A child developed frequent otitis media on the date of the first of the

*S. pneumoniae* is an important cause of otitis media, a common childhood illness that has resulted in an estimated $5.3 billion annually in direct medical costs across the United States. The efficacy of 7-valent pneumococcal conjugate vaccine (PCV7) in reducing otitis media was evaluated in 2 randomized, controlled trials. The Finnish and Kaiser Permanente trials found that young children who received PCV7 had a 6% and 7.8% overall reduction in the prevalence of otitis media, respectively, but this decline was statistically significant only in the Kaiser study. The vaccine efficacy for prevention of pressure-equalizing tube (PET) insertions, the most common surgical procedure in children, was 23% by 3.5 years in the Kaiser trial and 39% by 4 to 5 years in the Finnish trial.

Since PCV7 was incorporated into the routine immunization schedule in the United States by mid 2000, several studies have demonstrated a dramatic decrease in invasive pneumococcal disease. National survey data indicated that otitis media visits have decreased by 246 per 1000 children, a 20% decline with no compensatory increase in other respiratory visits. Our previous evaluation of children enrolled in Tennessee Medicaid and private insurance programs in the Rochester, New York, area showed declines in otitis media visits consistent with these national data. To date, there have been no evaluations of PCV7 program effectiveness by using longitudinal data from individual children to measure the change in risk of developing frequent otitis media or having PETs inserted.

In this study, we used an ecological analysis to determine the risk of frequent otitis media (3 episodes in 6 months or 4 episodes in 1 year) and PET insertions among 4 birth cohorts (1998–1999, 1999–2000, 2000–2001, and 2001–2002). We hypothesized that the risk of frequent otitis media and PETs would decrease from the 1998–1999 birth cohort, in which few children received PCV7 doses, to subsequent birth cohorts who had progressively increasing PCV7 uptake.

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TennCare is Tennessee’s managed care program that includes the Medicaid population and other low-income children. Each enrollee selects from 1 of 7 managed care organizations. During the study period, it included 50% of children born in Tennessee and all state children who were enrolled in Medicaid, with a high proportion of children from racial and ethnic minority groups and low-income families. The upstate New York database contains data from 3 commercial insurance managed care organizations, which together provided coverage for nearly 70% of children in the Rochester, New York, region.

Because of incomplete PCV7 vaccination information in these administrative databases, data from the National Immunization Surveys conducted in 2001–2004 were used to estimate PCV7 vaccination coverage among children born between February 1998 and May 2003. This survey is designed to measure vaccination coverage in a nationally representative sample of US children aged 19 to 35 months. The National Immunization Survey used random-digit dialing to identify households with age-appropriate children and followed these telephone interviews with mailed surveys to the children’s vaccination providers. Only provider-verified vaccination histories are included in the analysis.

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following: the third episode of otitis media within 6 months or the fourth episode within 1 year. A child was determined to have PET insertions on the date of the first visit with this procedure code (Current Procedural Terminology, Fourth Edition, 69433 or 69436).

Statistical Analysis
For each birth cohort, we used the Kaplan-Meier estimator to determine the cumulative proportion of children who developed frequent otitis media or had PETs inserted according to age in years; this method adjusts for children who drop out of the cohorts before experiencing the outcomes of interest. In addition, we used Cox regression models to evaluate the association between birth cohort (1998–1999, 1999–2000, 2000–2001, and 2001–2002) and risk of developing frequent otitis media or having PET insertion from birth through 2 years of age. Birth cohort was analyzed as a categorical variable using the 1998–1999 cohort as the reference. Of children enrolled at birth, 24% of Tennessee children and 39% of New York children, respectively, dropped out by 2 years of age. Separate analyses of outcomes in the first year of life for children who did and did not drop out showed similar patterns, suggesting absence of informative censoring (data not shown). To verify that the criteria for PET insertions were similar across cohorts, we compared the age-specific proportion of children with PETs who met the study criteria for frequent otitis media at the time of surgery.

We used National Immunization Survey (NIS) data (2001–2004) from Tennessee and New York to estimate PCV7 vaccination coverage by 2 years of age in the 4 birth cohorts of interest. For each birth cohort, we combined the NIS survey years that sampled children with appropriate birthdays. Because 2 to 3 NIS survey years were used for each estimate of PCV7 coverage by 2 years, each estimate was adjusted by dividing the individual weights for the included surveys by the total number of surveys used. Coverage estimates and 95% confidence intervals were calculated for the subgroup of children in the birth cohort, accounting for the complex survey design.

RESULTS
The demographics of the study populations are shown in Table 1. Each of the 4 birth cohorts from Tennessee accounted for 25% of the Tennessee population, whereas each birth cohort from New York accounted for 21% to 27% of the upstate New York population. The proportion of children who had either frequent otitis media or were continuously enrolled until 1 and 2 years of age was 77% and 63% in the TennCare population and 59% and 50% in the upstate New York private insurance population.

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Tennessee</th>
<th>New York</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998–1999</td>
<td>36 939 (25)</td>
<td>71 98 (27)</td>
</tr>
<tr>
<td>1999–2000</td>
<td>37 437 (25)</td>
<td>70 37 (27)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>37 841 (25)</td>
<td>55 86 (21)</td>
</tr>
</tbody>
</table>

Censored or continuously enrolled, a
1 116 279 (77) 18 408 (59)
2 94 290 (63) 13 215 (50)

<table>
<thead>
<tr>
<th>Insurance</th>
<th>n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Public</td>
<td>150 122 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Private</td>
<td>0 (0)</td>
<td>26 409 (100)</td>
</tr>
</tbody>
</table>

a Censored means that the children met criteria for frequent otitis media before this age. Children who were censored or were still enrolled are included in the data analysis.

Frequent Otitis Media

Tennessee
The TennCare population included 150 122 children with an average of 37 531 children per birth cohort. From the 1998–1999 through the 2001–2002 birth cohorts, 11 007 (7%) and 38 905 (26%) children lost enrollment during the first and second years of life, respectively. Overall, 39 763 (26%) children had frequent otitis media by 2 years of age. The cumulative proportion with frequent otitis media by 2 years old was 33% among children born in 1998–1999 compared with 29%, 29%, and 31% for the subsequent 3 birth cohorts (Fig 1A). In comparison to the 1998–1999 birth cohort, the decrease in frequent otitis media was 16% for the 1999–2000 cohort, 17% for the 2000–2001 cohort, and 8% for the 2001–2002 birth cohort (Table 2). Exclusion of serous otitis codes (ICD-9 381.0–381.4) from the definition of otitis media in the Tennessee data resulted in a 3% decrease in frequent otitis media visits for all birth cohorts and no change in any of the hazard ratios.

New York
The New York commercial insurance population included 26 409 children with an average of 6602 per birth cohort. In the first 3 birth cohorts, 5457 (26%) and 2656 (21%) children lost enrollment during the first and second years of life, respectively. Overall, 6067 (32%) children had frequent otitis media by 2 years of age. The cumulative proportion with frequent otitis media by 2 years old was 38% among children born 1998–1999 compared with 33%, 29%, and 27% in the 3 subsequent birth cohorts (Fig 1B). In comparison to the 1998–1999 birth cohort, there was a progressive decline in frequent otitis media that ranged from 16% to 33% (Table 2).
FIGURE 1
Cumulative percent with frequent otitis media in TennCare (A) and New York private insurance (B) according to age for each birth cohort. Note that for more recent cohorts, fewer years of follow-up were available.
The increase in frequent otitis media and PET insertions in the 2001–2002 birth cohort in Tennessee as compared with the 2 previous birth cohorts is a surprising development. The NIS PCV7 coverage estimates indicating that few children in the 1998–1999 birth cohort received PCV7 doses whereas progressively more children in the subsequent birth cohorts received PCV7.17 Interestingly, frequent otitis media and PET procedures progressively decreased for all birth cohorts in New York and through the 2000–2001 cohort in Tennessee. For the 2001–2002 Tennessee birth cohort, frequent otitis media was less than the 1998–1999 cohort but higher than the 2000–2001 cohort whereas PET procedures were similar to the 1998–1999 cohort. Although others have reported efficacy of PCV7, to our knowledge, this study is the first to evaluate the development of frequent otitis media and PET procedures in defined populations after PCV7 was recommended.

The reduction in the proportion of children with frequent otitis media and PET procedures was more marked in the New York private insurance population than in the TennCare population. Several factors likely contributed to this difference. According to the NIS data, PCV7 uptake and the proportion fully vaccinated was higher among New York children than among Tennessee children. Recent studies suggest that mucosal antibody response rarely develops after the primary series but is often demonstrated at age 13 or 14 months after receiving the booster dose, suggesting its importance for local mucosal immunity and, consequently, protection against otitis media.20 These children may have different rates of exposure to known risk factors, such as day care attendance and passive smoke exposure, which we did not measure. There may also be geographical differences among physicians as to what criteria they use to diagnose otitis media. Previous studies have found that children were more likely to have had PET procedures if they were from the South than the Northeast, were in day care, had no gaps in health coverage, or were of non-Hispanic white race and ethnicity.21 Furthermore, a higher proportion of New York than Tennessee children at each age group met criteria for frequent otitis media at the time of PET insertions, suggesting that the criteria for PET insertions may have been more stringent in the New York population.

### TABLE 2

<table>
<thead>
<tr>
<th>Birth Cohort</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequent Otitis Media</td>
</tr>
<tr>
<td>Tennessee</td>
<td></td>
</tr>
<tr>
<td>1998–1999</td>
<td>—</td>
</tr>
<tr>
<td>1999–2000</td>
<td>0.84 (0.81–0.86)</td>
</tr>
<tr>
<td>2000–2001</td>
<td>0.83 (0.81–0.86)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>0.92 (0.89–0.94)</td>
</tr>
<tr>
<td>New York</td>
<td></td>
</tr>
<tr>
<td>1998–1999</td>
<td>—</td>
</tr>
<tr>
<td>1999–2000</td>
<td>0.84 (0.79–0.89)</td>
</tr>
<tr>
<td>2000–2001</td>
<td>0.72 (0.67–0.77)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>0.67 (0.62–0.72)</td>
</tr>
</tbody>
</table>

— indicates reference group.

**DISCUSSION**

For the 2000–2001 birth cohort, we found a 17% and 28% decline, respectively, in frequent otitis media among Tennessee and New York children since PCV7 was incorporated into the childhood immunization schedule. Similarly, PET procedures by 2 years of age declined 16% and 23% since PCV7 introduction. This ecologic approach is supported by NIS PCV7 coverage estimates indicating that few children in the 1998–1999 birth cohort received PCV7 doses whereas progressively more children in the subsequent birth cohorts received PCV7.17 Interestingly, frequent otitis media and PET procedures progressively decreased for all birth cohorts in New York and through the 2000–2001 cohort in Tennessee. For the 2001–2002 Tennessee birth cohort, frequent otitis media was less than the 1998–1999 cohort but higher than the 2000–2001 cohort whereas PET procedures were similar to the 1998–1999 cohort. Although others have reported efficacy of PCV7, to our knowledge, this study is the first to evaluate the development of frequent otitis media and PET procedures in defined populations after PCV7 was recommended.

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The increase in frequent otitis media and PET insertions in the 2001–2002 birth cohort in Tennessee as compared with the 2 previous birth cohorts is a surpris-
ing and potentially important observation because the 2001–2002 cohort represents children with high PCV7 vaccination rates. It may reflect one or a combination of many factors. The increase in laboratory-confirmed pneumococcal disease from nonvaccine serotypes from the pre-PCV7 to post-PCV7 era has been reported for invasive disease and in one study on otitis media.\textsuperscript{22–26} Temporal changes in the children who are enrolled and

FIGURE 2
Cumulative percent with PETs in TennCare (A) or New York private insurance (B) placed according to age and birth cohort.
disenrolled from insurance plans may have contributed to this discrepancy. Overall medical care utilization may have increased, which may obscure the vaccine effect. An increase in medical care utilization could increase visit rates for otitis media even if disease rates remained stable or decreased.

The incidence of PET insertions in our study populations is comparable to those reported for other populations. In a large, rural Kentucky practice, 2.0% to 2.2% of children received PETs by 1 year of age and 4.0 to 5.8% received PETs during the second year of life.27 Similarly, Paradise et al28 reported 1.8% and 4.2% of children had PETs placed during the first and second years of life, respectively. Our cumulative frequency of PETs for the 1998–1999 birth cohorts was ~2.5% by 1 year of age and 7% by 2 years of age. Our 16% and 23% reduction in PETs in Tennessee and New York is comparable to the 20% decline reported in the Kaiser Permanente trial.29

Our results should be interpreted in light of some potential limitations. In this ecologic study, we cannot exclude the possibility that other concurrent factors, such as the encouragement of the judicious use of antibiotics, may have influenced physicians’ diagnostic patterns for otitis media.30 Furthermore, administrative data claims incompletely capture individual vaccinations and the PCV7 status of the study population is not known. However, national estimates show an increase in full PCV7 vaccination by 2 years of age from 2001–2002 to 2003–2004.17 Because few children in the 1998–1999 were vaccinated whereas most were vaccinated in the 2001–2002 cohort, we cannot compare those who did and did not receive PCV7 within each cohort. Even if feasible, comparing children who are or are not vaccinated is problematic because children who receive vaccinations are more likely to seek care and thus may be more likely to have otitis media diagnosed. In addition, it is possible that unvaccinated children indirectly benefited because of lower pneumococcal carriage rates and decreased transmission of vaccine serotypes with implementation of PCV7 vaccination in the populations.31–33

Study results were limited to the children who qual-
ified for TennCare and upstate New York commercial insurance. Because the eligibility criteria for Medicaid vary by state and over time, Tennessee results may not be representative of all Medicaid populations. The microbiology of otitis media and the proportion attributable to *S. pneumoniae* cannot be ascertained from this study. However, our results are compatible with findings through 2003 that the microbiology of acute otitis media has changed since the introduction of PCV7 with ~35% reduction in the prevalence of *S. pneumoniae* isolates among bacteria causing otitis media and minimal replacement with nonvaccine pneumococcal serotype isolates.34,35

We found a greater decline in frequent otitis media for the 2000–2001 birth cohort, 17% and 28% in Tennessee and New York, than the 9.3% decline in the Kaiser Permanente trial.29 The cumulative proportion of children with frequent otitis media in the 1998–1999 birth cohort was slightly higher (33% in Tennessee and 36% in New York) than in previous studies. In the Kaiser trial, 28% of control children had frequent otitis media (3 episodes within 6 months) by 3.5 years of age.29 In other populations, 17.3% of Boston children had 3 episodes of otitis media in their first year of life,16 and 28% to 31% of rural Kentucky children had 4 or more episodes of otitis media by age 1 year.37 Our definition of otitis media included the code for serous otitis media, which may account for our modestly higher estimates.36 In Tennessee, we found that the proportion with frequent otitis media decreased by 3% when serous otitis media was excluded and that the hazard ratios were not impacted. Another possible explanation for the greater reduction in frequent otitis media than that seen in clinical trials is that there could be both direct and indirect benefits of PCV7 for partially vaccinated and nonvaccinated children.31–33 From 2001 to 2004, there was a significant decline in nasopharyngeal carriage for vaccine-serotype pneumococcus among healthy children <7 years of age who resided in a state with high PCV7 coverage.37 In contrast, no change in nasopharyngeal carriage of vaccine-serotype pneumococcus was found among children 2 to 5 years of age who had participated in a PCV7 trial but lived in a largely unvaccinated community.38

Estimating PCV7 coverage for the study birth cohorts has some limitations. Because the NIS is designed for analysis by birth cohort but were adjusted by using a standard statistical technique.18 Finally, as in any survey, incomplete reporting may have resulted in an underestimate of coverage. However, this rapid rise of PCV7 coverage in the survey for New York correlated well and at the same time period noted by a community-wide random sample of medical charts in the Rochester, New York area, the same geographic area as this study.50

**CONCLUSIONS**

The declines in frequent otitis media and PET insertions matched or exceeded the results in randomized, controlled trials, suggesting direct and indirect benefits to children who were or were not fully vaccinated. These findings are particularly encouraging in light of PCV7 shortages. Furthermore, these reductions in frequent otitis media and PETs are higher than that seen in randomized, controlled trials and may have important implications on the cost-effectiveness analyses for PCV7. However, whether these findings continue or wane, as suggested by the 2001–2002 birth cohort from New York and Tennessee, respectively, is important and deserves additional study and monitoring.

**ACKNOWLEDGMENTS**

This project was supported by cooperative agreement U38/CCU417958 from the Centers for Disease Control and Prevention (CDC) and U50/CCU300886, TS-0825 from American Teachers of Preventive Medicine/CDC. Dr Poehling also received support from K23 AI065805 (National Institute of Allergy and Infectious Diseases, National Institutes of Health) and the Robert Wood Johnson Generalist Physician Faculty Scholars Program.

Data to conduct the study were obtained from the Tennessee Department of Health and the TennCare Bureau.

**REFERENCES**


Outcome at 2 Years of Age of Infants From the DART Study: A Multicenter, International, Randomized, Controlled Trial of Low-Dose Dexamethasone

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ABSTRACT

OBJECTIVE. Low-dose dexamethasone facilitates extubation in chronically ventilator-dependent infants with no obvious short-term complications. The objective of this study was to determine the long-term effects of low-dose dexamethasone.

METHODS. Very preterm (<28 weeks’ gestation) or extremely low birth weight (birth weight <1000 g) infants who were ventilator dependent after the first week of life for whom clinicians considered corticosteroids were indicated were eligible. After informed consent, infants were randomly assigned to masked dexamethasone (0.89 mg/kg over 10 days) or saline placebo. Survivors were assessed at 2 years’ corrected age by staff blinded to treatment group allocation to determine neurosensory outcome, growth, and health.

RESULTS. The trial was abandoned well short of its target sample size because of recruitment difficulties. Seventy infants were recruited from 11 centers, 35 in each group: 59 survived to 2 years of age, and 58 (98%) were assessed at follow-up, but data for cerebral palsy were available for only 56 survivors. There was little evidence for a difference in the major end point, the rate of the combined outcome of death, or major disability at 2 years of age (dexamethasone group: 46%; controls: 43%). Rates of mortality before follow-up (11% vs 20%), major disability (41% vs 31%), cerebral palsy (14% vs 22%), or of the combined outcomes of death or cerebral palsy (23% vs 37%) were not substantially different between the groups. There were no obvious effects of low-dose dexamethasone on growth or readmissions to hospital after discharge.

CONCLUSIONS. Although this trial was not able to provide definitive evidence on the long-term effects of low-dose dexamethasone after the first week of life in chronically ventilator-dependent infants, our data indicate no strong association with long-term morbidity.

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Key Words: infant, preterm, low birth weight, low dose-dexamethasone, cerebral palsy, impairment, disability

Abbreviations: ELBW—extremely low birth weight, MDI—mental developmental index, PDI—psychomotor developmental index, CI—confidence limit, CLD—chronic lung disease

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Corticosteroid treatment of ventilator-dependent very preterm infants facilitates extubation and reduces the rate of bronchopulmonary dysplasia. Studies of the long-term neurodevelopmental effects of corticosteroids are inconsistent. Some have shown a higher rate of cerebral palsy, some no difference, and 1 study even suggested long-term benefits at 15 years of age. The DART study was an international multicenter randomized, controlled trial with the main aim to assess the effects of low-dose dexamethasone on long-term survival free of major neurologic disability. However, enrollment had to stop when recruitment fell to a rate that was too low to complete the study.

The aim of this report was to examine the long-term effects, especially neurologic, of low-dose dexamethasone, given after the first week of life, in ventilator-dependent, very preterm/extremely low birth weight (ELBW) infants.

**METHODS**

Very preterm (<28 weeks’ gestation) or ELBW (birth weight <1000 g) infants who were ventilator dependent after the first week of life (>168 hours of age) and in whom the clinician considered corticosteroids were a treatment option were eligible for the study. As described in the original report, there were no standardized oxygen or ventilation criteria for entry to the study. After written informed consent, infants were allocated randomly to receive either a 10-day tapering course of dexamethasone sodium phosphate (0.89 mg/kg total) or an equivalent volume of 0.9% saline placebo. Full details of the exclusion criteria, randomization, and method of giving the drug were described in the report of the short-term effects during the primary hospitalization of low-dose dexamethasone. The study, including the follow-up component, was approved first by the Research and Ethics Committee at the Royal Women’s Hospital, Melbourne, and subsequently by the equivalent committees at each participating center.

Surviving children were assessed at 2 years of age, corrected for prematurity, by developmental pediatricians and psychologists masked to treatment group. The pediatric assessment included a medical history and a neurologic examination to determine outcomes such as cerebral palsy, defined as loss of motor function associated with definite abnormalities of muscle tone and reflexes. Children were assessed for blindness and deafness earlier in childhood; those not assessed who had problems with vision and hearing at the 2-year assessment were referred for a full assessment. Blindness was defined as visual acuity in both eyes worse than 6/60. Deafness was defined as hearing loss requiring amplification or worse. The psychological assessment included the mental developmental index (MDI) and psychomotor developmental index (PDI) of the Bayley Scales of Infant Development—Second Edition. Children unable to complete psychological tests because of severe developmental delay were assigned MDI or PDI scores of 49. A child was considered to have developmental delay if the MDI score was <85.

Children were considered to have a neurosensory impairment if they had cerebral palsy, blindness, deafness, or an MDI score <85. The severity of the neurosensory disability imposed by the impairment was graded as follows: Severe, bilateral blindness, or cerebral palsy with the child unlikely ever to walk, or an MDI score <55; moderate, deafness or cerebral palsy in children not walking at 2 years but expected to walk or an MDI score from 55 to <70; and mild, cerebral palsy but walking at 2 years with only minimal limitation of movement or an MDI score 70 to <85. The remaining children were considered to have no neurosensory disability. Major neurosensory disability comprised any of blindness, deafness, cerebral palsy in a child who was not walking at 2 years of age, or an MDI score <70; this is equivalent to combining severe and moderate disability, as defined above. For children not fully assessed at 2 years of age, we accepted the results of complete neuropsychological assessments at the age of at least 1 year if they were clearly neurologically normal or abnormal, including the results of alternative developmental tests.

Blood pressure was measured, as were weight, length, and head-circumference. BMI was calculated (weight [kg]/height [m]^2), and all growth measurements were converted to SD scores relative to the British Growth Reference. Data on the number of hospital readmissions and their duration, and the duration of oxygen therapy at home, if appropriate, were recorded.

The sample-size calculation for the original trial was based on detecting an improvement in survival free of major neurosensory disability from 50% to 60%, with a 2-sided type I error rate of 5% and 80% power, and it required 814 infants to be recruited.

Analysis was on an intention-to-treat basis and followed standard principles for randomized trials. Outcome comparisons based on dichotomous end points were assessed by \( \chi^2 \) test or Fisher’s exact test where expected cell frequencies were <5. Continuous variables were compared by t test or by Mann-Whitney U test where the data were strongly skewed. Data were analyzed by using Stata 9.1.

**RESULTS**

The first infant was recruited into the DART study in March 2000. Recruitment ceased in October 2002, after 70 infants were recruited from 11 centers in 3 countries. Details of why the study was stopped have been reported. The infants were very high risk, with a median gestational age of 25 completed weeks and a median birth weight of 680 g. The median age at entry to the study was in the fourth week of life in both groups. The perinatal characteristics and degree of assisted ventila-
tion of the 2 groups as randomized were comparable, as previously reported. The perinatal characteristics of the 2 groups who were followed were similar (Table 1), and there was little difference from the cohorts as randomized.

There was no clearcut difference in the mortality rate to 2 years old between the groups (Table 2; odds ratio: 0.52; 95% confidence limits [CLs] : 0.14, 1.95; \( P = .32 \)). Of the 11 infants who died, 3 died during the first 10-day course of the DART study, 5 died after the 10-day course but before discharge, and 3 died after discharge home. Causes of death have been reported.

Only 1 of the 59 children was completely lost to follow-up, but data on 2 other children were insufficient to determine the major neurosensory outcomes. Ninety-five percent (56 of 59) were assessed for the major neurosensory outcome of cerebral palsy and 93% (55 of 59) for the outcome of major disability. There were no substantial differences between the groups in the follow-up rates or ages of assessment (Table 2). Two children were assessed at 1 year of age, and another at 17 months of age; the remaining children were assessed closer to or beyond 2 years of age.

In the 56 children with cerebral palsy data, not all were able to complete all assessments (Table 2). As was expected with the small numbers, there were no significant differences between the groups in the rate or severity of cerebral palsy, or the rates of blindness, deafness or developmental delay (Table 2). The mean MDI and PDI scores were similar, with or without children who could not be formally tested because of severe developmental delay (Table 2). Rates of neurosensory disability were similar in the 2 groups (Table 2). The combined rates of death or cerebral palsy or death or major disability were not substantially different between the 2 groups (Table 2).

There were some children assessed who had missing data for growth and hospital readmissions, but there were more missing data for blood pressure (Table 3). In those with data, weight, height, and head-circumference SD scores were all substantially below 0 but not different between the treatment groups, as were the BMI and BMI SD scores (Table 3). There were no substantial differences between the groups in blood pressure or in the number or durations of hospital readmissions. In those discharged from the hospital on oxygen, the ages of stopping oxygen were similar.

**DISCUSSION**

Low-dose dexamethasone after the first week of life was associated with no obvious long-term harm related to neurosensory outcome, growth, blood pressure, or hospital readmissions. Clearly, however, the chance of finding substantial harmful effects was low, given that the study had to be abandoned with <10% of the target sample size recruited. Interestingly, low-dose dexamethasone was not associated with an increase in any of the short-term complications associated with higher doses or earlier courses of dexamethasone, such as gastrointestinal hemorrhage or intestinal perforation, and there were no obvious short-term effects on blood glucose or blood pressure. Although some other studies have reported higher rates of cerebral palsy, and there is clearly a higher rate of cerebral palsy in all studies overall, the increase is largely in studies where treatment started early, in the first week of life, and not later. There was a small reduction in the dexamethasone group in the change in weight over the 10 days of treatment of marginal clinical importance; however, this did not translate into substantial long-term growth effects at hospital discharge or at 2 years of age, as seen in our study.

The major weakness of our study is the small sample

### TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexamethasone ((n = 29))</th>
<th>Placebo ((n = 27))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother, (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22 (75.9)</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>26 (89.7)</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>12 (41.4)</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born in level III center, (n (%))</td>
<td>28 (96.6)</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td>Gestational age, median (IQR), completed wk</td>
<td>24 (24–25)</td>
<td>25 (24–26)</td>
</tr>
<tr>
<td>Birth weight, median (IQR), g</td>
<td>670 (630–740)</td>
<td>744 (630–836)</td>
</tr>
<tr>
<td>Male, (n (%))</td>
<td>12 (41.4)</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Multiple birth, (n (%))</td>
<td>9 (31.0)</td>
<td>13 (48.2)</td>
</tr>
<tr>
<td>Age at entry, median (IQR), d</td>
<td>24 (20–34)</td>
<td>22 (13–28)</td>
</tr>
<tr>
<td>Duration of IPPV, median (IQR), d</td>
<td>19 (11–23)</td>
<td>13 (4–23)</td>
</tr>
<tr>
<td>Duration of HFV, median (IQR), d</td>
<td>1 (0–11)</td>
<td>2 (0–13)</td>
</tr>
<tr>
<td>Mean airway pressure, median (IQR), cm H(_2)O</td>
<td>10 (8.6–10.6)</td>
<td>10 (9.1–11.4)</td>
</tr>
<tr>
<td>Inspired oxygen concentration, median (IQR), %</td>
<td>45 (40–55)</td>
<td>45 (33–60)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; IPPV, intermittent positive airways pressure; HFV, high-frequency ventilation.
size. However, the DART study is larger than 14 of the 20 other studies with long-term outcome data, and it contributes to the collective knowledge about long-term effects of corticosteroids. In addition, in common with other multicenter studies, it was not always possible to have all surviving children assessed as formally as desirable, and even in those assessed not all outcomes were obtained. All but 1 child was seen at follow-up, but not all of those seen could have the major neurosensory outcomes determined. Two-year-old children can be difficult to assess, and some measurements, such as blood pressure, cannot be obtained reliably from an uncooperative child.

The major strength of the study is the high follow-up rate; follow-up rates for long-term studies >90% are desirable. In addition, all outcomes were assessed blinded to treatment group allocation, eliminating any possibility of expectation bias, and survivors had standard developmental assessments where possible, eliminating any diagnostic suspicion bias.

The high rates of cerebral palsy reported from some randomized, controlled trials of postnatal corticosteroids

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexamethasone (n = 35)</th>
<th>Placebo (n = 35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death any time before follow-up, n (%)</td>
<td>4 (11.4)</td>
<td>7 (20.0)</td>
<td>.32</td>
</tr>
<tr>
<td>No. of survivors assessed for cerebral palsy, n/N (%) survivors</td>
<td>29/31 (93.5)</td>
<td>27/28 (96.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Corrected age assessed, mean (SD), y; n</td>
<td>2.0 (0.32); 29</td>
<td>2.0 (0.34); 27</td>
<td>.50</td>
</tr>
<tr>
<td>Impairments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy, n/N (%) assesseda</td>
<td>4/29 (13.8)</td>
<td>6/27 (22.2)</td>
<td>.50</td>
</tr>
<tr>
<td>Mild, n</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Moderate, n</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Severe, n</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Deafness, n/N (%) assessed</td>
<td>2/27 (7.4)</td>
<td>4/27 (14.8)</td>
<td>.67</td>
</tr>
<tr>
<td>Blindness, n/N (%) assessed</td>
<td>1/27 (3.7)</td>
<td>0/27 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Developmental delay, n/N (%) assessed</td>
<td>16/27 (59.3)</td>
<td>12/24 (50.0)</td>
<td>.58</td>
</tr>
<tr>
<td>Developmental scores, mean (SD); n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td>79.3 (24.7); 27</td>
<td>83.8 (22.0); 24</td>
<td>.50</td>
</tr>
<tr>
<td>MDIb</td>
<td>83.0 (23.6); 24</td>
<td>88.8 (18.7); 21</td>
<td>.38</td>
</tr>
<tr>
<td>PDI</td>
<td>84.1 (20.3); 26</td>
<td>79.1 (23.6); 24</td>
<td>.43</td>
</tr>
<tr>
<td>PDIb</td>
<td>85.5 (19.4); 25</td>
<td>83.4 (22.0); 21</td>
<td>.74</td>
</tr>
<tr>
<td>Disability, n/N (%) assessed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>12/29 (41.4)</td>
<td>12/26 (46.2)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>5/29 (17.2)</td>
<td>6/26 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4/29 (13.8)</td>
<td>4/26 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>8/29 (27.6)</td>
<td>4/26 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Major (moderate or severe) disability, n/N (%) assessed</td>
<td>12/29 (41.4)</td>
<td>8/26 (30.8)</td>
<td>.41</td>
</tr>
<tr>
<td>Combined outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or cerebral palsy, n/N (%) randomized</td>
<td>8/35 (22.9)</td>
<td>13/35 (37.1)</td>
<td>.19</td>
</tr>
<tr>
<td>Death or major disability, n/N (%) randomized</td>
<td>16/35 (45.7)</td>
<td>15/35 (42.9)</td>
<td>.81</td>
</tr>
</tbody>
</table>

TABLE 3 Other Infant Outcomes at 2 Years’ Corrected Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexamethasone (n = 29)</th>
<th>Placebo (n = 27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth, mean (SD); n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight SD score</td>
<td>−0.61 (2.08); 28</td>
<td>−1.12 (1.73); 26</td>
<td>.30</td>
</tr>
<tr>
<td>Height SD score</td>
<td>−0.92 (1.57); 28</td>
<td>−1.22 (1.98); 26</td>
<td>.54</td>
</tr>
<tr>
<td>Head-circumference SD score</td>
<td>−1.77 (1.40); 28</td>
<td>−1.27 (1.24); 26</td>
<td>.17</td>
</tr>
<tr>
<td>BMI</td>
<td>17.09 (4.11); 28</td>
<td>16.04 (2.05); 26</td>
<td>.25</td>
</tr>
<tr>
<td>BMI SD score</td>
<td>0.01 (1.83); 28</td>
<td>−0.58 (1.87); 26</td>
<td>.25</td>
</tr>
<tr>
<td>Blood pressure, mean (SD); n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>89.1 (16.0); 16</td>
<td>94.9 (13.8); 15</td>
<td>.29</td>
</tr>
<tr>
<td>Diastolic</td>
<td>58.1 (9.5); 15</td>
<td>54.7 (11.1); 15</td>
<td>.38</td>
</tr>
<tr>
<td>Hospital readmissions, median (IQR); n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>1 (1–2); 25</td>
<td>2 (1–4); 25</td>
<td>.14</td>
</tr>
<tr>
<td>Total days</td>
<td>3 (1–7); 25</td>
<td>5 (2–14); 24</td>
<td>.15</td>
</tr>
<tr>
<td>Duration of home oxygen therapy, median (IQR); wk; n</td>
<td>15 (11–38); 11</td>
<td>15 (11–46); 10</td>
<td>.89</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
in the late 1990s were the major reason for the warnings concerning dexamethasone use in very preterm infants.11–15 However, the higher rate of cerebral palsy is largely confined to randomized, controlled trials where treatment was started in the first week of life:7 the rate of the combined end point of either death or cerebral palsy in those who were randomly assigned when treatment was started after the first week of life was neutral (typical relative risk: 0.99; 95% CLs: 0.81, 1.21). In the DART study, where treatment also started after the first week of life, the rate of death or cerebral palsy was lower in the corticosteroid group. A systematic review demonstrated that the risk of the combined outcome of death or cerebral palsy varies with the baseline risk of chronic lung disease in the control group.7 For every 10% that the rate of chronic lung disease (CLD) increased in the control group, it was estimated in a meta–regression analysis that the risk difference for death or cerebral palsy fell by 3.8% (95% CLs: 1.4%, 6.2%; P = .002), according to the relationship: \( Y = 18.7 - 0.38X \), where \( Y \) = risk difference (%) for death or cerebral palsy, and \( X \) = rate (%) of CLD in those who were randomly assigned to the control group. The infants in the DART study had a very high rate of CLD, being 83% among all randomly assigned to the control group. Substituting \( X = 83\% \) in the estimated meta–regression equation gives an expected value of \( Y = -12.8\% \), meaning that a 12.8% reduction in the combined rate of death or cerebral palsy would be expected. The observed reduction of 14.3% in the DART study, therefore, was consistent with the expected value.

The DART study provided the first evidence that a low dose of dexamethasone after the first week of life in chronically ventilator-dependent infants has short-term benefits, such as facilitating extubation and improving lung function, without short-term complications associated with higher doses.9 The follow-up phase of the DART study suggests that low-dose dexamethasone in these infants may have short-term benefits without substantially increasing the risk of long-term neurologic disability. However, we still await the definitive trial of such therapy with enough power to give a clearcut answer to help clinicians in their current uncertainty in the care of chronically ventilator-dependent infants.

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The DART Study Investigators included the steering committee: L. W. Doyle (Chair), P. G. Davis, C. J. Morley (Royal Women’s Hospital Melbourne), A. McPhee (Women’s and Children’s Hospital, Adelaide), and J. B. Carlin (Murdoch Childrens Research Institute, Melbourne); participants in Australia: Royal Women’s Hospital, Melbourne (L. W. Doyle, P. G. Davis, C. J. Morley, M. Kaimakamis, C. Callanan, N. Davis, G. Ford, E. Kelly, and L. Ung), Monash Medical Centre, Melbourne (V. Yu, M. Hayes, R. Li, E. Carse, and M. Charlton), Mercy Hospital for Women (S. Fraser and E. Kelly), John Hunter Hospital, Newcastle (A. Gill, S. Wooderson, and A. Vimpani), Women’s and Children’s Hospital, Adelaide (A. McPhee, R. Lontis, and L. Goodchild), King Edward Memorial Hospital, Perth (N. French and H. Benninger), and Royal Prince Alfred Hospital, Sydney (N. Evans, S. Reid, and I. Rieger); participants in New Zealand: Christchurch Women’s Hospital (B. Darlow) and National Women’s Hospital, Auckland (C. Kuschel and A. Dezoete); participants in Canada: Health Sciences Centre, Winnipeg (R. Alvaro and A. Chiu), and Royal University Hospital, Saskatoon (K. Sankaran and B. Andreychuk); statistical analysts: J. B. Carlin, K. Jamsen, and C. Chionh (Clinical Epidemiology and Biostatistics Unit, Royal Children’s Hospital, Melbourne); and the external safety committee: J. Hiller (Chair) (University of Adelaide, Adelaide), J. Lumley (LaTrobe University, Melbourne), and J. C. Sinclair (McMaster University, Hamilton).

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Long-term Outcome and Clinical Spectrum of 73 Pediatric Patients With Mitochondrial Diseases

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Theauthorshaveindicatedtheyhaveno financialrelationshipsrelevantto thisarticletodisclose.

ABSTRACT

OBJECTIVES. We sought to determine the clinical spectrum, survival, and long-term functional outcome of a cohort of pediatric patients with mitochondrial diseases and to identify prognostic factors.

METHODS. Medical charts were reviewed for 73 children diagnosed between 1985 and 2005. The functional status of living patients was assessed prospectively by using the standardized Functional Independence Measure scales.

RESULTS. Patients fell into 7 phenotypic categories: neonatal-onset lactic acidosis (10%), Leigh syndrome (18%), nonspecific encephalopathy (32%), mitochondrial (encephalo)myopathy (19%), intermittent neurologic (5%), visceral (11%), and Leber hereditary optic neuropathy (5%). Age at first symptoms ranged from prenatal to 16 years (median: 7 months). Neurologic symptoms were the most common (90%). Visceral involvement was observed in 29% of the patients. A biochemical or molecular diagnosis was identified for 81% of the patients as follows: deficiency of complex IV (27%), of pyruvate dehydrogenase or complex I (25% each), of multiple complexes (13%), and of pyruvate carboxylase (5%) or complexes II/III (5%). A mitochondrial DNA mutation was found in 20% of patients. At present, 46% of patients have died (median age: 13 months), 80% of whom were <3 years of age. Multivariate analysis showed that age at first symptoms was a major independent predictor of mortality: patients with first symptoms before 6 months had a highly increased risk of mortality. Cardiac or visceral involvement and neurologic crises were not independent prognostic factors. Living patients showed a wide range of independence levels that correlated positively with age at first symptoms. Among patients aged >5 years (n = 32), 62% had Functional Independence Measure quotients of >0.75.

CONCLUSIONS. Mitochondrial diseases in children span a wide range of symptoms and severities. Age at first symptoms is the strongest predictor mortality. Despite a high mortality rate in the cohort, 62% of patients aged >5 years have only mild impairment or normal functional outcome.
MITOCHONDRIAL DISEASES (MDS) represent a vast group of inherited disorders of energy metabolism that encompass a wide range of symptoms and presentations, severity, and outcome. Together, they form one of the most prevalent groups of inherited metabolic diseases. The minimum birth prevalence of MDS for onset at any age has been estimated at 1 of 7634. However, given the diversity of clinical presentations, including nonspecific courses, and because of the difficulty in establishing a diagnosis, this must be considered a minimal estimate. Because oxidative phosphorylation is a fundamental pathway of cellular metabolism, any organ can be involved. Hence, MDS may present in any of numerous subspecialties. Clinical pediatric reports described the spectrum of signs and symptoms associated with MDS, but the long-term clinical course of this heterogeneous group remains imprecise. In particular, little is known about the long-term functional outcome of pediatric patients with MDS. The aims of this study were to evaluate the long-term functional outcome of pediatric patients with MDS. The aims of this study were to evaluate the clinical course, mortality, and morbidity in a cohort of pediatric patients with MDS. Here, we describe the phenotypic spectrum of these patients based on long-term follow-up and report, to our knowledge, the first standardized evaluation of the functional independence level of pediatric patients with MDS. We tested the ability to predict mortality and morbidity of several clinical and biochemical characteristics.

METHODS

Case Ascertainment

We reviewed hospital charts of all patients evaluated for congenital lactic acidosis or presumed MD by the Genetics Division of CHU Sainte-Justine (Montreal, Canada) between January 1985 and December 2005. Thirty-five patients with Saguenay-Lac-St-Jean cytochrome c oxidase deficiency (Online Mendelian Inheritance in Man No. 220111) were excluded from the study. Because of a French-Canadian founder effect, this condition forms a substantial fraction of our patients. Excluding these patients rendered our cohort more representative of the spectrum of MDS encountered elsewhere in the world. Among the remaining patients (n = 99), 26 were excluded because of insufficient clinical data or lack of sufficient criteria for the diagnosis of MD. Seventy-three patients from 66 families had long-term follow-up data and evidence of MD. Sixty-seven had a score of 3 with the modified Walker criteria scoring system for MD. Six patients had a score of 2 but were included because they had strong evidence of MD based on long-term clinical, biological, and neuroradiological follow-up (mean follow-up time of 66 months in this group) and the absence of other potential etiologies. All 6 patients had declined muscle and/or liver biopsy, impeding definite biochemical diagnosis. Three were sibs of patients with enzymatically proven respiratory chain deficiency, which in addition to suggestive clinical signs was considered as a major criterion for the diagnosis of MD.

Clinical Data and Phenotypic Classification

For these 73 patients, we retrospectively reviewed all available clinical, neuroradiological, pathologic, biochemical, and molecular data. The clinical variables that were specifically noted were: antenatal and neonatal history, developmental course, abnormalities of muscle tone, epilepsy, movement disorders, myopathic or neuropathic weakness, neurologic crisis, gastric tube feeding requirement, growth parameters (including cranial circumference), visceral involvement (cardiomyopathy, liver disease, renal dysfunction, etc), ophthalmologic involvement, and hearing loss. Neurologic crises were defined as acute or subacute neurologic deterioration with loss of previously acquired skills and appearance of new neurologic symptoms and included episodes of Leigh disease and stroke-like episodes. Available biochemical data (blood gases, lactate, and pyruvate concentrations in blood and cerebrospinal fluid (CSF) and plasma amino acids) were averaged for each patient.

Patients were classified into 7 clinical categories (Table 1): (1) neonatal-onset lactic acidosis, characterized by fulminant acidosis; (2) Leigh syndrome, including

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n (%)</th>
<th>PDH</th>
<th>PC</th>
<th>Complex I</th>
<th>Complex IV</th>
<th>Complex II + III</th>
<th>MCD</th>
<th>mtDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal-onset lactic acidosis</td>
<td>7 (10)</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>Leigh syndrome</td>
<td>13 (18)</td>
<td>1</td>
<td>—</td>
<td>6</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mitochondrial (encephalo)myopathy</td>
<td>14 (19)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>8</td>
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<tr>
<td>Nonspecific encephalopathy</td>
<td>23 (32)</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Visceral presentation</td>
<td>8 (11)</td>
<td>—</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intermittent neurological</td>
<td>4 (5)</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LHON</td>
<td>4 (5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>73 (100)</td>
<td>11</td>
<td>2</td>
<td>11</td>
<td>13</td>
<td>2</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

PC indicates pyruvate carboxylase deficiency; MCD, multiple complex deficiency; —, not detected.
typical Leigh syndrome and Leigh-like syndrome according
to Rhamann et al13; (3) visceral, in which marked
involvement of ≥1 organ dominates the clinical picture;
(4) mitochondrial myopathy, including patients with
myopathy or encephalomyopathy with ragged red fibers
(RRF) and patients with classical mitochondrial syn-
dromes: Kearns-Sayre syndrome (n = 2), mitochondrial
encephalomyopathy with lactic acidosis and stroke-like
episodes [MELAS] (n = 4), and mitochondrial neurogas-
trointestinal encephalomyopathy (n = 1); (5) Leber her-
editary optic neuropathy (LHON, n = 4) (because their
clinical course was strikingly different from that of other
patients with MD, patients with LHON were not in-
cluded to study frequency of early manifestations of
MD); (6) 4 patients had only intermittent neurologic
symptoms (recurrent ataxia or episodic weakness) that
recurred over several years, and they were classified as
an “intermittent neurologic group”; and (7) the remain-
ing patients had nonspecific encephalopathy. In the text,
numbers and percentages of patients, when used alone,
decide that were available for all 73 patients.

Etiologic Investigations
Muscle biopsy was performed in 45 patients (62%). The
tissue was snap-frozen and submitted to a standard his-
topathology examination including hematoxylin and eo-
sin, adenosine triphosphatase, reduced nicotinamide
adenine dinucleotide (NADH)-tetrazolium reductase, oil
red O, periodic acid Schiff, and modified Gomori
tricrome stains. After 1999, succinate dehydrogenase
activity was measured spectrophotometrically as de-
scribed.14–16 Pyruvate dehydrogenase (PDH) complex
(native and dichloroacetate-activated), pyruvate carbox-
ylase, complex II+III, and complex IV activities were
determined in cultured fibroblasts from 51 patients
(70%). Complete respiratory chain studies were per-
formed in muscle (24 patients, 33%) and liver (21 pa-
tients, 29%). Blue native gel analysis was also performed
as described17 on cultured fibroblasts from 20 patients.

Molecular analysis of mitochondrial DNA (mtDNA)
included testing for large deletions-duplications and for
point mutations related to classical mitochondrial cyto-
pathies: MELAS, A3243G and T3271C; MERRF, A8344G
and T8356C; neuropathy, ataxia and retinitis pigmen-
tosa (NARP), T8993G and T8993C; LHON, G11778A,
G3460A, T14484C, and G14459A and was performed in
patients with symptoms suggesting these conditions and
in patients without definite biochemical diagnosis and
for whom tissues were available. Complete mtDNA se-
quencing was performed as described18 in 6 patients in
whom muscle biopsy had revealed RRF suggesting pos-
sible heteroplasmic, and in whom screening mtDNA
analyses had failed to find a mutation.

Informed consent was obtained from parents or legal
guardians for all diagnostic procedures and molecular
studies.

Outcome: Mortality and Morbidity
Mortality was ascertained by medical charts review. For
72 of 73 patients (97%), complete follow-up was avail-
able (defined as until death or December 2005). Mortal-
ity rate was analyzed according to several potential
prognostic factors: age at first symptoms, phenotypic
category, presence of visceral involvement, mean plasma
lactate concentration, occurrence of metabolic and neu-
rologic crisis, and presence of an mtDNA mutation. For
Kaplan-Meier analysis, the cohort was divided into 2
subgroups: patients presenting their first symptoms be-
fore the age of 6 months and those presenting thereafter.

Morbidity was evaluated prospectively for living pa-
tients using the Functional Independence Measure
(FIM)/Functional Independence Measure for Children
(WeeFIM) scoring systems, which provide a standard-
ized way to obtain information about functional status
for individuals at least 8 years of age and children aged 6
months to 8 years, respectively.19–21 These scales were
administered in 2005 by a single physician as part of
clinical follow-up and monitoring of the patients at rou-
tine visits at the genetics clinic. In both scales, a score
from 1 to 7 (1 = total dependence; 7 = complete auton-
omy) is assigned for 18 items in 3 main domains: (1)
sel-care (including eating, grooming, bathing, dressing
upper and lower body, toileting, and bladder and bowel
management), (2) mobility (including transfer from
wheelchair, transfer to toilet, to tub or shower, walking/
wheelchair/crawling distance, and moving up and down
stairs), and (3) cognition (evaluating comprehension,
expression, social interactions, problem solving, and
memory). To standardize for patient age, WeeFIM and
FIM raw scores were divided by the age-specific mean
(±4 months) and expressed as quotients. Quotients
<50% are considered to represent severe impairment,
between 50% and 75% are moderate, and >75%, mild
or no impairment. For additional analysis, WeeFIM and
FIM quotients were combined as described.22

Statistical Analysis
A t test for independent groups was used to compare
means, and a χ² test was used to compare proportions
between groups. We tested the association between pos-
sible predictors and mortality with Cox’s proportional
hazard ratio model. Variables significant at P < .01 on
univariate analysis were included in the multivariate
model. We used Kaplan-Meier curves to describe the
survival in some subgroups. The mortality rates were
compared between subgroups by using the log-rank test.
FIM and WeeFIM quotients were compared between the
3 domains (self-care versus mobility, self-care versus cognition, and mobility versus cognition) with a Wilcoxon rank test for matched pairs. We used analysis of variance and linear regression to test the association between potential predictors (age at first symptoms, mean lactate concentration during follow-up, and occurrence of metabolic and neurologic crises) and the global functional quotient. Statistical analyses were performed with SPSS software (SPSS Inc, Chicago, IL).

RESULTS

Of the 73 patients selected, 42 boys (58%) and 31 girls (42%) presented from the fetal period to 16 years old. Over the period examined, the number of new cases constantly increased: 1985–1989, 7 new cases; 1990–1994, 12; 1995–1999, 21; 2000–2005, 32. Sixty-eight patients (93%) were of white ancestry. Other ethnic origins were: Haitian black, Indian, Turkish, Pakistani, and Moroccan (1 patient each). Global mortality rate in the cohort was 46%, and the median age at death was 13 months (range: 1 day to 20 years). Among living patients, all but 1 had complete follow-up; mean follow-up time for living patients was 12.4 ± 7.5 years. A family history consistent with MD was found in 17 patients (28%). Consanguinity (7 families) or recurrence within the family (7 sibling pairs) was present for 14 of 66 families (21%). Two of these sibling pairs had PDH deficiency because of mutations in the X-linked E1α gene. Matrilineal transmission was documented in 7 patients (10%) who had mtDNA mutations.

Clinical Presentation

The first manifestations of the disease were recorded at a median age of 7 months (range: 0–16 years) and encompassed a wide range of symptoms including: nonspecific psychomotor delay (38%), metabolic acidosis (14%), failure to thrive (10%), acute or subacute regression (9%), visceral involvement (liver dysfunction, 4%; hypertrophic cardiomyopathy, 3%), and various combinations of focal neurologic symptoms (22%), including seizures, ataxia, extrapyramidal signs, muscle weakness or pain, ptosis, and headache. Excluding patients with LHON, median age at first symptoms was 5 months (range: 0–14 years), and a MD was first suspected at a median age of 10 months (range: 0–203). The median delay between first symptoms and diagnosis was 3 months (range: 0–121). The number of patients in each clinical category is shown in Table 1.

In the neonatal subgroup, patients presented immediately at birth with fulminant lactic acidosis and neurologic distress. All died in the first months (median age at death: 4 days). Interestingly, prenatal evaluation of these patients showed hydrocephalus in a girl with PDH deficiency, and intraventricular hemorrhage, asymmetric ventricular dilatation, and periventricular leucomalacia in a male patient with pyruvate carboxylase deficiency.21 Of note, we found a high rate of pregnancy complications for the whole cohort including gestational diabetes (8 [11%] of 73); hypertension/preeclampsia (5 [7%] of 73); intrauterine growth retardation (4 [5%] of 73; hemolytic anemia, elevated liver enzymes, and low platelets (HELLP) syndrome (1 of 73); and steatohepatitis (1 of 73). Birth weight was below the third percentile in 13 of 66 patients (20%; P < .0001).

Over follow-up, 66 patients (90%) presented clinical signs of cerebral involvement. Developmental delay was common (48 [79%] of 61) in all subgroups except LHON, but it was less frequent in the myopathic category (7 [50%] of 14) than in other subgroups, with the exclusion of LHON (P < .02). Hypotonia in the first year was found in 44 (69%) of 64 patients. Thirty-one (60%) of 51 patients aged >15 months learned to walk at a mean age of 20 ± 11 months. At follow-up, 7 (23%) had lost the ability to walk. Microcephaly was present in 32 patients (44%) and was progressive in 20. Three patients had macrocephaly, 2 with pyruvate carboxylase deficiency and 1 with complex IV deficiency. Seizures were observed in 25 patients (34%). They were the dominant clinical feature in 4 patients. In 5 patients, the seizure type was myoclonic. Nine patients (12%) exhibited extrapyramidal movement disorders ranging from dystonia to choreoathetosis. Ataxia was present in 14 (32%) of 44 patients aged >2 years. In this group, 2 patients with PDH deficiency experienced recurrent episodes of ataxia over the course of several years, separated by symptom-free intervals. Whereas hypertonia and spasticity were found in 20 (29%) of 69 patients, another 10 (14%) had hypo/areflexia and peripheral weakness, suggesting possible neuropathic or myopathic involvement. Of these 10 patients, 6 had electrophysiologic or neuropathological evidence of peripheral neuropathy. In the intermittent neurologic group, 2 patients with PDH deficiency experienced recurrent episodes of isolated peripheral weakness, initially mimicking Guillain-Barré syndrome.24

Acute neurologic events were common: 19 patients (26%) experienced neurologic crisis corresponding to stroke-like episodes (6 cases) or Leigh syndrome (13 cases). In addition, 3 other patients had recurrent episodes of severe muscle cramp with or without myoglobinuria, 2 had intermittent ataxia, and 2 others, intermittent peripheral weakness (see above). In stroke-like episodes, combinations of aphasia, dysarthria, hemiparesis, facial diplegia, hemianopsy, and cortical blindness were observed. The first stroke was recorded at a median age of 13 years (range: 1.3–14.8). Neuroradiology revealed focal cortical lesions in all cases with stroke-like episode. By contrast, Leigh crises occurred at a median age of 0.9 years (range: 2 weeks to 6.4 years). In Leigh syndrome, disturbances of respiratory pattern (including ataxic breathing, intermittent tachypnea with respiratory alkalosis alternating with bradypnea, and hypercap-
nia requiring endotracheal intubation) were observed in 10 patients (77%), whereas such respiratory findings were much less common in the rest of the cohort (12%). Other signs of brainstem dysfunction in Leigh syndrome included swallowing disturbances, hypertension, and nuclear and internuclear ophthalmoplegia.

Twenty-one patients (29%) had visceral involvement: heart (13 patients, 18%), liver (12 patients, 16%), kidney (8 patients, 11%), gastrointestinal tract (6 patients, 8%), and bone marrow (5 patients, 7%). The distribution of organ involvement according clinical category and diagnosis is shown in Table 2. In most of these patients (15 [71%] of 21), >1 organ was involved. All patients with cardiac signs had hypertrophic nonobstructive cardiomyopathy. In 8 patients (11%, Table 1), visceral disease was the predominant clinical manifestation. Paradoxically, cardiac symptoms were infrequent in this group (2 of 8).

Failure to thrive was a frequent observation (38 patients, 52%) and a presenting symptom in 10% of the patients. Forty-two patients (58%) required gastric tube feeding for neurologic and/or nutritional reasons. However, in 8 patients, oral feeding could later be reintroduced. Three patients had major gastrointestinal dysmotility requiring continuous enteral feeding; despite having jejunostomies, 2 required prolonged periods of parenteral nutrition. Nine patients developed hypoglycemia, which was recurrent after short fasting in 4 of them. Two patients had diabetes mellitus, and another 2 had impaired glucose tolerance.

Excluding the 4 patients with LHON, all of whom had isolated optic atrophy, 29 (42%) of 69 patients had ophthalmologic involvement. The spectrum of ophthalmologic manifestations in these patients included optic atrophy (38%), pigmentary retinopathy (21%), ophthalmoplegia (45%), ptosis (31%), nystagmus (28%), and cortical blindness (10%). Neurosensory deafness was present in 26% of the patients (18 of 69).

### Metabolic Status

Long-term metabolic follow-up revealed that 72% of the patients had chronic lactic acidemia, defined as mean plasma lactate level >2.2 mmol/L. Conversely, 61% of the patients had ≥1 plasma lactate concentration in the reference range, showing the high variability of this biochemical parameter. The median number of measurements per patient was 12. Abnormal plasma amino acids showed raised alanine and/or proline, consistent with lactic acidosis, in 47 (73%) of 64 of the patients tested. Abnormal urinary organic acids, that is, various combinations of elevated lactic and pyruvic acids, ketone bodies, and Krebs cycle intermediates, were found in 42 (70%) of 60 patients. The CSF lactate level was raised in 37 (88%) of 42 patients. Four patients with normal plasma lactate levels had increased CSF lactate levels. Conversely, 2 patients with intermittent elevations of plasma lactate levels were found to have normal CSF lactate levels. Both had PDH deficiency and PDH E1α gene mutation and presented with intermittent ataxia. There was no association between lactate, alanine, and

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**TABLE 2** Organ Involvement According to Clinical Category and Diagnosis

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>Visceral Involvement*</th>
<th>No. of Systems</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart</td>
<td>Kidney</td>
<td>Liver</td>
</tr>
<tr>
<td>Neonatal</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leigh</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(Encephalo)myopathy</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visceral</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

MCD indicates multiple complex deficiency; KSS, Kearns Sayre syndrome.

* Each row represents 1 patient. An “X” in the box indicates that involvement of the indicated organ is present.
proline concentrations and the type of biochemical and molecular diagnoses. Mean lactate to pyruvate molar ratios were significantly different between patients with respiratory chain deficiencies or mtDNA mutation and those with PDH deficiency (31.7 ± 13.5 vs 19.6 ± 4.5, respectively; P < .001).

Twenty-two patients (30%) experienced acute crisis of metabolic acidosis defined as plasma bicarbonate concentration ≤10 mmol/L and/or requirement for continuous intravenous bicarbonate infusion. Sixteen of these patients (73%) subsequently died, 10 (45%) during one of these episodes. Mean of average individual plasma lactate concentration during crises was 11.6 ± 7.0 mmol/L. Metabolic crises recurred in 5 patients. Median age at the first acute acidotic episode was 9.5 months (range: birth to 56 months).

Neuroradiology
Neuroimaging studies were available in 59 patients (81%), including magnetic resonance imaging for fifty patients. A wide range of neuroradiological abnormalities were observed: the most common were basal ganglia hyperintensities (27 [46%] of 59) and cerebral atrophy (28 [47%] of 59). Brainstem lesions were identified in 34% of magnetic resonance imaging studies. Stroke-like cortical infarcts were less frequent (10%). Some neuroradiological features less specific to MD were also commonly observed: white matter abnormalities (21 [40%] of 59), corpus callosum hyperintensities (5 [10%] of 59), and cerebellar atrophy (9 [15%] of 59). Of note, brainstem and basal ganglia lesions were not restricted to patients with Leigh disease but were also observed in other clinical presentations (19 [41%] of 46), including nonspecific encephalopathy and visceral subgroups.

Pathology
Mitochondrial proliferation or ultrastructural morphologic abnormalities were identified in 32 (80%) of 40 of the muscle samples examined with electron microscopy. However, using NADH-TR, modified Gomori or succinate dehydrogenase-cytochrome C oxidase stains, only 21 (47%) of 45 muscle biopsies showed evidence of mitochondrial proliferation. Twelve patients (16%) exhibited RRFs with Gomori trichrome staining. In 19 liver samples, histology was normal in 7 and revealed widespread steatosis in 8, active hepatitis and fibrosis in 2, and micronodular cirrhosis in 2 others. Widespread mitochondrial proliferation and abnormalities were found by electron microscopy in 10 (71%) of 14 liver and 2 of 2 kidney biopsies.

Biochemical and Molecular Studies
A biochemical or molecular diagnosis was identified in 81% of subjects. The distribution of specific diagnoses according to clinical category is shown in Table 1. Evaluation for respiratory chain defects or PDH deficiency was not performed in patients with a known pathogenic mtDNA mutation. An enzyme defect was identified in 44 patients. Complex IV deficiency was the most frequent enzyme defect (27%), followed by PDH and complex I deficiencies (25% each). Relative frequencies of enzyme defects are shown in Fig 1. All PDH deficiencies were found in cultured fibroblasts, whereas diagnosis of respiratory chain deficiencies by spectrophotometry required investigations of several tissues: fibroblasts (6 subjects), muscle (10 subjects), liver (14 subjects), and heart (4 subjects). Blue native gel studies revealed a specific enzyme defect in fibroblasts of 11 subjects, including 6 complex IV and 5 complex I deficiencies. Diagnostic yields of spectrophotometric assays and blue native gel studies for each tissue are shown in Fig 2.

An mtDNA mutation was found in 15 patients (20%): “MELAS” A3243G in tRNA^Leu(UUR) (4 patients with classical MELAS phenotype), large heteroplasmic mtDNA deletions (2 patients with Kearns-Sayre syndrome).
“NARP” T8993G/C in MTATP6 (3 patients with Leigh syndrome), and “LHON” T14484C in MTND6 (4 patients with LHON). MtDNA whole genome sequencing detected a new homoplasmic mutation in tRNAser(UCN) (7466_7471delC) and another previously undescribed heteroplasmic mutation in the MTCOIII gene (G9984A, G260X) in 2 patients with mitochondrial myopathy.

Among the 12 patients with RRF, a mtDNA mutation was found in 7 (58%). A mutation in the E1a PDH subunit gene was found in 5 patients with PDH deficiency. Except for the intermittent neurologic subgroup (4 patients with PDH deficiency), there were no correlations between the biochemical defect and type of presentation. As expected, the finding of mtDNA mutation was associated with later-onset presentation \((P < .001)\) and was more common in the (encephalomyopathic and LHON subgroups (8 of 14 and 4 of 4, respectively, vs 3 of 55 for other groups; \(P < .001\)).

**Outcome: Mortality and Morbidity**

The overall mortality rate in the cohort was 46%, based on an observation period of 1.5 to 32 years (median follow-up time of 12 years for living patients). Higher mortality rate was observed in patients in the neonatal, visceral, and Leigh subgroups (100%, 85%, and 69%, respectively). Eighty percent of deaths occurred before the age of 3 years. No association was found between the biochemical defect and type of presentation. As expected, the finding of mtDNA mutation was associated with later-onset presentation \((P = .001)\) and was more common in the (encephalomyopathic and LHON subgroups (8 of 14 and 4 of 4, respectively, vs 3 of 55 for other groups; \(P = .001\)).

**TABLE 3** Predictors of Mortality: Univariate Analysis With Cox’s Proportional Hazard Ratio Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First signs &lt; 6 mo</td>
<td>13.9</td>
<td>4.8–40.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visceral involvement</td>
<td>1.6</td>
<td>0.8–3.3</td>
<td>.16</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>1.0</td>
<td>0.4–2.5</td>
<td>.95</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>2.8</td>
<td>1.3–6.0</td>
<td>.006</td>
</tr>
<tr>
<td>Metabolic crisis</td>
<td>3.4</td>
<td>1.7–6.7</td>
<td>.001</td>
</tr>
<tr>
<td>Neurologic crisis</td>
<td>1.3</td>
<td>0.6–2.7</td>
<td>.50</td>
</tr>
<tr>
<td>Mean lactate concentration(^a)</td>
<td>1.23</td>
<td>1.12–1.37</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>mtDNA mutation</td>
<td>0.06</td>
<td>0.08–0.46</td>
<td>.007</td>
</tr>
<tr>
<td>mtDNA mutation(^b)</td>
<td>0.09</td>
<td>0.01–0.69</td>
<td>.02</td>
</tr>
</tbody>
</table>

\(^a\) Hazard ratio represents the change in mortality risk for each increase of 1 mmol/L in mean lactate level.

\(^b\) Excluding patients with LHON \((n = 69)\).

**TABLE 4** Predictors of Mortality: Multivariate Analysis With Cox’s Proportional Hazard Ratio Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First signs &lt; 6 mo</td>
<td>10.4</td>
<td>3.5–30.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visceral involvement</td>
<td>1.0</td>
<td>0.4–2.7</td>
<td>.98</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>1.7</td>
<td>0.6–4.5</td>
<td>.30</td>
</tr>
<tr>
<td>Mean lactate concentration(^a)</td>
<td>1.16</td>
<td>1.03–3.12</td>
<td>.015</td>
</tr>
</tbody>
</table>

\(^a\) Hazard ratio represents the change in mortality risk for each increase of 1 mmol/L in mean lactate level.
and the presence of metabolic crises, the average plasma lactate concentration was only weakly associated with mortality rate.

Morbidity was assessed in 38 patients with long-term survival. Only 1 patient was lost to follow-up at 12 years old. Median age at last evaluation was 12.1 year (range: 1.5–32 years). Prospective assessment of functional status showed a wide spectrum in outcome, ranging from near complete independence to severe encephalopathy requiring total assistance. Median FIM and WeeFIM scores expressed as quotients of age-related norms are shown in Table 5. Among the 38 survivors with long-term follow-up, self-care and cognition were more severely affected than mobility (Table 5; \( P = .01 \) and \( P < .001 \), respectively). There was no association between specific biochemical diagnosis and the FIM/WeeFIM scores, but because of the small numbers of patients in each category, this does not eliminate the possibility that such an association may exist. After adjustment for occurrence of neurologic and metabolic crises, analysis of variance identified age at first symptoms as the only predictive factor of the global functional outcome (\( P = .009 \)). In a linear regression model, for each year of delay in appearance of initial symptoms, global quotient increased by 5 U. Chronic metabolic status (mean plasma lactate levels), metabolic and neurologic crises were not identified as independent predictors of the functional outcome of patients. However, the relatively small sample size limits the power of these analyses. Global FIM and WeeFIM quotients against age of the patients and according to clinical category are presented in Fig 4. Interestingly, among patients >5 years old (\( n = 32 \)), 62% had global FIM/WeeFIM quotients >0.75.

### DISCUSSION

Nearly any pediatric specialist may be confronted with the initial presentation of MD, to which the mnemonic “any age, any symptom, any organ” has been applied.\(^7\) Patients of this study, identified in a community-based tertiary care pediatric center, illustrate the need for a high level of suspicion for MD in patients with unexplained organ dysfunction. The wide base of referring symptoms of our patient sample suggests a relatively unbiased selection, which may reflect the spectrum of MDs in childhood more accurately than in series based on laboratory recruitment. Of note, the increasing num-

![FIGURE 3](image-url)

Kaplan-Meier survival analysis.

| Table 5: Median (Range) of FIM/WeeFIM Quotients of Living Patients |
|-----------------------------|-----------------------------|-----------------------------|
|                             | WeeFIM         | FIM            | FIM/WeeFIM       |
|                             | \((n = 15)\)    | \((n = 23)\)   | \((n = 38)\)     |
| Age, y                      | 6.0 (1.5–8.2)  | 14.8 (9.0–32.9)| 10.3 (1.5–32.9) |
| Domains                     |               |                |                 |
| Self-care                   | 0.62 (0.24–0.97)| 0.89 (0.14–1.00)| 0.76 (0.14–1.00)|
| Mobility                    | 0.68 (0.14–1.00)| 0.97 (0.14–1.00)| 0.94 (0.14–1.00)|
| Cognition                   | 0.71 (0.21–0.92)| 0.77 (0.14–1.00)| 0.75 (0.14–1.00)|
| Global                      | 0.66 (0.20–0.95)| 0.89 (0.14–1.00)| 0.81 (0.14–1.00)|

No. at risk

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms &gt; 6 mo</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>Symptoms &lt; 6 mo</td>
<td>35</td>
<td>3</td>
</tr>
</tbody>
</table>

Log-rank test, \( P < .0001 \)
bers of patients diagnosed over time suggests that in the past, diagnosis was reserved for patients with severe or classic presentations. By extension, many MDs probably remain undiagnosed, particularly in their early stages.

We identified a high frequency of pregnancy complications. This was previously suggested by only 1 study. The prevalence of low birth weight in our cohort (20%) is similar to that reported by von Kleist et al. Association between fetal mitochondrial disorders and gestational diabetes, preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy has not been previously reported. Although these associations could be fortuitous, the repercussions of energy defects in the fetoplacental unit are essentially unknown. Interestingly, maternal HELLP syndrome is a well-recognized complication of fetal fatty acid oxidation defects. Although more data are necessary, we suggest careful monitoring of pregnancies at risk for an affected fetus.

The overall frequency of neurologic manifestations is similar to previous studies. However, we found a high frequency (35%) of acute neurologic presentations. This has not previously been emphasized in pediatric patients with MD. In addition to Leigh crises and stroke-like episodes, the spectrum of episodic neurologic events included intermittent ataxia, episodic peripheral weakness, and recurrent muscle cramps. Inherited disorders of energy metabolism should be considered in any child with unexplained acute and/or recurrent neurologic symptoms.

Although visceral involvement was frequent in our cohort, we did not observe the previously reported frequency and the high mortality of cardiomyopathies in patients with MD. In our series, cardiomyopathy was often a mild and asymptomatic echocardiographic finding. By contrast, hepatic involvement was frequent and associated with high mortality. Such discrepancies between studies illustrate that the incidence of clinical manifestations in MD remains incompletely characterized and that additional multicentric studies may be necessary to understand the complete spectrum of the MD in childhood. Interestingly, we showed that patients with visceral manifestations often have multiple organ involvement, suggesting that close follow-up and periodic multivisceral evaluation is required in this group.

Measurement of lactic acid in plasma is a useful but nonspecific test. Although 72% of the patients have chronic lactic acidemia, up to 60% had at least 1 normal lactate concentration, illustrating the variability of this biological parameter and emphasizing that a normal lactate concentration does not exclude MD. Conversely, imperfect blood sampling conditions involving tissue hypoxia or physical exertion such as struggling or crying in infants can falsely increase lactate levels or the lactate/pyruvate molar ratio. Repeated blood lactate measurements can clarify the true metabolic status of the patients. CSF lactate measurement is less variable and is essential in some patients having “cerebral” lactic acidosis, as illustrated by the 4 patients with normal lactic acidemia.
acid in blood who had clearly increased CSF lactate levels. In contrast, 2 sibs with recurrent episodes of ataxia, enzymatically proven PDH deficiency, and PDH E1α gene mutation had normal lactate levels in both blood and CSF, showing that even a normal CSF lactate level cannot exclude MD.

A third of our patients developed acute acidotic crisis, usually in association with otherwise benign infectious diseases. This life-threatening complication, little emphasized in the literature, is a major issue in patient management, requiring ICU admission for intravenous bicarbonate administration and other supportive measures, despite which mortality remains nearly 50%. Most acidotic crises occurred during infancy. We did not find any correlation between clinical or biochemical parameters and the occurrence of metabolic crises. In our practice, we have the impression that optimal nutritional status and complete immunization may reduce the frequency of these metabolic crises.

Diagnostic yield of biochemical analyses according to the tissue tested illustrates the complexity of diagnostic process in MD. On one hand, some respiratory chain defects have a tissue specific expression; on the other hand, technical problems in tissue handling and storage can give rise to artifactually low enzyme activities. In addition, tissues may be affected by nonmetabolic disorders like disuse muscle atrophy or liver failure of various etiologies. This can also result in nonspecific low respiratory chain activity. The overall yield of liver testing in our cohort was higher than those of muscle and fibroblast. Liver biopsy is invasive and associated with a small but not insignificant risk of complications, particularly in fragile patients such as those suffering from MD. Our study shows that fibroblast analyses reveal a substantial proportion of respiratory chain defects, especially when spectrophotometric assays and blue native gel analysis are combined. Moreover, PDH deficiency is reliably identified in fibroblasts. The utility of blue native gel studies in fibroblasts was already reported, and we now routinely perform this in patients suspected of MD.

In our series, PDH deficiency is a frequent diagnosis (15%). Similar or lower PDH deficiency frequencies were reported previously in series of patients in whom PDH activity was measured. However, PDH deficiency has not been reported consistently in cohorts with MD. PDH deficiency was excluded from some published series because it is not a respiratory chain defect and is not routinely assayed in all diagnostic laboratories. In our experience, the distinction between respiratory chain and PDH deficiencies is often not pos-
sible clinically at presentation. Both disorders belong to the broad group of congenital lactic acidosis, justifying the inclusion of PDH deficiency in clinical review of MD in childhood. Importantly, PDH deficiency is one of the few conditions in this group for which specific treatments exist.\(^\text{36–39}\) Patients with PDH deficiency in our cohort had no visceral involvement, which is in accordance with the most recent literature.\(^\text{40}\) Although the L/P ratio was significantly lower in patients with PDH deficiency compared with others, overlap between these groups shows that the L/P ratio can not be used alone to discriminate individual patients. We suggest that PDH deficiency should be considered in any patient with congenital lactic acidosis, particularly those with predominant neurologic symptoms. Measurement of PDH activity in fibroblasts should be routinely performed in such cases.

On the basis of these considerations, we propose an algorithm of investigations for patients with congenital lactic acidosis or presumed MD (Fig 5). Because most of these conditions are currently untreatable, we suggest starting with the least-invasive techniques (fibroblast culture, blood DNA testing for specific etiologies as indicated) before performing muscle and/or liver biopsy. Such tests have a substantial yield. In some cases, the strategy of sequential testing eliminates the need for invasive procedures. For example, 3 of 13 patients with Leigh syndrome in our series were found to have mtDNA T8993G/C mutation in blood leukocytes. Moreover, identification of a respiratory chain defect on fibroblasts is sometimes the first step toward a molecular diagnosis, using complementation studies in research protocols.\(^\text{42,43}\)

The age at first symptoms was a major prognostic factor for mortality. Infants presenting their first symptoms before 6 months of age have a tenfold increased risk of mortality during the observation period compared with those presenting later. Although previously suggested,\(^\text{9}\) this has never been evaluated previously by multivariate analysis. Higher plasma lactate concentration was also positively associated with mortality.

Because the clinical course of MD is chronic, progressive, and unpredictable, long-term follow-up of large cohorts is necessary for a better understanding of the spectrum of severity of these conditions. Except for 1 recent study of MD presenting in the neonatal period,\(^\text{44}\) there is no report in the medical literature on long-term outcome of pediatric patients with MD. Because of the wide range of age and severity in our cohort, and because we were interested in quality of life and disease burden for patients and families, we evaluated outcome in terms of functional status rather than with classical cognitive testing. In our series, age at first symptoms was positively correlated with the global FIM/WeeFIM quotient. Figure 4 suggests that there may be 2 groups of patients, 1 with a stable course and preserved function, and 1 with deterioration and/or low functional level and encephalopathy. Larger numbers of patients and longer follow-up will be required to draw a definitive conclusion, but encouragingly, a substantial proportion of the patients aged >5 years had mild or no impairment.

**CONCLUSIONS**

We report the first systematic prospective evaluation of the functional outcome of pediatric patients with MD. We identified age at first symptoms as a major prognostic factor for mortality and morbidity. Although a high mortality rate was observed in the first years, the functional status of survivors, based on long-term follow-up, was more favorable than previously thought: a substantial proportion of patients have an unimpaired functional independence level.

**ACKNOWLEDGMENTS**

We acknowledge the excellent work of Yolande Lefevre, Danielle Regimbalde, and Manon Bouchard in the support and treatment of patients during the course of this study.

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42. Zuh Z, Yao J, Johns T, et al. SURF1, encoding a factor involved in the biogenesis of cytochrome c oxidase, is mutated in Leigh syndrome. Nat Genet. 1998;20:337–343


Association Between Passive Smoking and Infection With Mycobacterium tuberculosis in Children

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Tuberculosis and smoking are both significant public health problems. The association between passive smoking and Mycobacterium tuberculosis infection is not well documented. The objective of this study was to examine the influence of passive smoking on M tuberculosis infection in children.

METHODS. A community survey was conducted in 15% of addresses in 2 adjacent low-income suburbs in Cape Town, South Africa. All children (<15 years of age) and their adult household members residing at these addresses were included in the study. Children underwent tuberculin skin testing. An induration of ≥10 mm was considered to define M tuberculosis infection. Passive smoking was defined as living in the household with at least 1 adult who smoked for at least 1 year. Random-effects logistic regression analysis was performed, and odds ratios were adjusted for age, presence of a patient with tuberculosis in the household, average household income, and clustering at the household level.

RESULTS. Of 1344 children, 432 (32%) had a positive tuberculin skin test. Passive smoking was significantly associated with M tuberculosis infection in the unadjusted analyses but not in the adjusted analyses. In the 172 households with a patient with tuberculosis, passive smoking was significantly associated with a positive tuberculin skin test (but not in the 492 households without a patient with tuberculosis.

CONCLUSIONS. Passive smoking is associated with M tuberculosis infection in children living in a household with a patient with tuberculosis. More studies are needed to confirm this observation, but the possible association is a cause of great concern, considering the high prevalence of smoking and tuberculosis in most developing countries.
Recently, we reported that cigarette smoking is associated with Mycobacterium tuberculosis infection in adults, a finding confirmed in several other studies. Few studies have investigated the association between environmental tobacco smoke exposure (passive smoking) and M tuberculosis infection.

Passive smoking may have particularly harmful effects in children compared with adults because children’s respiratory and immune systems are not fully developed. In addition, children spend more time at home and are, therefore, likely to experience more intense and prolonged smoke exposure if adult household members smoke. Passive smoking increases a child’s risk to develop asthma, bronchitis, pneumonia, otitis media, and sudden infant death syndrome and to undergo procedures such as tympanostomies, tonsillectomies, and adenoidectomies. At present, there is insufficient information to establish whether there is an association between passive smoking and M tuberculosis infection in children. We conducted a cross-sectional community survey allowing an assessment of the association between M tuberculosis infection and passive smoking in children. We hypothesized that passive smoking was associated with M tuberculosis infection in children.

METHODS

Study Area and Study Population

The study was performed in 2 adjacent urban low-income to middle-income communities (Ravensmead and Uitsig) in Cape Town, South Africa, with a population of 36,334 in 2001. The tuberculosis notification rate was 341 per 100,000 for new smear-positive tuberculosis and 841 per 100,000 for total adult tuberculosis (pulmonary and extra-pulmonary tuberculosis) in 2002. Childhood tuberculosis cases comprise ~18% of the total tuberculosis case load. The prevalence of human immunodeficiency virus infection in antenatal women in the district in which Ravensmead and Uitsig are located increased from 7.9% in 2001 to 15.1% in 2004.

Data Collection

This study was part of a comprehensive lung-health survey and was conducted between July 1 and December 15, 2002. Eight hundred thirty-seven (15%) residential addresses were selected randomly from a Geographical Information System containing the exact location of all 5,592 addresses in the study area. If the head of the address did not give consent, the adjacent address was selected, first to the right and then to the left. All residents living at the selected addresses were eligible for participation in the study. Signed informed consent was obtained from all adult (~15 years of age) participants and from the parents or legal guardians of the children (<15 years of age). All children received an intradermal tuberculinn skin test (TST) of 2 TU (0.1 mL) purified protein derivative RT 23 on the ventral aspect of the left forearm. The induration was measured after 48 to 120 hours by trained nurses. A reaction of ≥10 mm was considered to represent M tuberculosis infection. All adult household members completed a questionnaire containing questions on smoking behavior, income, and past diagnosis of tuberculosis.

Statistical Analysis

Passive smoking was defined as living in the household with at least 1 adult who smoked for at least 1 year. Average income of the adult household members was calculated as the total income of all household members together, divided by the number of adult household members. Children who were active smokers and children for whom no data on passive smoking was available were excluded from the analysis. A random-effects logistic regression was used to model M tuberculosis infection on passive smoking. The clustering at the household level was accounted for by including household as the random effect in the model. Unadjusted and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated. Confounding factors that were taken into consideration were age of the child, average income of the adult household members, and the presence of a patient with tuberculosis in the household. We also used a random-effects logistic regression model to determine the association between M tuberculosis infection in children and the number of smokers in the household and the average number of cigarettes smoked per day in the household. Separate analyses were conducted for children living in households where at least 1 of the adults ever had tuberculosis and for children living in households where none of the adults ever had tuberculosis. The TST distributions of children who had the induration measured after 48 to 72 hours and those who had it measured after 96 to 120 hours were compared by using the Mann-Whitney test.

Ethics approval was obtained from Stellenbosch University and the University of Cape Town. The study was conducted in accordance with the ethical standards of the World Medical Association’s Helsinki Declaration.

RESULTS

A total of 1,811 children were eligible for the study. For 1,593 (88%) children, consent was obtained from the parents or legal caregivers. Three children were excluded because no data on passive smoking was available, and 220 children were excluded because the TST was not done or read within 48 to 120 hours. There was no difference in TST size distribution between those who had the inductions read between 48 and 72 hours and those who had it read up to 120 hours after administration (P = .4242). Therefore, all children with TST read between 48 and 120 hours were used in the analyses. Twenty-six children were excluded from the analyses
because they were active smokers. All these children were also passive smokers. A total of 1344 (84%) of 1593 children from 664 households were included in the analyses. The children who were included in the analyses did not differ in gender or age from the children who were not included in the analyses or those for whom no consent was obtained (Table 1).

Four hundred thirty-two children (32%) had a TST induration of $\geq 10$ mm. Older children were more often infected than younger children (Table 2). A total of 1170 (87%) children were passive smokers in the household, and these children more often had a positive TST (34%) than children who were not passive smokers (21%) (unadjusted OR: 1.89; 95% CI: 1.24–2.86). However, the significance of this finding was not maintained after adjustment for the variables age of the child, average income of the adults in the household, and the presence of a patient with tuberculosis in the household (adjusted OR for each additional smoker: 1.03; 95% CI: 0.94–1.13) and the number of cigarettes smoked per day in the household (adjusted OR for each additional cigarette: 1.005; 95% CI: 0.999–1.011).

There was a significant relationship between $M. tuberculosis$ infection in children and both the number of smokers in the household (OR for each additional smoker: 1.12; 95% CI: 1.03–1.20) and the number of cigarettes smoked per day in the household (OR for each additional cigarette: 1.009; 95% CI: 1.003–1.014). However, this was no longer significant after adjustment for the variables age of the child, average income of the adults in the household, and the presence of a patient with tuberculosis in the household. The OR for each additional smoker was 1.03 (95% CI: 0.86–2.12) and the number of cigarettes smoked per day in the household was 4.09 (95% CI: 0.95–17.54; $P = .058$). In the analysis stratified by the presence of a patient with tuberculosis in the household, we could not detect a quantitative effect for the number of smokers in the household or for the average number of cigarettes smoked per day in the households.

DISCUSSION

Passive smoking was not in general associated with $M. tuberculosis$ infection. However, a stratified analysis by households with a patient with tuberculosis demonstrated a significant association between passive smoking and $M. tuberculosis$ infection in children. This finding suggests that passive smoking may increase the risk to acquire $M. tuberculosis$ infection, given household exposure to an adult index case. The association is a cause of great concern, because in many developing countries with a

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**TABLE 1** Characteristics of Children Who Were Sampled and Children Who Were Included in the Analyses

<table>
<thead>
<tr>
<th>Total Sampled</th>
<th>Included</th>
<th>% Included</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>899</td>
<td>679</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>909</td>
<td>665</td>
<td>73</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>561</td>
<td>415</td>
<td>74</td>
</tr>
<tr>
<td>5–9</td>
<td>638</td>
<td>490</td>
<td>77</td>
</tr>
<tr>
<td>10–14</td>
<td>610</td>
<td>439</td>
<td>72</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1811</td>
<td>1344</td>
<td>74</td>
</tr>
</tbody>
</table>

---

**TABLE 2** Risk Factors for $M. tuberculosis$ Infection in Children <15 Years Old

<table>
<thead>
<tr>
<th>Total</th>
<th>$\geq 10$ mm, $n$</th>
<th>$\geq 10$ mm, %</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker in household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>174</td>
<td>37</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>$\geq 1$</td>
<td>1170</td>
<td>395</td>
<td>34</td>
<td>1.89 (1.24–2.86)</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>415</td>
<td>78</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>5–9</td>
<td>490</td>
<td>161</td>
<td>33</td>
<td>2.11 (1.57–2.84)</td>
</tr>
<tr>
<td>10–14</td>
<td>439</td>
<td>193</td>
<td>44</td>
<td>3.39 (2.46–4.67)</td>
</tr>
<tr>
<td>Average monthly income of adults, Rand$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;500$</td>
<td>246</td>
<td>93</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>500–999</td>
<td>511</td>
<td>182</td>
<td>36</td>
<td>0.91 (0.63–1.32)</td>
</tr>
<tr>
<td>1000–1999</td>
<td>386</td>
<td>118</td>
<td>31</td>
<td>0.72 (0.49–1.07)</td>
</tr>
<tr>
<td>$\geq 2000$</td>
<td>199</td>
<td>39</td>
<td>20</td>
<td>0.40 (0.25–0.65)</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patient with tuberculosis in household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>943</td>
<td>253</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>401</td>
<td>179</td>
<td>45</td>
<td>2.20 (1.63–2.96)</td>
</tr>
<tr>
<td>Total</td>
<td>1344</td>
<td>432</td>
<td>32</td>
<td>2.01 (1.46–2.77)</td>
</tr>
</tbody>
</table>

$^a$1 US dollar = ~6 South African Rand.
high burden of tuberculosis, the prevalence of smoking is rapidly increasing, especially among women.\textsuperscript{19,20} In 1995, 58\% of men and 59\% of women from the ethnic group that we studied were smokers.\textsuperscript{21} In our study, 87\% of the children experienced passive smoking at home, which is higher than was reported by Reddy et al,\textsuperscript{21} who found that 67\% of children had at least 1 household member who smoked. The difference may be explained by the fact that we included current smokers as well as ex-smokers. However, we think that few smokers in this community stop smoking. The high proportion of women who smoke is of particular concern because they expose their children to tobacco smoke. Passive smoking might affect the immune system of the child, thus increasing the risk of getting infected. Exposure to tobacco smoke leads to alterations in the epithelial function, such as reduced mucociliary activity, decreased clearance of inhaled substances, and abnormal vascular and epithelial permeability.\textsuperscript{3,22–25} Furthermore, smoking can change the amount, consistency, and permeability of the mucus.\textsuperscript{3,26,27} The number of alveolar macrophages increases because of tobacco smoke exposure, but their ability to phagocytose and/or kill bacteria decreases.\textsuperscript{28–30} As a result, the innate immunity of the lung is compromised, and it is easier for infectious agents to reach the alveolar tissue. T cells are highly susceptible to cigarette smoke, which could impair their cytotoxic capacity to fight infections.\textsuperscript{26} Furthermore, cigarette smoking is associated with reductions in serum immunoglobulins, T-lymphocyte helper/suppressor cell ratios, and natural killer cytotoxic activity,\textsuperscript{31–33} which may result in a decreased immune response of the body to \textit{M tuberculosis} infection.

Few other studies have looked at the association between passive smoking and \textit{M tuberculosis} infection. Kuemmerer and Comstock\textsuperscript{34} noted that tuberculin reac-

### Table 3: Risk Factors for \textit{M Tuberculosis} Infection in Children <15 Years Old if a Patient With Tuberculosis had Lived in the Dwelling

<table>
<thead>
<tr>
<th>Smoker in household</th>
<th>Total</th>
<th>≥10 mm, n</th>
<th>≥10 mm, %</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13</td>
<td>2</td>
<td>15</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥1</td>
<td>388</td>
<td>177</td>
<td>46</td>
<td>4.61 (1.15–18.47)</td>
<td>4.60 (1.29–16.45)</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>120</td>
<td>32</td>
<td>27</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5–9</td>
<td>151</td>
<td>72</td>
<td>48</td>
<td>2.51 (1.50–4.19)</td>
<td>2.46 (1.45–4.19)</td>
</tr>
<tr>
<td>10–14</td>
<td>130</td>
<td>75</td>
<td>58</td>
<td>3.75 (2.12–6.63)</td>
<td>4.02 (2.25–7.18)</td>
</tr>
<tr>
<td>Average monthly income of adults, Rand\textsuperscript{a}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>93</td>
<td>46</td>
<td>50</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>500–999</td>
<td>197</td>
<td>86</td>
<td>44</td>
<td>0.79 (0.44–1.43)</td>
<td>0.89 (0.46–1.71)</td>
</tr>
<tr>
<td>1000–1999</td>
<td>85</td>
<td>42</td>
<td>49</td>
<td>1.00 (0.53–1.88)</td>
<td>1.21 (0.57–2.58)</td>
</tr>
<tr>
<td>≥2000</td>
<td>26</td>
<td>5</td>
<td>19</td>
<td>0.24 (0.09–0.69)</td>
<td>0.28 (0.10–0.79)</td>
</tr>
<tr>
<td>Patient with tuberculosis in household</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>306</td>
<td>126</td>
<td>41</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥2</td>
<td>95</td>
<td>53</td>
<td>56</td>
<td>1.80 (1.04–3.12)</td>
<td>1.91 (1.00–3.67)</td>
</tr>
<tr>
<td>Total</td>
<td>401</td>
<td>179</td>
<td>45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}1 US dollar = ~6 South African Rand.

### Table 4: Risk Factors for \textit{M Tuberculosis} Infection in Children <15 Years Old if There Was Never a Patient With Tuberculosis Living in the Dwelling

<table>
<thead>
<tr>
<th>Smoker in household</th>
<th>Total</th>
<th>≥10 mm, n</th>
<th>≥10 mm, %</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>161</td>
<td>35</td>
<td>22</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥1</td>
<td>782</td>
<td>218</td>
<td>28</td>
<td>1.39 (0.89–2.18)</td>
<td>1.20 (0.75–1.93)</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>295</td>
<td>46</td>
<td>16</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5–9</td>
<td>339</td>
<td>89</td>
<td>26</td>
<td>1.93 (1.33–2.80)</td>
<td>1.96 (1.35–2.86)</td>
</tr>
<tr>
<td>Average monthly income of adults, Rand\textsuperscript{a}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>153</td>
<td>47</td>
<td>31</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>500–999</td>
<td>314</td>
<td>96</td>
<td>31</td>
<td>0.99 (0.61–1.61)</td>
<td>0.94 (0.56–1.98)</td>
</tr>
<tr>
<td>1000–1999</td>
<td>301</td>
<td>76</td>
<td>25</td>
<td>0.76 (0.47–1.24)</td>
<td>0.72 (0.43–1.20)</td>
</tr>
<tr>
<td>≥2000 Rand</td>
<td>173</td>
<td>34</td>
<td>20</td>
<td>0.55 (0.31–0.97)</td>
<td>0.51 (0.29–0.92)</td>
</tr>
<tr>
<td>Total</td>
<td>943</td>
<td>253</td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}1 US dollar = ~6 South African Rand.
tions were larger in children where both parents smoked. A study in India reported a relative risk of 2.68 (95% CI: 1.52–4.71) for *M. tuberculosis* infection in children under the age of 5 years who lived with an adult patient with tuberculosis and who were exposed to environmental tobacco smoke compared with children who were not exposed to environmental tobacco smoke. Multivariate analysis included sputum positivity of the index case and malnutrition of the child, but no adjustments were made for socioeconomic status, which may have biased the results. Current smoking status of the tuberculosis index case was a significant univariate risk factor for tuberculosis infection in adult and child contacts in a study by Gerald et al. However, they excluded smoking from their final model because of small numbers.

Our study has some limitations. In the analysis on the subgroup of children who were exposed to a patient with tuberculosis in the household, the number of children without a smoker in the household was very small. Although the OR was large, suggesting that there is an association between passive smoking and *M. tuberculosis* infection, the small sample size is reflected in a wide CI and, therefore, we must interpret the findings with caution. Smoking status was based on self-reporting and might have been influenced by reporting bias. We did not measure biological markers such as urine cotinine levels to confirm exposure to tobacco smoke. Another possible bias is that smoking households may differ from nonsmoking households in aspects other than the smoking of tobacco. We tried to control for socioeconomic status by adjusting for average income. Education and crowding were not significantly associated with *M. tuberculosis* infection and were, therefore, not included in the analyses. We could not adjust for nutritional status. We did control for the presence of a patient with tuberculosis in the household because it is an important confounder because smokers are more likely to have tuberculosis than nonsmokers. Cough in heavy smokers can also lead to delay in the diagnosis of tuberculosis, resulting in more time to transmit the disease. Patients with tuberculosis who smoke might also be more infectious because of more coughing. The TST as a measure of tuberculosis infection has its limitations. Small indurations may be because of exposure to environmental mycobacteria and/or cross-reactivity because of BCG. However, we do not think environmental mycobacteria are highly prevalent in the study area as we found an unimodal distribution of TST responses with hardly any small indurations. Furthermore, tuberculin reactivity after BCG vaccination is primarily affected by age at vaccination. If the vaccine is given in infancy, as is the case in our communities, tuberculin reactions wane rapidly in all individuals. Therefore, we think that the cutoff point of 10 mm used to indicate *M. tuberculosis* infection is justified in children from this population.

**CONCLUSIONS**

Although passive smoking, in general, was not associated with *M. tuberculosis* infection, passive smoking was significantly associated with *M. tuberculosis* infection in the stratified analysis by households with a patient with tuberculosis. More studies are needed to confirm this observation, but the possible association is a cause of great concern considering the high prevalence of smoking and tuberculosis in most developing countries.

**ACKNOWLEDGMENTS**

We thank Dr Ivan Toms, Director of Health of the City of Cape Town, for the permission to conduct epidemiologic research in the communities of Ravensmead and Uitsig. We also thank Katherine Lawrence for data management.

**REFERENCES**

15. Western Cape Tuberculosis Program. *Health Facility Report for...*
Incidence, Complications, and Risk Factors for Prolonged Stay in Children Hospitalized With Community-Acquired Influenza

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. Few studies have examined the characteristics and clinical course of children hospitalized with laboratory-confirmed influenza. We sought to (1) estimate the age-specific incidence of influenza-related hospitalizations, (2) describe the characteristics and clinical course of children hospitalized with influenza, and (3) identify risk factors for prolonged hospitalization.

PATIENTS AND METHODS. Children ≤21 years of age hospitalized with community-acquired laboratory-confirmed influenza at a large urban children’s hospital were identified through review of laboratory records and administrative data sources. A neighborhood cohort embedded within our study population was used to estimate the incidence of community-acquired laboratory-confirmed influenza hospitalizations among children <18 years old. Risk factors for prolonged hospitalization (>6 days) were determined by using logistic regression.

RESULTS. We identified 745 children hospitalized with community-acquired laboratory-confirmed influenza during the 4-year study period. In this urban cohort, the incidence of community-acquired laboratory-confirmed influenza hospitalization was 7 per 10,000 child-years of observation. The median age was 1.8 years; 25% were infants <6 months old, and 77% were children <5 years old. Many children (49%) had a medical condition associated with an increased risk of influenza-related complications. The incidence of influenza-related complications was higher among children with a preexisting high-risk condition than for previously healthy children (29% vs 21%). However, only cardiac and neurologic/neuromuscular diseases were found to be independent risk factors for prolonged hospitalization.

CONCLUSIONS. Influenza is a common cause of hospitalization among both healthy and chronically ill children. Children with cardiac or neurologic/neuromuscular disease are at increased risk of prolonged hospitalization; therefore, children with these conditions and their contacts should be a high priority to receive vaccine. The impact on pediatric hospitalization of the new recommendation to vaccinate all children 6 months to <5 years old should be assessed.
Influenza is a common cause of illness in children. Although the burden of disease in children is incompletely understood, studies suggest that children with selected underlying medical conditions are at increased risk of hospitalization or complications associated with influenza virus infection.1-6 Over the past 4 years, public health officials have expanded the groups of children recommended to receive annual influenza immunization. Children now recommended to receive influenza vaccine include preschool-aged children ages 6 months to ≤5 years and children with underlying neurologic/neuromuscular disease.7,8 Debate continues about the need for and logistic impediments associated with extending influenza vaccination recommendations to all children.9,10

Although influenza is a relatively common cause of hospitalization among children during the winter months, few studies have described the characteristics of a large cohort of children with laboratory-confirmed influenza who require hospitalization. Previous studies of influenza-related hospitalizations, complications, and deaths in children have relied primarily on administrative data and have not been based on cases of laboratory-confirmed influenza (LCI). In this study, we used hospital laboratory results to identify all children with LCI. Detailed clinical data were obtained from electronic hospital billing records and systematic chart review of children hospitalized with community-associated (CA) LCI. In this report we (1) determined the age-specific incidence of hospitalization attributable to influenza, (2) described the clinical characteristics and complications of children hospitalized with influenza, and (3) identified risk factors for prolonged hospitalization attributable to influenza.

Methods
Design, Setting, and Patients
We conducted a retrospective cohort study of children hospitalized with CA LCI during 4 consecutive seasons (July 2000 through June 2004) at the Children’s Hospital of Philadelphia (CHOP). CHOP is an academic, tertiary-care hospital with 418 patient beds and 24,000 hospital admissions each year. At CHOP, hospitalized patients with acute respiratory symptoms of unclear etiology routinely undergo testing for respiratory viral pathogens to facilitate the appropriate cohorting of patients and assignment of nursing staff for infection control purposes. We have described previously the methods used for identifying cases of CA LCI during the study period.11 Briefly, we identified cases using both clinical virology laboratory records and hospital administrative data (influenza-specific International Classification of Diseases, Ninth Revision [ICD-9] admission or discharge codes 487, 487.0, 487.1, and 487.8). Patients identified by ICD-9 codes required laboratory confirmation to be included as subjects in the study cohort. As part of routine care at CHOP, nasal aspirate specimens were collected from children with acute respiratory symptoms of unclear etiology and were initially tested by solid-phase immunoassay (SPIA) for respiratory syncytial virus (Binax NOW RSV; Binax; Portland, ME) and influenza (Binax NOW FluA and FluB). Direct fluorescent antibody (DFA) testing for adenovirus, influenza A and B, parainfluenza virus types 1, 2, and 3, and respiratory syncytial virus was performed on specimens that tested negative by SPIA for respiratory syncytial virus and influenza A and B. Finally, comprehensive viral culture was established for all specimens that were negative for respiratory viruses on DFA.

Study Definitions
CA LCI
A patient was determined to have a health care-associated infection if the first diagnostic specimen positive for influenza was obtained >72 hours after hospital admission or if the patient was rehospitalized with new-onset LCI within 72 hours of discharge from a previous hospitalization; patients with health care-associated influenza were excluded from the analysis.

Chronic Medical Conditions
To identify preexisting chronic medical conditions that might predispose a child to serious influenza infection, we performed a detailed chart review to provide us with information about the presence of Advisory Committee on Immunization Practices (ACIP)–designated, high-risk medical characteristics as previously described,12 such as asthma, chronic lung diseases, cardiac disease, immunosuppression, hemoglobinopathies, chronic renal dysfunction, diabetes mellitus, and inborn errors of metabolism, long-term salicylate therapy, neurologic/neuromuscular disease (NMD), and pregnancy. Infants <12 months of age were defined as premature if their estimated gestational age at birth was <36 weeks. For patients with multiple hospitalizations during the 4-year study period, we included only the first hospitalization in the analysis.

Major Complications
Complications among patients hospitalized with CA LCI were identified by using data from discharge summaries, consultants’ reports, and billing records. Respiratory failure was defined as the need for mechanical ventilation. We identified patients who had altered mental status for >24 hours as having encephalopathy, consistent with the definition of influenza-related encephalopathy developed by the Centers for Disease Control and Prevention (CDC).12 In addition, patients with new-onset or increased frequency of seizures were also categorized as having influenza-related seizures. We defined myocarditis as new abnormalities of cardiac electrical or con-
tractile function documented by a cardiologist. Myositis was defined by a peak serum creatine kinase concentration twofold greater than normal for age. Suspected bacterial pneumonia was identified if an attending radiologist read a chest radiograph as having a focal infiltrate or opacity or pleural effusion. Radiographs with diffuse interstitial infiltrates were not included in this category. Influenza-related bacteremia was identified if a patient had evidence of a laboratory-confirmed bloodstream infection based on definitions from the CDC within 48 hours of hospitalization. Prolonged hospital stay was defined as hospitalization for longer than 6 consecutive days, which corresponded to \( \pm 2 \) SDs beyond the median length of stay (LOS).

**Data Collection**
Clinical data were retrieved by systematic review of the medical charts using a structured data collection instrument. Demographic and cost data were abstracted from hospital billing records and administrative data sets and validated as previously described.11

**Clinical Data**
The physician admission and discharge notes, physician discharge summary, laboratory and radiology records were searched for the following clinical variables: hospital discharge within 72 hours of current admission; presence of chronic conditions; and laboratory results, chest radiograph, and neuroimaging results. Notes from subspecialty consultants were also reviewed to identify possible influenza-related complications. Race and ethnicity are self-reported at the time of hospital registration and recorded by registrars using 4 categories of race and 2 categories of ethnicity. We collected information about race/ethnicity to assess the generalizability of our findings and to determine whether the study sample was reflective of the CHOP inpatient population.

**Administrative Data**
Demographic data collected included patient age and gender. The following clinical data were captured from administrative data sets: duration of hospitalization, need for admission to an ICU, mechanical ventilation, and radiographic and laboratory diagnostic testing.

To verify the accuracy of the administrative and billing data sources used to capture clinical variables, we conducted an audit of 10% of randomly selected records and compared data gathered from administrative sources with those obtained from chart review as previously described.11 Discrepant results were found in <3% of audited data points.

**Estimation of Incidence of Pediatric Hospitalizations Because of Influenza**
To estimate the incidence of pediatric hospitalizations attributable to CA LCI, a neighborhood cohort was defined. Administrative claims data from all acute care hospitals in Pennsylvania and New Jersey were queried (Solucient Corporation, New Orleans, LA) to identify zip-code areas with documented preferential admission to CHOP for acute asthma exacerbation (ICD-9 code 493.02 [extrinsic asthma, acute exacerbation]). Nine contiguous zip-code areas were identified from which >70% of all children \(< 18\) years of age who required hospitalization for asthma were admitted to the study hospital during the first 42 months of the 48-month study period. These zip-code areas with documented preferential admission to CHOP defined the neighborhood cohort (Table 1). Data from the US Census 2000 Factfinder were used to estimate the numbers of child-years of observation during the study period (July 2000 through June 2004). Age-specific estimates of child-years of observation were also obtained through the US Census Bureau Web site (www.census.gov).

**Statistical Methods**

**Descriptive Statistics**
Descriptive analyses included calculating the means or medians with 95% confidence intervals (CIs) for continuous variables and the frequencies for categorical variables. Categorical variables were compared by using \( \chi^2 \) or the Fisher’s exact test, whereas continuous variables were compared by using the Wilcoxon rank-sum test. For categorical variables, odds ratios (ORs) and corresponding 95% CIs were derived. We used univariate logistic regression to estimate ORs and corresponding 95% CIs for the association between the independent and dependent variables.

**Predictors of Prolonged Length of Hospital Stay**
To identify additional risk factors associated with serious influenza infection, we examined the association between prolonged hospitalization and various demographic and clinical characteristics using multivariable logistic regression. We defined prolonged hospitalization as \( > 6\) days, which corresponded approximately to the median plus 2 SDs when we examined the distribution of LOS. To identify additional factors associated with serious influenza infection, we examined the association

<table>
<thead>
<tr>
<th>TABLE 1 Description of Neighborhood Cohort Used to Estimate the Incidence of Pediatric Hospitalizations Attributable to Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (all ages) 348 411</td>
</tr>
<tr>
<td>Total population (&lt; 18) y 85 135</td>
</tr>
<tr>
<td>Median household income within each zip code (range), $22 808–111 683</td>
</tr>
<tr>
<td>Percent families below poverty level 23</td>
</tr>
<tr>
<td>Percent black race among children (&lt; 18) y 77</td>
</tr>
</tbody>
</table>

**Neighborhood cohort was defined by home residence within 9 contiguous zip-code areas with >70% acute asthma exacerbations admitted to the study hospital (CHOP) for asthma.**

\( ^* \) **Total population \(< 18\) years of age based on the 2000 US Census.**
between prolonged hospitalization and various demographic and clinical characteristics. We performed a multivariate analysis using a logistic regression model to determine factors associated with prolonged LOS. Variables statistically significant at the .05 level on univariate analysis were included in the model. Effect modification between age and several chronic conditions was also considered. Unadjusted and adjusted ORs and corresponding 95% CIs were derived. All statistical calculations were performed by using SAS 9.1 (SAS Institute, Cary, NC) and Stata 8 (Stata Corp, College Station, TX). A 2-tailed P value of <.05 was considered significant for all statistical tests.

### RESULTS

**Estimated Incidence of Influenza-Related Hospitalization Among Children**

Among a total of 745 case-patients identified with CA LCI, 231 (31%) resided in the neighborhood cohort. The demographic and clinical characteristics of children hospitalized with CA LCI from the neighborhood cohort were comparable to that of the entire study cohort with the following exceptions: hospitalized children in the neighborhood cohort were more likely to be black (90% vs 55%) or have asthma (31% vs 24%) (Table 2). However, the neighborhood case-patients were of similar

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 745)</td>
<td>Healthy Children (n = 382)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>309 (41)</td>
<td>168 (44)</td>
</tr>
<tr>
<td>Male</td>
<td>436 (59)</td>
<td>214 (56)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 mo</td>
<td>188 (25)</td>
<td>168 (44)</td>
</tr>
<tr>
<td>6–23 mo</td>
<td>250 (34)</td>
<td>130 (34)</td>
</tr>
<tr>
<td>2–4 y</td>
<td>135 (18)</td>
<td>53 (14)</td>
</tr>
<tr>
<td>5–11 y</td>
<td>92 (12)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>12–17 y</td>
<td>53 (7)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>18–21 y</td>
<td>27 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>249 (34)</td>
<td>139 (37)</td>
</tr>
<tr>
<td>Black</td>
<td>408 (55)</td>
<td>189 (50)</td>
</tr>
<tr>
<td>Asian</td>
<td>18 (2)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>64 (9)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Viral type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza A</td>
<td>591 (79)</td>
<td>312 (82)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>154 (21)</td>
<td>70 (18)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000–2001</td>
<td>107 (14)</td>
<td>48 (13)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>252 (34)</td>
<td>134 (35)</td>
</tr>
<tr>
<td>2002–2003</td>
<td>135 (18)</td>
<td>71 (19)</td>
</tr>
<tr>
<td>2003–2004</td>
<td>251 (34)</td>
<td>129 (34)</td>
</tr>
<tr>
<td>ACIP high-risk medical conditions&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None&lt;sup&gt;a&lt;/sup&gt;</td>
<td>382 (51)</td>
<td>—</td>
</tr>
<tr>
<td>Asthma</td>
<td>181 (24)</td>
<td>—</td>
</tr>
<tr>
<td>Other chronic pulmonary disease</td>
<td>27 (4)</td>
<td>—</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>52 (7)</td>
<td>—</td>
</tr>
<tr>
<td>Immunosuppression&lt;sup&gt;d&lt;/sup&gt;</td>
<td>59 (8)</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobinopathy</td>
<td>41 (6)</td>
<td>—</td>
</tr>
<tr>
<td>Long-term salicylate therapy</td>
<td>14 (2)</td>
<td>—</td>
</tr>
<tr>
<td>Chronic renal dysfunction</td>
<td>10 (1)</td>
<td>—</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>20 (3)</td>
<td>—</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>NNMD (including seizures)</td>
<td>89 (12)</td>
<td>—</td>
</tr>
<tr>
<td>Any ACIP high-risk condition</td>
<td>363 (49)</td>
<td>—</td>
</tr>
<tr>
<td>&gt;2 ACIP high-risk conditions</td>
<td>106 (14)</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> Children who lack any chronic medical conditions recognized by the ACIP as increasing the risk of influenza-related complications.

<sup>b</sup> Neighborhood cohort was defined by home residence within 9 contiguous zip-code areas with >70% acute asthma exacerbations admitted to the study hospital (CHOP) and <18 years of age.

<sup>c</sup> Chronic medical conditions recognized by the ACIP as increasing the risk of influenza-related complications.

<sup>d</sup> Immunosuppressive disorders included human immunodeficiency virus infection and malignancies.
race/ethnicity distribution as the overall neighborhood cohort. Information on asthma prevalence in the neighborhood cohort was not available for comparison.

Most study subjects from the neighborhood (222 [96%] of 231) had either a chronic medical condition or were <5 years of age (data not shown), similar to the prevalence noted in the entire study cohort. On the basis of calculated 340 540 child-years of observation, we estimated that the total incidence of influenza-related hospitalization in this cohort was 7 per 10 000 child-years. To assess the impact of referral bias, we calculated the incidence of influenza-related hospitalization for a subgroup of children who lived in the 6 zip-code areas with ≥90% referral to the study hospital; the incidence of influenza-related hospitalization in this cohort was 8 per 10 000 child-years (data not shown). We also calculated the age-specific incidence of hospitalization attributable to influenza in the 9–zip-code neighborhood cohort (Table 3). We found that children 0 to 23 months of age had the highest risk of hospitalization attributable to influenza (41.6 per 10 000 child-years). Among premature infants, the incidence of influenza-related hospitalization was 19 per 10 000 child-years (data not shown).

**Characteristics of Children Hospitalized With CA LCI**

Over the 4-year study period we identified 826 patients who experienced 842 hospitalizations with LCI. Seventy patients with health care-associated LCI were excluded from all subsequent analyses. We excluded 8 patients who were >21 years of age from this analysis. Thirteen patients had >1 hospitalization attributable to CA LCI; only the first hospitalization for each patient was included in this analysis (n = 745). Overall, 591 (79%) of the study subjects were infected with influenza A; the annual proportion of infections attributable to influenza A ranged from 33% to 98% (data not shown). Greater than 60% of children hospitalized with CA LCI were <24 months of age, and 18% were 2 to 4 years of age (Fig 1). Influenza virus infection was confirmed by SPIA (n = 529), DFA (n = 100), and viral culture (n = 104). Two patients underwent diagnostic testing at an outside hospital before admission to the study hospital, and the type of diagnostic assay used was unknown.

The majority of children <2 years old (298 [68%] of 438), and many were 2 to 4 years of age (53 [39%] of 135) were previously healthy. Approximately half of the children (49%) hospitalized with CA LCI had an ACIP-recognized high-risk medical condition, including asthma (24%), NNMD (12%), immunosuppression (8%), and cardiac condition (7%) (Table 2). We identified 106 children (14%) with ≥2 medical high-risk conditions. Children with ≥1 medical high-risk conditions were older than otherwise healthy children hospitalized with CA LCI (median age: 3.1 vs 0.7 years; P < .001).

**Hospital Course and Influenza-Related Complications**

Five children died while hospitalized for CA LCI, including 2 children with congenital cardiac disease, 1 previously healthy child who was 14 months old, 1 patient with static encephalopathy attributable to severe birth trauma, and a 4-month-old former premature infant without active medical issues. There was no influenza season predominance in the distribution of these deaths. Among previously healthy children who required hospitalization for CA LCI, the case fatality rate was 2 per 382 (5.2 per 1000).

A total of 186 children experienced ≥1 influenza-related complication (Table 4). The incidence of influenza-related complications was higher among children who had a preexisting high-risk condition than for previously healthy children (29% vs 21%; OR: 1.6; 95% confidence interval [CI] 1.1–2.2). Among healthy children, infants <6 months had the lowest rate of complications (8%). The rates of complications in healthy children in other age groups were not statistically different: 6 to 23 months, 25%; 2 to 4 years, 40%; 5 to 11 years, 37%; 12 to 17 years, 44%, and >17 years, 33%.

Overall, suspected bacterial pneumonia was the most frequent complication and occurred in 110 children (15%). Children with high-risk medical conditions were more likely than healthy children to require intensive care (OR: 1.6; 95% CI: 1.2–2.5) or develop respiratory failure (OR: 2.8; 95% CI: 1.3–6.1). However, 56 children (15%) who lacked a high-risk medical condition were admitted to an ICU. During this 4-year study period, no child was diagnosed with influenza-related cardiomyopathy.

**Predictors of Prolonged Length of Hospital Stay**

The median duration of hospitalization for CA LCI was 2 days (interquartile range: 1–4 days), and 12% of our study population was hospitalized for >6 days, which was defined as prolonged LOS. On univariate analysis, there was no association between prolonged LOS and race/ethnicity, season, or influenza type. We performed multivariate analysis to identify independent factors as-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number Hospitalized With Influenza</th>
<th>Child-Years of Observation</th>
<th>Estimated Incidence* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All age groups</td>
<td>231</td>
<td>340 540</td>
<td>6.8 (2.6–14.4)</td>
</tr>
<tr>
<td>0–23 mo</td>
<td>146</td>
<td>35 080</td>
<td>41.6 (30.2–56.7)</td>
</tr>
<tr>
<td>2–4 y</td>
<td>37</td>
<td>52 136</td>
<td>7.0 (2.8–14.4)</td>
</tr>
<tr>
<td>5–11 y</td>
<td>27</td>
<td>142 060</td>
<td>1.9 (0.7–2.2)</td>
</tr>
<tr>
<td>12–17 y</td>
<td>21</td>
<td>111 264</td>
<td>1.8 (0.7–2.2)</td>
</tr>
</tbody>
</table>

*Estimated incidence is the number of cases of influenza hospitalizations per 10 000 child-years of observation.
Associated with prolonged LOS. After adjusting for age, we found that specific preexisting conditions were independently associated with prolonged LOS, including cardiac disease (OR: 3.6; 95% CI: 1.8–7.1) and NNMD (OR: 5.7; 95% CI: 3.3–9.7).

Figure 2 illustrates the predicted probability of prolonged LOS for the variables in our final multivariate model: age, cardiac disease, and NNMD. Nonpremature infants 0 to 5 months old without cardiac disease or NNMD who were hospitalized with CA LCI had a 4% probability of a prolonged hospitalization. In contrast, premature infants 0 to 5 months old without cardiac disease or NNMD had a 22% probability of a prolonged hospitalization. The probability of a prolonged hospitalization was 8% for patients either 6 months to 4 years or ≥5 years of age. Patients with cardiac disease or those with a NNMD had an increased probability of a prolonged LOS (23% and 33%, respectively). Patients with
both cardiac disease and a NNMD had a markedly increased probability of a prolonged LOS to 68%, regardless of the age of the child (Fig 2).

DISCUSSION

In this report, we describe the largest US cohort study of children hospitalized with CA LCI and provide important new clinical and epidemiologic information about children hospitalized with influenza. First, we found that 7 of 10 000 inner-city children <18 years of age were hospitalized each year attributable influenza in this cohort, and many of these children, particularly those <5 years of age, were otherwise healthy. This study also provides strong supporting evidence for the prevention of influenza among children with NNMD, a group newly recommended to receive annual influenza vaccination.7 Finally, we identified groups of chronically ill children at highest risk of prolonged hospitalization attributable to influenza, in particular, children with NNMD and cardiac disease.

Our data provide additional estimates of the incidence of influenza-related hospitalizations. By analyzing a subset of our study population who resided within an urban neighborhood cohort, we found that the incidence of hospitalization with laboratory-confirmed influenza for children <18 years of age was 7 per 10 000 child-years. This estimate is similar to that calculated by Neuzil and others14–17 and provides support for previous analyses that relied on large administrative data sets to calculate the rates of influenza-attributable hospitalizations. In a prospective multisite study of laboratory-confirmed infections, the CDC-supported New Vaccine Surveillance Network estimated the influenza-hospitalization rate to be 9.0 per 10 000 children for children <5 years of age.17 They also noted that children of black race/ethnicity or with chronic underlying illnesses had higher rates of influenza hospitalization. Surveillance for laboratory-confirmed influenza-associated hospitalizations in children was performed by the CDC-supported Emerging Infections Program, which noted an overall incidence of 3.6 per 10 000 children.18 Rates of hospitalization found in our study might be somewhat higher than those observed by the Emerging Infections Program because of differences in use of viral diagnostic testing. In addition, we hypothesize that a higher prevalence of certain chronic medical conditions in our neighborhood cohort than in the general population might have led to increased rates of hospitalization for children in our inner-city cohort. For example, asthma and sickle cell disease are 2 diseases that are associated with influenza complications and were more prevalent in this population. In addition, over three quarters of the children residing in our neighborhood cohort were black, a racial group that has been previously found to be at higher risk of pediatric influenza-related hospitalizations compared with white children.16 Interestingly, 90% of hospitalized children from our neighborhood cohort were black although data from the 2000 US Census estimated that 77% of children living in this geographic area were black. We have identified several possible reasons for the apparent excess rate of hospitalization among black children in our neighborhood cohort. First, the prevalences of diseases such as hemoglobinopathies and asthma are higher among black than nonblack children and are likely to have contributed to an increased rate of hospitalization among the black children in our cohort. The proportion of children from this community who were immunized against influenza might vary on the basis of
race as has been noted by other investigators. In addition, misclassification bias might have contributed to the apparent racial discrepancy in influenza hospitalizations. Although racial data from both hospital administrative data sets and the US Census are self-reported, different categories of race are used. For example, the 2000 US Census offered respondents to report “two or more races” but the hospital admission form did not. Finally, differential referral might have led black children to be admitted to the study hospital more frequently than nonblack children. Future population-based studies are needed to examine the association between race and need for influenza hospitalization.

We found that one quarter of all pediatric hospitalizations attributable to influenza occurred in infants <6 months of age, a group for whom neither influenza vaccines nor antiviral medications are currently licensed. Other investigators also noted that influenza leads to a substantial burden of disease among young infants. Current recommendations to prevent influenza infection of young infants include vaccination of pregnant women, members of households that include young infants, and childcare providers. However, recent data suggest that these groups of individuals often do not receive influenza vaccine as recommended. Given the substantial burden of disease among young infants, more aggressive campaigns to vaccinate healthy individuals who surround these children are needed. In addition, future studies of active immunization of young infants will address these issues.

We found that many of the previously healthy children hospitalized with influenza were 2 to 4 years of age and that the rate of hospitalization among preschool-aged children was second only to that of children <2 years of age. These findings support the recent recommendation by the ACIP that children 2 to 4 years of age should receive influenza vaccination each year. We observed a higher rate of hospitalization among children of this age group than previously estimated by Izurieta and colleagues. In a study of children enrolled in 2 large managed care organizations, these investigators calculated the rate of excess hospitalizations attributable to influenza to be 1.8 to 4.4 per 10 000 child-years. The lower rates observed in these studies might be related to difficulties estimating the rate of influenza hospitalizations during periods when other respiratory viruses are circulating. Differences in the race/ethnicity or economic background of the populations of the study populations, or differences in the regional burden of disease during the seasons of study.

We observed a relatively high rate of complications among children hospitalized with influenza. Pneumonia was the most common complication and occurred in 15% of hospitalized children. Although high-risk children were at greater risk of developing an influenza-related complication, 1 in 5 previously healthy children also experienced an influenza-related complication. These findings provide additional support for the vaccination of healthy children.

Most children hospitalized with influenza had a short hospital stay with a median LOS of 2 days; however, 15% of high-risk children and 7% of other children were hospitalized for >6 days. Prolonged hospital stay was significantly associated with cardiac disease or NNMD. The presence of both disease categories further increased the likelihood of prolonged hospitalization. This study confirmed the findings of other recent studies regarding NNMD as a risk factor for serious influenza infection and supports the addition of this group of chronically ill children to other populations recommended to receive annual influenza vaccination. These data can guide clinicians and public health officials on the optimal use of vaccine during times of vaccine shortage. In addition, health care organizations that provide care to chronically ill children might use this knowledge to enhance vaccination rates among their patients at highest risk of prolonged hospitalization.

We recognize several limitations of this study. First, ascertainment bias might have reduced the number of mild or atypical cases of influenza detected among children admitted to our hospital. Although a highly sensitive algorithm for the detection of influenza infection is routinely used to diagnose children hospitalized with respiratory symptoms during the winter, it is possible that patients with minimal respiratory symptoms might not have undergone diagnostic testing for influenza. In addition, it is possible that either false-positive or false-negative viral assay determinations might have contributed to ascertainment bias. However, we believe our algorithm is highly specific on the basis of the absence of positive determinations during months when influenza virus is not in circulation. The racial and economic composition of the population-based cohort from which we derived our estimated rates of influenza-associated hospitalization limits the ability to generalize these findings to other populations. Finally, we were unable to capture accurate influenza immunization data for the children in our cohort and thus could not assess how vaccination might have influenced the risk of prolonged hospitalization.

CONCLUSIONS

Most children hospitalized with influenza were in groups either currently recommended to receive influenza vaccination or were <6 months of age. In addition, the presence of NNMD, a condition recently added to the ACIP list of high-risk conditions in 2005, was found to be an important risk factor for prolonged hospitalization. Current efforts should be made to vaccinate eligible high-risk children and their close contacts. Additional data are needed to define the relative benefits of influenza vaccination of high-risk children as compared with
healthy school-aged children and the benefit of vaccinating all children ≥6 months.

ACKNOWLEDGMENT
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REFERENCES
Previous Head Injury Is a Risk Factor for Subsequent Head Injury in Children: A Longitudinal Cohort Study

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ABSTRACT

OBJECTIVE. The objective of this study was to determine whether children who sought care for a head injury were at greater risk of having a subsequent head injury within the following 6 and 12 months compared with children who sought care for an injury other than to the head.

DESIGN/SETTING. This was a longitudinal cohort study conducted in the emergency departments of 2 Montreal (Quebec, Canada) pediatric hospitals.

PARTICIPANTS. The parents of 11,867 injured children aged 1 to 18 years were interviewed by telephone at 6 (n = 10,315) and 12 (n = 9,486) months after their child’s injury to ascertain outcome (ie, subsequent head injury) and to provide information on potential risk factors (age, gender, chronic medical condition, activity level, and socioeconomic status).

MAIN OUTCOME MEASURE. The outcome of interest was a head injury requiring medical attention within the following year ascertained by parental recall or physician claims data.

RESULTS. A total of 245 and 386 previously head-injured children sustained a subsequent head injury within 6 and 12 months, respectively. Children who sought care for an initial head injury (n = 3,599) were at higher risk of having a subsequent head injury within 6 months than children who sought care for an injury not to the head (n = 6,716). The adjusted odds ratio suggested weak confounding by age, gender, and history of previous head injury. Results were consistent on the basis of physician claims data and 12-month follow-up interview data.

CONCLUSIONS. These results provide evidence that having a head injury increases a child’s risk of having a subsequent head injury. Although age, gender, and history of previous head injury confound the relationship, the effect remains substantial.
Circumstantial evidence suggests that among children a previous head injury (HI) increases the risk of subsequent HI, the consequences of which may be serious. This study provides evidence that having an HI is associated with an increased risk of having a subsequent HI.

HI is an important public health problem among children and youth. Schneier et al\(^1\) estimated that there were 50 658 hospital admissions for HI among children ≤17 years of age in the United States in 2000. Others have reported that HI accounts for >10% of all emergency department (ED) visits.\(^2\) Between 1994 and 2000, 24% of injuries to Canadian children (≤12 months old) for whom care was sought at an ED involved the head.\(^3\)

Most HIs in children are mild, that is, the children are able to return to their previous activities.\(^4\) Some, however, are serious, causing an extended period of unconsciousness and cognitive, psychosocial, or physical sequelae.\(^5,7\) Furthermore, some researchers believe 1 HI may increase the risk of a subsequent HI, although there is still no strong evidence to support this view.\(^8-10\) Studies with children have been retrospective and methodologically flawed, usually because they lacked adequate comparison groups. Also, injury reoccurrence has typically been ascertained solely on the basis of nonstandardized questionnaires. Finally, only anecdotal evidence suggests that an athlete is more prone to future concussive injury after having sustained a sport-related concussion.\(^11\) Here, the likelihood of repeat injury may simply reflect the amount of playing time or a player’s style of play (ie, using dangerous game strategies) rather than any inherent risk.\(^12\)

However, the evidence from animal and human studies concerning the potential consequences of repeated concussion is conflicting.\(^13-17\) Given the possible consequences of subsequent HI among children, this issue warrants additional investigation. The objective of this study was, therefore, to determine whether previous HI is a risk factor for subsequent HI among children. Secondary objectives were to (1) examine the effect of other factors (eg, age, gender, socioeconomic status, preexisting disabling conditions, comorbidity, and injury severity) on subsequent HI and (2) estimate the time to subsequent HI among injured children.

Children were recruited by using data routinely collected through an ED-based injury surveillance system, the Canadian Hospital Injury Research and Prevention Program (CHIRPP).\(^18\) The CHIRPP database contains information about the circumstances of the injury provided by the patient or an accompanying adult on a 1-page self-administered questionnaire. On the back of the same form, diagnostic codes, injured body part, and level of treatment provided are recorded. The child’s unique health insurance number, date of birth, gender, postal code, and date of visit are also recorded.

The institutional review boards at both hospitals approved this study. Parents gave verbal consent to participate in the interviews, as well as approval to be contacted on the forms. Permission to access the physician claims database was obtained from the Quebec Commission for Access to Information.

Two groups of children were studied. The exposed group included all children seeking care for an HI during the study period. This group was defined by using a diagnosis recorded on the CHIRPP form: minor HI, skull fracture, intracranial injury, or concussion. Also included were children with injuries to the eyes, facial fractures, dental injuries, or facial lacerations if the mechanism of injury involved being struck forcefully against a hard surface, a fall from a height, or both. Athletes who sustain a fractured mandible or maxilla almost always sustain a coexistent concussion\(^19\) because the forces required to fracture bones often exceed the impact threshold to cause a mild HI or concussion.\(^20\) This broad definition of HI was used to include children with definite HI and those with probable HI. The CHIRPP form does not contain information on amnesia or loss of consciousness or the Glasgow Coma scale, making it difficult to obtain a more precise diagnosis, including the presence or absence of brain injury. This definition was used by others in earlier descriptive studies on repetitive HI among children.\(^9,10\)

Two unexposed (without an HI) children were selected randomly to serve as controls for each exposed child.\(^21\) These were children seeking care for a musculoskeletal injury to the extremities during the same period. Children with at least 1 of the following diagnoses recorded on the CHIRPP form were recruited: fracture, laceration, sprain, and soft tissue injury to an upper or lower extremity. The choice of this comparison group (ie, injured children as opposed to those with medical disorders) was made to control for potential confounders, such as exposure to hazards and children’s developmental abilities.

CHIRPP data were entered into the study database each week. Only children whose parents indicated on the CHIRPP form their consent to receive a follow-up telephone call were recruited. The child’s first visit to the ED during the study period was identified as the index visit.

METHODS

Participants
Participants in this longitudinal cohort study were children aged 1 to 18 years who sought care for an injury at the ED of either of the 2 pediatric hospitals in Montreal from December 2000 to March 2003. Both hospitals are designated provincial neurotrauma centers that serve most head-injured children and youth in Montreal. Each year, ~30 000 children seek care for an injury at the ED of these centers, and HI accounts for >3000 visits.
Main Outcome Measure
The outcome of interest was ≥1 medical care visits for a subsequent HI at 6 and 12 months after the index visit. It was measured separately by using 2 data sources: parental report and physician claims data.

Parental Report
During standardized telephone interviews with established interrater and intrarater reliability,22 1 of 2 trained individuals asked parents to respond to the following question: Since the injury in (month of index injury or 6 months ago), has (name of child) had another injury that required medical attention? In the case of a repeat injury, parents were asked about the type and nature of injury, when it occurred, whether they considered it to be “serious” (eg, a concussion or skull fracture), and whether and for how long the child was hospitalized. In addition, they were asked about the reason(s) that prompted them to seek care for the subsequent HI (eg, it was serious or because you were worried about what you were told during the last visit and wanted to be sure that everything was ok). Parents also provided details about discharge recommendations regarding activity restrictions (for the index injury), usual level of activity of their child compared with others of the same age and gender, and other child-, injury-, and parent-related variables (Table 1). Answers were recorded on digitized response forms to maximize data quality.

The choice of questionnaire items was based on pediatric injury literature and on clinical experience with the patient population.23–26 The reliability of the questionnaire and the scoring of parental responses was investigated with 42 parents of injured children (33% with an HI). Parents participated in 2 telephone interviews separated by a 2-week interval; the first interviews were tape recorded to be reassessed 4 weeks later. \( \kappa \) values exceeding 0.75, indicating “substantial” reliability27 were found for the majority of the questions, including the one about subsequent HI.

Physician Claims
Provincial health records for all 11867 children (exposed and unexposed, including those not participating in telephone interviews) were accessed from the database of the provincial health insurance board of Quebec, Canada (Régie de l’assurance-maladie du Québec [RAMQ]). These data were acquired through linkage by using the health insurance number on the CHIRPP form. The RAMQ database contains diagnostic codes of all insurable health care services provided to eligible Quebec residents and is used to reimburse fee-for-service providers (eg, physicians).

A file of CHIRPP-based data (each child’s index date, diagnostic group, and RAMQ number) was sent to the RAMQ where health insurance numbers were linked to subsequent medical care visits for each child over the 12 months after the index visit. The returned file contained the children’s age, gender, the first 3 digits of the postal code of residence, and the complete record of services paid to fee-for-service physicians who provided care during the study period. The postal code data served as a proxy for socioeconomic status (SES) by giving the median household income in the child’s area of residence. The following variables were included for each medical visit: diagnostic codes, medical procedures and their costs, type of physician, and facility type. Confidentiality

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Characteristics of Respondents in the 6-Month Telephone Interview According to Exposure Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Children</td>
</tr>
<tr>
<td>Gender (males)</td>
</tr>
<tr>
<td>Mean age, y</td>
</tr>
<tr>
<td>Oldest child in family</td>
</tr>
<tr>
<td>Fall-related injury</td>
</tr>
<tr>
<td>Hospitalized</td>
</tr>
<tr>
<td>HI during previous year</td>
</tr>
<tr>
<td>Site of injury (residence)</td>
</tr>
<tr>
<td>Received discharge instructions regarding physical activities</td>
</tr>
<tr>
<td>Activity level (same or more as age-gender peers)</td>
</tr>
<tr>
<td>Chronic medical condition</td>
</tr>
<tr>
<td>Child’s health excellent</td>
</tr>
<tr>
<td>Parents</td>
</tr>
<tr>
<td>Mother’s education beyond high school level</td>
</tr>
<tr>
<td>Mother ≥30 y</td>
</tr>
<tr>
<td>Single parent</td>
</tr>
<tr>
<td>Anxious parent</td>
</tr>
</tbody>
</table>

* N varies because of missing data.
was maintained by using a scrambled personal insurance number. Consequently, we were unable to link children’s RAMQ data with those based on the parent report; therefore, the physician claims data were analyzed separately.

Ascertaining subsequent HI using the physician claims data was based on the results of earlier work examining the concordance between diagnoses recorded in the injury surveillance system (CHIRPP) and those recorded in the physician claims for 3049 injured children. Briefly, we demonstrated that using a combination of diagnostic and procedure codes in the RAMQ physician claims database was a valid method of estimating HI occurrence among children. Substantial concordance (weighted κ: 0.66; 95% confidence interval [CI]: 0.63–0.69) was found between the 2 data sources. The sensitivity of diagnostic and procedure codes in the RAMQ database for identifying HI and musculoskeletal injury were 0.61 (95% CI: 0.57–0.64) and 0.97 (95% CI: 0.96–0.98), respectively, whereas the specificities for identifying HI and musculoskeletal injury were 0.97 (95% CI: 0.96–0.98) and 0.58 (95% CI: 0.56–0.63), respectively.

The data sources for the other potential predictors of subsequent HI included parent responses to the telephone interview, physician claims, and the CHIRPP records.

Statistical Analyses
Exposed and unexposed groups (and respondents and nonrespondents) were compared with regard to categorical and continuous variables using χ² and t tests, respectively. Bivariate analyses were performed to explore factors associated with subsequent HI. Child-related factors included age, gender, parental perception of child’s level of physical activity compared with children of same age and gender (more active, about the same, or less active than other children), chronic medical condition (yes/no), general health (excellent, good, or poor), and history of previous HI in the year preceding the index injury (yes/no). Those related to the child’s family included family structure (single parent, yes/no; oldest child, yes/no; mother’s age in categories), maternal education (highest level education completed), parental perception of being anxious (yes/no), and median household income (a proxy for SES). Injury-related factors included injury type (ie, exposure group), involvement in a recreational activity at time of injury (yes/no), receipt of discharge instructions about activity restrictions (yes/no), place of injury (home, daycare, or elsewhere), and hospitalization for index injury (yes/no).

Using the Mantel-Haenszel method,29 crude and adjusted relative risks and 95% CIs were calculated for exposed and unexposed groups. Multivariable analysis included fitting 2 logistic regression models to evaluate factors associated with risk of subsequent HI while adjusting for potential confounders: 1 used parental responses to questionnaires and the other used physician claims data. Potential confounders (covariates) included child-, parent-, and index injury-related variables. Their selection was data driven but based on substantive knowledge where feasible.

Additional exploratory logistic regressions were calculated to examine the possibility of a dose-response and the sensitivity of the result to errors in classification. These analyses determined whether the risk of subsequent HI could vary according to the type/severity of the index HI (ie, definite versus probable HI) or according to the type of the subsequent HI (ie, definite versus probable HI). In the context of this study, definite HI referred to a concussion/mild HI, skull fracture or intracranial injury to the head (ie, high degree of certainty of sustaining a genuine HI). Probable HI included injuries to the eyes, facial fractures, dental injuries, or facial lacerations if the mechanism of injury involved being struck forcefully against a hard surface, a fall from a height, or both. These analyses were conducted by using interview and physician claims data from the 12-month follow-up to provide sufficient numbers of children with subsequent HI. Goodness of fit statistics were calculated for all models.

Finally, a Kaplan-Meier survival analysis30 was performed for each exposure group to determine the probability of subsequent HI over time using each data source. Cox regression was also performed with the 2 groups to estimate the (hazard) risk ratio of subsequent HI at any given time.31 Data were analyzed using SAS 8.2 (SAS Institute, Cary, NC).

A power calculation, based on previously observed rates of subsequent HI (exposed 2.5%, unexposed 1.0% per year), determined that a minimum of 9000 children (6000 unexposed, 3000 exposed) were required at the 12-month follow-up to detect a relative risk of ≥2.5 (α: .05) with at least 90% power using logistic regression.21

RESULTS
CHIRPP records for 11 867 children were obtained. Response rates of 87% and 80% were attained for the 6- and 12-month interviews, respectively, and 90% of parents participating in the 6-months interview participated at 12 months. The main reason for loss to follow-up was the inability to obtain an accurate family telephone number (63% of losses). Only 278 and 19 parents refused to participate in the 6- and 12-month interviews, respectively. Physician claims data were unattainable for 176 children because of missing RAMQ numbers, thus providing RAMQ data for a total of 11 691 children. A participant flow diagram describes the records included in the various analyses (Fig 1).

The mean age of respondents in the 6- and 12-month follow-up interviews was slightly higher (but within 6 months) than that of nonrespondents. Respondents and
nonrespondents had similar proportions of anglophone and francophone parents and of male and female children. Exposed and unexposed children among participants in the 6- and 12-month interviews differed with respect to age (9.5 years for unexposed vs 6.5 years for exposed; \( P < .001 \)). The child’s mother was the most frequent respondent.

Within 6 months after the index injury, 245 (2.4%) of the 10 315 children were reported to have had a subsequent HI requiring medical attention. Among those with an index HI, the percentage of children with a second HI was 3.2%. Within 12 months, 386 children (4.1%) had had an HI, 12 of whom sustained a subsequent HI within the first 6-month interval. Among those with an index HI, the rate of subsequent HI at 12 months was 5.5%. The children’s characteristics are presented in Table 1 according to exposure status. Only data for respondents of the 6-month interview are presented; the 12-month data are almost identical (ie, within 1–2 percentage points).

The results of the bivariate analyses regarding the predictors of subsequent HI within 6 and 12 months are presented in Table 2. Children who sought care for an HI \(( n = 3599)\) were at higher risk of having a subsequent HI at 6 months than were children who sought care for a non-HI \(( n = 6716)\); odds ratio (OR) at 6 months: 1.7; 95% CI: 1.3–2.2). Similar results were found at 12 months. Other predictors included having sustained the HI during a recreational activity (6 months only), injury sustained at daycare, child’s age, being male, having had a previous HI, and being less or equally active as a child of the same age and gender (6 months only).

Table 3 presents the adjusted ORs (aORs) for subsequent HI at 6 and 12 months using both data sources. At 6 months, the aOR (parental interviews) was 1.6 (95% CI: 1.2–2.0), suggesting some confounding by age, gender, and history of previous HI. Results were generally consistent at the 12-month follow-up (aOR: 1.5; 95% CI: 1.2–1.9) and were comparable to those based on analysis of physician claims data for services received during the following 12 months. (aOR: 1.7; 95% CI: 1.4–2.0).

The exploratory subgroup analyses (ie, dose effect) using data from both sources yielded the following results (Table 4): Children who sought care for a definite HI were at higher risk of having a subsequent definite HI than children who sought care for a non-HI, (parental report: aOR: 2.1; 95% CI: 1.5–2.9; physician claims: aOR: 2.6; 95% CI: 1.9–3.6). In general, it seems that having a definite HI compared with an injury not to the head increases a child’s risk of any type of subsequent HI within 12 months. Children and youth who had a definite HI are even more likely to have a definite subsequent HI, regardless of their age. Goodness-of-fit statistics were nonsignificant for all models \(( P > .3)\).

Finally, among those reporting a subsequent HI (all categories) within 6 months, 72% of parents considered the subsequent HI “minor,” whereas 23% considered it “serious.” Approximately 42% of parents reported the subsequent injury to the head as being an HI or concussion, with the remainder reporting open wounds or “bumps to the head.” Parents reported consulting medical care either because they thought the HI was serious (46%), were worried (51%), or for other reasons (8%). Only 8 children spent ≥1 night in hospital. Finally, among parents who remembered the exact date of the subsequent injury, 65% reported it as occurring within the fourth and sixth month after the index visit, and 20% reported it occurring within the first month. Similar results were found on the basis of the analyses of the responses from parents of children who had sustained a subsequent HI within 12 months.

The estimated time (in months) to subsequent HI shows the differential probability of such an event over the 12-month period among exposed and unexposed children who had sustained a subsequent HI.
children, accounting for time and for censoring because of loss to follow-up. Figures 2 and 3 demonstrate (by using interview and RAMQ data) that the survivor function for the exposed (HI) group consistently lies below that for the unexposed group (at all points of follow-up). Cox regression models calculated with interview data (hazard ratio: 1.5; 95% CI:1.2–1.9) and RAMQ data (hazard ratio: 1.7; 95% CI: 1.4–2.2) were consistent with the results of the logistic regression models.

**DISCUSSION**

To our knowledge, this is the first study of its kind using 2 data sources for a large cohort of injured children to provide evidence that having an HI is associated with an

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**TABLE 2** Injury-, Child-, and Parent-Related Predictors of Subsequent HI Within 6 and 12 Months: Bivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>6 mo (n = 10 315)</th>
<th>12 mo (n = 9 486)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Injury-related predictors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>1.70^*</td>
<td>1.32–2.19^*</td>
</tr>
<tr>
<td>Recreational</td>
<td>0.77^*</td>
<td>0.59–0.99^*</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>1.39</td>
<td>0.83–2.33</td>
</tr>
<tr>
<td>Received discharge instructions regarding physical activities</td>
<td>1.34</td>
<td>0.97–1.87</td>
</tr>
</tbody>
</table>

**Place**

<table>
<thead>
<tr>
<th>Residence</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daycare</td>
<td>2.03^*</td>
<td>1.10–3.76^*</td>
<td>2.34^*</td>
<td>1.42–3.83^*</td>
</tr>
<tr>
<td>Elsewhere</td>
<td>0.86</td>
<td>0.66–1.12</td>
<td>0.97</td>
<td>0.78–1.20</td>
</tr>
</tbody>
</table>

**Child-related predictors**

| Age (≥6 vs 0–5 y) | 0.63^* | 0.49–0.81^* | 0.62^* | 0.48–0.81^* |
| Oldest child       | 0.93    | 0.72–1.20   | 1.13    | 0.92–1.39   |
| Chronic medical condition | 1.41   | 0.92–2.16   | b       | b           |
| Male               | 1.74^*  | 1.31–2.31^* | 1.65^*  | 1.32–2.07^* |
| Previous HI (12 mo before index) | 2.69^* | 1.83–3.94^* | 2.56^* | 1.86–3.51^* |
| Less or equally active as peers | 0.54^* | 0.42–0.70^* | b       | b           |

**Parent-related predictors**

| Single mother            | 0.95     | 0.69–1.32   | 0.87     | 0.67–1.15   |
| Young mother (≤29 y)     | 1.42     | 0.94–2.15   | 1.28     | 0.89–1.83   |
| Anxious parent           | 1.11     | 0.84–1.47   | 0.88     | 0.71–1.11   |
| Postsecondary education  | 1.32     | 0.98–1.78   | 1.38     | 1.08–1.75   |
| Median household income below poverty level | 0.88 | 0.67–1.16 | 0.84 | 0.67–1.06 |

^* Significant.

---

**TABLE 3** Logistic Regression Models: Association Between Injury-, Child-, and Parent-Related Predictors and Subsequent HI Within 6 and 12 Months After Injury

<table>
<thead>
<tr>
<th></th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Telephone interview (n = 10 315 at 6 mo and 9486 at 12 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>1.55</td>
<td>1.18–2.04</td>
</tr>
<tr>
<td>Previous HI^*</td>
<td>2.32</td>
<td>1.56–3.45</td>
</tr>
<tr>
<td>Age (≥6 vs 0–5 y)</td>
<td>0.74</td>
<td>0.56–0.78</td>
</tr>
<tr>
<td>Male</td>
<td>1.66</td>
<td>1.24–2.22</td>
</tr>
<tr>
<td>Physician claims data (n = 11 691 at 12 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age (≥6 vs 0–5 y)</td>
<td>—</td>
<td>0.76</td>
</tr>
<tr>
<td>Male</td>
<td>—</td>
<td>1.29</td>
</tr>
</tbody>
</table>

^* Significant.

---

**TABLE 4** Exploratory Regression Models of the Association Between Injury- and Child-Related Predictors and Subsequent Definite and Probable HI Within 12 Months After Injury According to the Type of Index HI

<table>
<thead>
<tr>
<th></th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Telephone interview (12-mo follow-up)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite index HI, subsequent definite HI vs no HI</td>
<td>2.09^*</td>
<td>1.49–2.94^*</td>
</tr>
<tr>
<td>Probable index HI, subsequent definite HI vs no HI</td>
<td>1.17</td>
<td>0.77–1.79</td>
</tr>
<tr>
<td>Age (≥6 vs 0–5 y)</td>
<td>1.17</td>
<td>0.84–1.63</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.47</td>
<td>1.07–2.03</td>
</tr>
<tr>
<td>Previous HI</td>
<td>2.84^*</td>
<td>1.87–4.29^*</td>
</tr>
<tr>
<td>Definite index HI, any subsequent HI vs no HI</td>
<td>1.59^*</td>
<td>1.23–2.05^*</td>
</tr>
<tr>
<td>Probable index HI, any subsequent HI vs no HI</td>
<td>1.38^*</td>
<td>1.05–1.82^*</td>
</tr>
<tr>
<td>Age (≥6 vs 0–5 y)</td>
<td>0.76^*</td>
<td>0.61–0.95^*</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.63^*</td>
<td>1.29–2.04^*</td>
</tr>
<tr>
<td>Previous HI</td>
<td>2.33^*</td>
<td>1.69–3.20^*</td>
</tr>
<tr>
<td>Physician claims data (12-mo follow-up)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite index HI, subsequent definite HI vs no HI</td>
<td>2.62</td>
<td>1.90–3.61</td>
</tr>
<tr>
<td>Probable index HI, subsequent definite HI vs no HI</td>
<td>1.07</td>
<td>0.61–1.88</td>
</tr>
<tr>
<td>Age (≥6 vs 0–5 y)</td>
<td>0.85</td>
<td>0.63–1.16</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.32</td>
<td>0.97–1.80</td>
</tr>
<tr>
<td>Definite index HI, any subsequent HI vs no HI</td>
<td>1.93^*</td>
<td>1.49–2.52^*</td>
</tr>
<tr>
<td>Probable index HI, any subsequent HI vs no HI</td>
<td>1.38</td>
<td>0.95–2.01</td>
</tr>
<tr>
<td>Age (≥6 vs 0–5 y)</td>
<td>0.76^*</td>
<td>0.60–0.95^*</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.30^*</td>
<td>1.02–1.64^*</td>
</tr>
</tbody>
</table>

^* Significant.
increased risk of having a subsequent HI. Our results further indicate that age, gender, and history of previous HI confound the relationship. Age and gender are well-established determinants of injury among children; boys have more injuries than girls and risk of injury typically increases with age. Children with a history of previous HI demonstrated more than a twofold risk for subsequent HI, indicating that some children seem to be predisposed to having recurrent injuries similar to that of the original injury. In a study where HI was the most frequent injury sustained by the children involved, the number of injuries before age 5 years was found to be the best predictor of injuries reported between 5 and 10 years later. 

Because the cohort consisted of children and youth with different types of HI, we were able to explore the possibility of a dose-response relationship. Clearly, having had a concussion, skull fracture, or intracranial injury compared with a musculoskeletal injury is associated with an increased risk of subsequent HI (any type) within 12 months. These children and youth are even more likely to have a definite subsequent HI, regardless of their age. The association between probable HI and subsequent HI is, however, less clear, and no definitive conclusions can be made about the issue of age within this context.

The study results were consistent using both data sources. The risk of subsequent HI calculated with the
RAMQ data were somewhat higher than that calculated with the interview data, probably because of the absence in the model of a variable for “previous HI.” This variable was not available from the physician claims data. These findings are consistent with exploratory work based on injury surveillance data alone (ie, CHIRPP) examining repeat injuries at 1 hospital. They are not in agreement, however, with those of an early report of equal rates of previous HI among children with an HI compared with school-based controls. Our selection of the control group (injured-based controls) may explain the inconsistency. The observed rates of subsequent HI among children with an HI of 3.2% and 5.5% within the following 6 and 12 months, respectively, however lie within the range of previous descriptive studies (1.6%–23%).

Despite asking parents questions about a broad range of topics to examine the factors associated with subsequent HI, this study was unable to further delineate specific characteristics of children with repeated HIs. The mechanisms related to subsequent HI remain unclear and suggest that the phenomenon is likely to be multifactorial involving a complex interaction between children and their personal and social environments.

In terms of human factors, it is reasonable that children with an HI who do not regain their preinjury state of health could be at risk for another injury. An HI (even mild HI) can result in a wide range of physical, cognitive, and behavioral sequelae. Even subtle deficits in coordination, balance, or endurance, combined with cognitive and behavioral limitations, might reduce a child’s ability to meet the demands of a difficult task, thus increasing a child’s risk for reinjury. In terms of environmental factors, children who sustain an HI may be more exposed to hazardous environments than other injured children. Children with HI might participate more in contact sports or have lower SES status (eg, less parental supervision, less use of prevention strategies) that puts them at greater risk for HI. This study was not able to support this notion.

The observed increased risk of subsequent HI may simply be a reflection of parents’ health-seeking behavior, that is, a lower threshold for bringing younger children to medical attention, or of higher rates of service use among parents of children with HI. With regards to the former, information received at the ED about an HI and when to call or return to the hospital may have sensitized parents to the potential seriousness of an HI. This may prompt parents to seek care for another HI for which they may not otherwise have sought care. In an attempt to address this issue, parents were asked whether they considered themselves to be anxious. Such parents may have greater difficulty interpreting symptoms associated with a mild HI and worry more, making them more likely to seek care for another HI. Self-reported parental anxiety, however, was not found to be a predictor of subsequent HI.

One could also argue that the results reflect the increased chances of parents of a child who had an HI to remember that the child had a subsequent one, which is a reporting issue. This is also unlikely because the results were corroborated with physician claims data that are free of recall bias.

Finally, one cannot rule out the possibility that other factors, not measured in our study, may be responsible for the observed association. More research is needed to understand the causal pathways that lead to the increased risk of a second HI. In-depth interviews are currently underway with the parents of the children with repeated HIs in an attempt to clarify the complex interactions between the child and his personal and social environments.

Several possible clinical implications arise from this study. The actual number of children with a subsequent HI was small. Nonetheless, it is important to prevent these injuries in children, particularly given that so little is known about their cumulative effects. On the basis of these findings, health care providers should be able to better identify the children who are at highest risk of subsequent HI. Individual-focused prevention interventions (including parental and child counseling on injury risk) may be beneficial for this group of children. Considerable thought needs to be given to the specific content of these interventions, because most current prevention strategies, aimed in part at reducing the risk of a subsequent HI (or the duration of post concussion symptoms), do not seem to have been successful. In fact, our study found that children who received instructions about activity restrictions tended to have an increased risk. Moreover, given that the majority of subsequent HIs were found to occur 5 or 6 months after the initial HI, a 4-week restriction of activity may need to be reexamined.

STUDY LIMITATIONS

Neither data source we used is perfect, and it is possible that misclassification of injury exposures and of subsequent HI occurred. For example, those with multiple injuries, of which at least 1 was an HI, were classified into the HI group. The method of detection of outcome by parent report and by using physician claims data did not, however, differ by exposure status. There were adequate data to describe the baseline state of the cohort, and measurable differences between the groups were controlled for at the analysis stage. Sampling bias may also have been a limitation. To recruit a representative sample from the population, all children seeking care for an HI at the 2 centers were identified and highly acceptable response rates were obtained in both groups and at both follow-up times. Some attrition was inev-
table, but the losses did not occur differentially by exposure and outcome.

CONCLUSIONS
This study provides strong evidence that having an HI increases a child’s risk of having a subsequent HI. Although age, gender, and history of previous HI confound the phenomenon, when considering all types of HI, the effect remains substantial. Children who sustain a concussion, skull fracture, or intracranial injury are more than twice as likely to have a subsequent HI of similar type within 12 months than are children seeking care for an injury not to the head, regardless of their age.

ACKNOWLEDGMENTS
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ARTICLE

Quantification of Deep Gray Matter in Preterm Infants at Term-Equivalent Age Using Manual Volumetry of 3-Tesla Magnetic Resonance Images

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<sup>a</sup>Department of Pediatrics, Hammersmith Hospital, London, United Kingdom; <sup>b</sup>Imaging Sciences Department, Division of Clinical Sciences, Imperial College, London, United Kingdom

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Nonhypothesis-based MRI-analysis techniques including deformation-based morphometry and automated tissue segmentation have suggested that preterm infants at term-equivalent age have reduced tissue volume in the basal ganglia and thalami, which is most apparent among infants with supratentorial lesions. The aim of our study was to test this hypothesis by direct measurement of thalamic and lentiform nuclei volumes in preterm infants at term-equivalent age and term-born controls using manual volumetry.

DESIGN/METHODS. Forty preterm infants at term-equivalent age (median gestational age: 29.5 weeks; median birth weight: 1.3 kg) and 8 term-born controls were examined using a 3-T Philips (Best, Netherlands) system. T1-weighted volume images and T2-weighted fast-spin echo pseudovolumes were acquired. There was no significant difference in postmenstrual age at image acquisition between the 2 groups. ImageJ 1.34 (National Institutes of Health, Bethesda, MD) was used for manual segmentations.

RESULTS. The median thalamic and lentiform nuclei volumes for preterm infants at term-equivalent age were 13.6 and 3.07 cm<sup>3</sup>, respectively, significantly smaller than term-control volumes of 16.3 and 5.6 cm<sup>3</sup>, respectively. Ten preterm infants at term-equivalent age had supratentorial lesions (intraventricular hemorrhage, periventricular leukomalacia, or hemorrhagic parenchymal infarction), and the median thalamic and lentiform volumes for this group were 10.4 and 1.7 cm<sup>3</sup>, respectively. When this group was excluded, the remaining infants who had mild or moderate diffuse excessive high signal intensity in the white matter on T2-weighted images had a smaller, yet significant, volume reduction compared with controls. Tissue volumes were not related to weight and gestational age at birth.

CONCLUSIONS. Manual volumetry confirms that preterm infants at term-equivalent age have reduced thalamic and lentiform volumes compared with controls. This was most marked among infants with supratentorial lesions but was also seen among those with nonfocal white matter abnormalities.

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Key Words
basal ganglia and thalamus, preterm infants, magnetic resonance volumetry

Abbreviations
WM—white matter
DEHSI—diffuse excessive high signal intensity
DBM—deformation-based morphometry
PAT—preterm at term-equivalent age
GA—gestational age

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics.
The increasing survival of premature infants is associated with an increased risk of cognitive and behavioral disorders.\textsuperscript{1,2} This leads to the investigation of the cortex, white matter (WM), basal ganglia, and cerebellum as putative neuroanatomical sites where abnormalities may contribute to these neurodevelopmental abnormalities.

WM disease, both cystic (diagnosed by MRI and cranial ultrasound imaging as periventricular leucomalacia) and noncystic (detected by MRI as diffuse excessive high signal intensity \textsuperscript{3,4} on T2-weighted scans,\textsuperscript{5} have been the focus of much recent research because the incidence of WM disease (50\%–70\%)\textsuperscript{5} parallels the incidence of neurodevelopmental impairment.\textsuperscript{1} The basal ganglia and thalamus also were shown to have both diffuse and focal punctuate hyperechogenicity on ultrasound in preterm infants during the early neonatal period,\textsuperscript{6} although by term-equivalent age only 4\% of infants have major persisting thalamic abnormality detected by conventional MRI.\textsuperscript{7}

Some studies have suggested that WM disease may be linked to abnormalities in the basal ganglia and thalamus. Lin et al\textsuperscript{8} examined the relationship of WM disease and thalamic abnormality by manual delineation of the thalamic area on 2-dimensional MRIs in ex-preterm infants; the finding of a reduction in the ratio of area of the thalami to the cerebellum at 9 to 12 months in children with periventricular leucomalacia was compared with patient controls. However, this simple approach was potentially flawed because Lin et al did not measure tissue volumes, and comparison of thalamic areas with cerebellar areas were not ideal because the latter may be also compromised by the presence of WM injury.\textsuperscript{9} Recently, more advanced image analysis approaches have been applied. Boardman et al\textsuperscript{10} used deformation-based morphometry (DBM) to show that preterm at term-equivalent age (PAT) infants have reduced lentiform nuclei and thalamic volumes; this reduction was associated with both lower gestational age (GA) and the presence of noncystic WM disease. Inder et al,\textsuperscript{11} using an automatic segmentation technique, found a reduction in cortical, deep gray matter and WM volumes in PAT infants, although the deep gray matter reductions seen in this study were in a mixed group of infants with and without apparent WM injury.

Both DBM and automated segmentation techniques are nonhypothesis-driven methods that survey the whole brain to detect differences between 2 groups of patients, and the results clearly raise the specific hypothesis that PAT infants have smaller basal ganglia and thalami compared with term-born controls, which may be more severe in the presence of overt WM disease. Our study addresses this hypothesis.

Our study used manual volumetry to measure the volume of thalamic and lentiform nuclei in PAT infants and term-born controls to test the hypothesis that the size of these structures is reduced in PAT infants, particularly in the presence of overt WM disease.

METHODS

Patient Characteristics

The preterm infants were recruited from the NICU at Hammersmith Hospital, and term-born control infants were recruited from the postnatal wards. Infants with congenital anomalies, metabolic disease, or congenital infections were excluded. The study was conducted with approval from Hammersmith Hospital Research Ethics Committee, and the infants were scanned after written parental consent was obtained. The preterm infants were <34 weeks’ GA at birth and were scanned at term-equivalent age (37–44 weeks’ GA). All neonates had standard neonatal management with serial cranial ultrasounds as part of their clinical care. Information about GA, birth weight, head circumference, chronic lung disease (defined as a need for supplemental oxygen at 36 weeks’ GA), days to full enteral feeding, necrotizing enterocolitis, and sepsis were obtained from the clinical notes.

MRI Acquisition

MRIs were acquired on a 3-T Philips Intera system (Best, Netherlands). The preterm infants were sedated with chloral hydrate, and a trained neonatologist was present throughout scanning. Term-born controls were fed and swaddled, and the examination was conducted in natural sleep. All infants were monitored with pulse oximetry and electrocardiographic monitoring. Ear protection, consisting of silicon-based dental putty individually molded and fitted into the external ear- and minimuffs (Natus Medical, San Carlos, CA), was used to achieve ~30-dB sound attenuation. The infant’s position was stabilized using a suction-evacuated pillow.\textsuperscript{12}

The magnetic resonance sequence parameters were as follows: T1-weighted magnetization prepared rapid-acquisition gradient echo volumes: repetition time, 17 milliseconds; echo time, 4.6 milliseconds; field of view, 210 mm; matrix, 256 × 256; flip angle, 30°; number of acquisitions, 1; and voxel size, 0.86 × 0.86 × 0.8 mm; T2-weighted fast-spin echo pseudovolumes: repetition time, 8000 milliseconds; echo time, 160 milliseconds; field of view, 220 mm; matrix, 224 × 224; and flip angle, 90°. T1-weighted volume images were acquired in the sagittal plane and reformatted into transverse and coronal planes. T2-weighted images were acquired in the transverse plane.

Image Analysis

Images were visually assessed for normal anatomic appearance to the cerebral cortex, basal ganglia and thalamus, WM, and cerebellum. The presence of overt focal lesions, such as cystic periventricular leucomalacia,
hemorrhagic parenchymal infarction, and ventricular dilatation with or without residual intraventricular hemorrhage was noted. DEHSI was defined as high signal intensity in the WM on T2-weighted images and visually classified as mild, moderate, and severe: mild if there was increased signal intensity confined to a small region of the posterior periventricular WM; moderate if there was increased signal intensity in posterior and anterior periventricular region extending into the centrum semiovale; and severe if the high signal intensity extended from the periventricular area into the subcortical WM.

Thalamic and Lentiform Nuclei Quantification

ImageJ 1.34 (National Institutes of Health, Bethesda, MD) software was used for image processing and manual segmentation. The lentiform nuclei were measured by one observer (Mr Dutta) and the thalami by another (Dr Srinivasan). Intraobserver variability was calculated for each observer. Measurements were performed on all T1-weighted images, and in a subset of patients the thalamic measurements were performed on both T1- and T2-weighted images to check consistency between the 2 images. Each patient had a total of 100 image slices of which ~40 slices contained deep gray matter structures. The start and end points for the anatomic position of each structure of interest were defined with the aid of a reference brain atlas.13

Putamina and Globi Pallidi

The lentiform nuclei are situated lateral to the caudate nuclei heads and thalami. Anteriorly, they are separated by the anterior limb of the internal capsule from the caudate nuclei and posteriorly from the thalami by the posterior limb. The external capsules form the lateral borders and separate them from the adjacent WM. Inferiorly, the segmentation included the nuclei accumbens, substantia innominata, and the amygdala to the level of the anterior commissure. An example of the manual segmentation of the lentiform nuclei at several anatomic levels is given in Fig 1.

Thalami

The thalami are composed of many nuclei, all of which were included in the segmentation. Each thalamus is situated between the head and the tails of the caudate nucleus. The third ventricle forms the medial border and the posterior limb of the internal capsule forms the lateral border; the lateral ventricle forms the posterior border, and the subthalamic nuclei along with the geniculate bodies form the inferior border. An example of the manual segmentation of the thalami at several anatomic levels is also given in Fig 1.

Statistics

Statistical analysis was performed by using StatsDirect 2.0.1 (StatsDirect Ltd, Altrincham, United Kingdom). The data were tested for Normality by Shapiro-Wilk test before each analysis. Intraobserver variabilities for the thalamic and lentiform nuclei measurements were calculated by using an intraclass correlation coefficient. The correlation of thalamic volumes measured using T1- and T2-weighted sequences were tested by using simple linear regression and Bland-Altman analysis. A Mann-Whitney U test was used to compare the medians of volumes between individual groups, followed by the Kruskal-Wallis test to allow multiple comparison testing.
Exploratory analysis with clinical variables was conducted using simple and multiple regressions.

RESULTS

Patient Characteristics
Forty preterm infants were recruited with a median GA of 29.5 weeks (range: 25–33 weeks), median birth weight of 1.3 kg (range: 0.6–2.3 kg), and median head circumference at birth of 27.2 cm (range: 22.5–34.5 cm). The preterm infants were scanned at term-equivalent age; the median GA at scan was 40 weeks’ corrected (range: 37–44 weeks). Eight term-born control infants were scanned at a mean of 42.5 weeks (range: 38–45 weeks). The median weight at scan was 3.09 kg (range: 2–4.3 kg) for the PAT infants and 3.65 kg for the term-born controls (range: 3.3–4.7 kg). There was no significant difference in the postmenstrual age at scan or weight at scan between the 2 groups of infants. The median head circumference at scan for the PAT infants was 36.1 cm (range: 32.5–38.5 cm) and for the term-born controls was 36.2 cm (range: 35–38 cm).

Three preterm infants developed chronic lung disease, 2 needed inotropes, and 3 had significant patent ductus ateriosus, which was treated with ibuprofen. Seven preterm infants were diagnosed as suffering sepsis during their hospital admission by a positive blood culture or a clinical diagnosis accompanied by raised C-reactive protein and white cell counts; 3 infants had coagulase negative staphylococcus and 1 had enterobacter. The 2 infants had early culture negative sepsis, and the remaining infant had late onset culture negative sepsis. The preterm infants received total parenteral nutrition for a median of 4 days and achieved full enteral nutrition at a median of 6 days. One infant had suffered from necrotizing enterocolitis.

Intraobserver Correlation
Initial training was conducted by segmentation of the lentiform nuclei in 1 infant 50 times. Then, intraclass correlation for both the lentiform nuclei and thalamus were obtained by repeating the segmentation twice in 10 infants. The intraclass correlation coefficient from the repeated measurements for lentiform nuclei was 0.99 and for the thalamus was 0.96.

Comparison of Volumetry Using T1- and T2-Weighted Sequences
In a subset of 15 infants, the thalamic measurements were performed by using both T1- and T2-weighted images. Simple linear regression showed a significant correlation; and Bland-Altman analysis showed a mean difference of 1.6 cm³ and limits of agreement of −5.2 to 2.8 cm³. The Bland-Altman plot for these measurements is given in Fig 2. The T1-weighted images were used in all additional analysis because these were true volume acquisition scans as opposed to T2 scans, which were acquired as pseudo volumes with overlapping slices.

Thalamic and Lentiform Volumes
Term-born controls had a median thalamic volume of 16.3 cm³ and a median lentiform nuclei volume of 5.6 cm³. PAT infants had a median thalamic volume of 13.6 cm³ and a median lentiform nuclei volume of 3.07 cm³, which were significantly smaller compared with term-born controls infants (P < .0001). There was a wide range for the thalamic and lentiform nuclei volumes in PAT infants as shown in Fig 3, and additional analysis was conducted to determine whether the presence of supratentorial lesions explained this variance, together with an exploratory analysis of the effect of perinatal factors.

Cerebral Lesions and Deep Gray Matter Volumes
Ten of the preterm infants had overt supratentorial lesions, such as intraventricular hemorrhage (3 infants), periventricular leucomalacia (3 infants), or hemorrhagic parenchymal infarction (4 infants). In 1 of the 3 infants who had hemorrhage, the hemorrhage extended into the basal ganglia and thalami. Infants with supratentorial lesions showed the most significant reduction in volume of both thalami and lentiform nuclei (Figs 4 and 5). The median thalamic volume and lentiform nuclei volumes in infants with lesions were 10.4 and 1.7 cm³, respectively. The median thalamic volume and lentiform nuclei volumes in infants without lesions were 14 and 3.07 cm³, respectively; these remaining infants had mild to moderate DEHSI on visual inspection of their T2-weighted images. Kruskal-Wallis analysis with pairwise comparisons (Dwass-Steel-Chritchlow-Fligner) showed significant differences between term controls and PAT infants without lesions (P = .0002), term controls versus PAT infants with lesions (P = .0015), and PAT infants...
with and without lesions \((P < .0001)\). At a descriptive level, the severity of supratentorial lesion was related to the volume reduction; however, because there were only 10 infants with lesions, we were unable to make any statistical inference.

**Exploratory Analysis**

Thalamic and lentiform nuclei volumes were not significantly related to any of the clinical variables: weight and GA at birth, postmenstrual age, weight at scan, and head circumference at birth and at scan. The effect of these variables on thalamic and lentiform volumes were initially tested by using simple regression analysis for each individual variable. To confirm the noncorrelation seen in the simple regression, a multiple regression analysis was performed with all the above-mentioned variables as covariates for the thalamic and lentiform volumes. When the infants were divided into 2 groups (<28 weeks [extreme preterm] and >28 weeks), there was still no significant difference. The deep gray matter volumes were not related to days of ventilation, chronic lung disease, days to full enteral feeding, necrotizing enterocolitis, or sepsis.

**DISCUSSION**

This study supports the suggestion raised by nonhypothesis image analysis techniques that PAT infants show a reduction in lentiform nuclei and thalamic volume, and that the reduction is more pronounced in the presence of supratentorial lesions, predominantly focal WM.

DBM showed previously a reduction in the volume of the basal ganglia and thalamus, with no reduction in cortical or WM volumes. This reduction was only seen in the more preterm group and those with WM disease. This technique is a high dimensional registration technique that is highly sensitivity to local changes that are globally summated to reveal significant differences between patient groups.\(^1^4\) However, this approach to morphometric measurement provides a whole brain survey that is not based on any previous hypothesis, and formal statistical inference can be problematic. Our study effec-
tively tests the hypothesis raised by the survey, confirming and clarifying the results.

Inder et al. used automated segmentation to make another hypothesis-free survey and found reductions in the cortical, WM, and deep gray matter volumes in a mixed group of infants with and without WM lesions. The reduction in the deep gray matter volumes in this cohort depended on GA and was associated with more severe respiratory illness. Although automated segmentation is thought to be problematic in the neonatal brain because of the overlapping signal intensities from the different tissue types, our study provides confirmation of these deep gray matter results.

The deep gray matter and thalamus have become an important focus of investigation because all the information to and from the cortex is relayed through and is modulated by the thalamus. Traditionally, basal ganglia dysfunctions were associated with a range of debilitating movement and psychiatric disorders in conditions, including Parkinson’s disease, Huntington chorea, schizophrenia, attention-deficit disorder, Tourette syndrome, and various addictive behaviors. In neonates with hypoxic ischemic encephalopathy, the basal ganglia and thalamus are the main sites of injury in infants who develop predominantly motor impairments, such as cerebral palsy. However, when the lesions are severe, cognition is also affected. This led to an increasing recognition that the basal ganglia and thalamus may have an impact on normal cognition and affective functions.

The basal ganglia and thalamus are known to have very high metabolic rates and to be sensitive to hypoxic ischemic injury in infants. Hence, primary damage to the thalamus resulting in reduced size cannot be ruled out without the benefit of early imaging. This early imaging may need to include measures of tissue microstructure, provided by diffusion tensor imaging, because acute or subtle injury may not be visually detectable on conventional MRIs.

However, confirmation of the coherent reduction in the deep gray matter and WM damage suggests the possibility that WM injury might be a mechanism that leads to secondary damage and abnormal thalamocortical connectivity, resulting in a reduction in lentiform nuclei and thalamic volume. Lesions in the developing WM may be associated with a particular damage to the cortical subplate. There is animal evidence that injury to the subplate leads to thalamocortical disturbances. The subplate contains a transient set of neurons surrounded by a rich extracellular matrix and is maximally visible on MRI and histology during the second trimester when premature infants are undergoing intensive care. The subplate, with its neurons and extracellular matrix, forms a waiting zone for the thalamocortical afferents and efferents and receives guidance molecules that guide these fibers to the appropriate cortical regions. It is possible that diffuse WM disease includes injury to the subplate, maximizing the thalamocortical disturbances seen in preterm infants and causing a secondary reduction in deep gray matter volumes.

Abnormalities in the thalamus were shown in animal studies after lesions in the cerebral cortex. The subsequent axotomy leads to retrograde microglial-induced reduction in the number of thalamic neurons. The microglia are thought to mediate injury by excitotoxic glutaminergic mechanisms. The injury leads to a reduction in the thalamic volume and a relative increase in the cell density. Hence, in preterm infants the disturbances within the WM either focally, such as periventricular leukomalacia, or diffusely, such as DEHSI, may be associated with concomitant injury to the vulnerable cortical subplate, and these may precede and result in thalamic and basal ganglia abnormalities.

Some potential limitations of this study deserve consideration. First, diffuse WM injury (DEHSI) was identified by visual inspection and not by objective quantification of diffusion parameters. However, it has been shown by previous studies that infants with visually classified DEHSI have a reduction in fractional anisotropy and an increase in apparent diffusion coefficient in their WM. Second, there is some potential for confounding of the data by growth, because there was a nonsignificant trend of increased age in the term-born controls. It is known that cerebral and cerebellar volumes increase between 40 and 44 weeks’ GA, hence there is a potential that the basal ganglia and thalamus may also increase in volume during this period. However, no growth was detected over this time period in both the control infants and PAT infants, although the study was not powered to detect the growth issue and, therefore, cannot be formally excluded.

CONCLUSIONS

Using manual techniques, we have shown that the volume of the lentiform and thalamic nuclei are reduced in preterm infants at term-equivalent age compared with term-born controls. Although preterm infants with overt supratentorial cerebral lesions have the most marked reduction in volume, significant reductions were also seen with milder diffuse WM changes consistent with DEHSI. These results support and extend the conclusions of studies using DBM and automatic segmentation.

ACKNOWLEDGMENTS

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REFERENCES


Paracetamol (Acetaminophen) Penetrates Readily Into the Cerebrospinal Fluid of Children After Intravenous Administration

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ABSTRACT

INTRODUCTION. The main action of paracetamol (acetaminophen) is presumed to be in the central nervous system. The central nervous system penetration of paracetamol has been described in children with intracranial pathologies but not in children with an intact blood-brain barrier.

OBJECTIVE. We investigated the cerebrospinal fluid penetration of paracetamol in 32 healthy children, aged 3 months to 12 years, who were undergoing surgery in the lower body using spinal anesthesia.

MATERIALS AND METHODS. In this open-label prospective study, children were given a single intravenous injection of paracetamol (15 mg/kg). Cerebrospinal fluid and venous blood samples were obtained between 5 minutes and 5 hours after injection. Paracetamol concentrations were determined from the cerebrospinal fluid and plasma by using a fluorescence polarization immunoassay.

RESULTS. Paracetamol was detected in cerebrospinal fluid from the earliest sample at 5 minutes, although in this sample paracetamol concentration was below the limit of quantification of 1.0 mg/L. Subsequent paracetamol concentrations in cerebrospinal fluid ranged between 1.3 and 18 mg/L (median: 7.2 mg/L), plasma concentrations ranged between 2.4 and 33 mg/L, and cerebrospinal fluid/plasma ratios ranged between 0.06 and 2.0. The highest CSF paracetamol concentration was detected at 57 minutes.

CONCLUSIONS. Paracetamol permeates readily into the cerebrospinal fluid of children. This fast and extensive transfer enables the rapid central analgesic and antipyretic action of intravenous paracetamol.
PARACETAMOL (acetaminophen) is the most commonly used antipyretic analgesic in children for the symptomatic treatment of acute pain and fever. At sufficient enteral dosage, paracetamol is effective alone for the treatment of mild and moderate pain, but in the acute situation, the intravenous preparation is more convenient and may perform better. With intravenous administration, the onset of analgesic and antipyretic action is rapid, with the analgesic action occurring within 15 minutes and fever reduction occurring within 30 minutes.

The mechanism of action of paracetamol has not been fully established. However, paracetamol has analgesic and antipyretic properties and weak antiinflammatory activity, thus it is likely that analgesic action may be attributable to inhibition of prostaglandin synthesis in the central nervous system (CNS) and in peripheral tissues. The analgesic action of paracetamol is likely to be linked also with the serotoninergic system. Serotonin has an important role in pain modulation in the CNS. In adult volunteers the serotonin receptor 5-HT3 antagonists tropisetron and granisetron completely block the analgesic effect of paracetamol.

To have effects within the CNS, paracetamol must penetrate the blood-brain barrier (BBB). The penetration of paracetamol into cerebrospinal fluid (CSF) was evaluated in adults, as well as in 2 studies in children. However, the children studied had significant pathology, such as head trauma, raised intracranial pressure, or tumors, which may affect the BBB permeability. We designed this study to investigate the CSF penetration of intravenous paracetamol (15 mg/kg) in healthy children undergoing surgery in the lower part of the body using spinal anesthesia.

MATERIALS AND METHODS

The study protocol was approved by the research ethics committee of the Hospital District of Northern Savo, Kuopio, Finland (No. 120/2004). The Finnish National Agency for Medicines was notified (No. 161/2004); the trial was recorded in the EudraCT database (No. 2004-001702-27), and it was conducted in accordance with the latest revision of the Declaration of Helsinki. The parents and children, if old enough to understand the trial protocol and the interventions, were informed, and the parents gave written consent and children assented.

Thirty-four children were asked to participate, but the parents of 2 children refused to consent (not wanting anything “extra” for their child), hence leaving a group of 32 children (19 boys and 13 girls) in the study population. The children were scheduled for genitourlogic surgery (15 children), herniotomy (11 children), and orthopedic surgery (6 children), all to be performed under spinal anesthesia. Children were excluded if they had contraindications to the use of paracetamol or spinal anesthesia.

The children were premedicated with buccal midazolam (0.375 mg/kg up to 7.5 mg) and ketamine (1.25 mg/kg up to 25 mg) 15 to 30 minutes before anesthesia. All children were sedated with midazolam, thiopental, and/or propofol before lumbar puncture for spinal anesthesia (n = 28) or combined spinal-epidural anesthesia (n = 4).

The children received an intravenous infusion of paracetamol (15 mg/kg) (Perfalgan 10 mg/mL, lot SH00568, expiration date August 2007 [Bristol-Myers Squibb AB, Bromma, Sweden]) over 10 minutes into a dorsal hand vein 5 minutes to 5 hours before lumbar puncture. One mL of CSF was collected into a polypropylene tube during lumbar puncture before the injection of local anesthetic. An indwelling catheter was inserted in a dorsal foot vein, and a 3-mL blood sample was obtained for paracetamol assay into a heparinized tube. Plasma was obtained by centrifugation at 3000g at 20°C for 10 minutes. The plasma was divided into 2 polypropylene tubes to obtain 2 samples of at least 0.5 mL each. One sample was tested, and another was kept as a control. The plasma and CSF were protected from light and stored at −72°C.

After the surgery, children were transferred to the postanesthesia care unit (PACU) for monitoring of vital signs, pain, and adverse effects. The pain intensity at rest and with movement was assessed by a research nurse on an 11-point numeric rating scale (0 [no pain] to 10 [worst possible pain]) and was recorded at every hour after the end of surgery. After the surgery, the children received an intravenous injection of ketoprofen (1 mg/kg). If the child was in pain (pain score at rest ≥3 or with movement ≥5), fentanyl (1 μg/mL, intravenously) or oxycodone (0.05 mg/kg, intravenously) was given for rescue analgesia.

Paracetamol Assay

Paracetamol concentrations in plasma and CSF samples were determined in 1 run using fluorescence polarization immunoassay technology (TDxFLx; Abbott Laboratories, Abbott Park, IL). The sensitivity of the paracetamol assay, defined as the lowest measurable concentration that can be distinguished from 0 with 95% confidence, was 1.0 mg/L. Within-run variations for controls at paracetamol concentrations of 15, 35, and 150 mg/L were 4.9% (n = 4), 3.6% (n = 4), and 3.8% (n = 4), respectively.

Statistics

No formal sample size calculation was performed, but a sample of 30 children was considered to provide sufficient information on CSF penetration of paracetamol in healthy children.

Data were entered and analyzed with the SPSS 13.0 (SPSS Inc, Chicago, IL). Correlations between paracetamol concentrations and patient characteristics were
tested with the Pearson correlation test. A gender difference in mean CSF-paracetamol concentration was tested with independent samples t tests, including Levene’s test for equality of variances, and both pooled- and separate-variances t tests for equality of means. A P value of .05 was considered as the limit of statistical significance.

RESULTS

The patient characteristics are presented in Table 1. There were few minor protocol deviations that were unlikely to affect the study results: 1 child (patient 1) had paracetamol (20 mg/kg), 1 child (patient 4) had paracetamol (12.5 mg/kg), and for 2 children (patients 26 and 15), the infusion time was 30 and 40 minutes, respectively. All other children received the study medication as defined in the protocol, and all CSF and plasma samples were collected as defined in the protocol. In 1 child (patient 5), the CSF sample was blood stained, but the paracetamol concentration was similar to others and, therefore, it was included in the analysis. All the other CSF samples were visually clear.

The individual sampling times and paracetamol concentrations are presented in Table 2 and Fig 1. Paracetamol was detected from the earliest CSF sample taken at 5 minutes after injection, but in this sample the concentration was below the sensitivity of the assay (1.0 mg/L). In the other CSF samples, paracetamol concentrations ranged between 1.3 and 18 mg/L (median: 7.2 mg/L), and plasma concentrations were between 2.4 and 33 mg/L (14 mg/L).

The CSF to plasma concentration ratio ranged between 0 and 2 (median: 0.8). There was a positive correlation between sampling time and CSF to plasma concentration ratio ($r = 0.89; P < .001$) (Fig 2).

There was no correlation between CSF paracetamol concentration and age, height, or weight. However, in a post hoc analysis there was a significant gender difference in the CSF paracetamol concentrations, with girls having higher concentrations than boys ($P = .001$) (Fig 3).

Six children developed adverse effects: 3 children were agitated in the recovery room, 1 vomited, 1 had nausea, and 1 developed shivering. None of the children complained of pain during paracetamol injection.

For pain treatment in the PACU, the children received ketoprofen (1 mg/kg intravenously; $n = 17$), naproxen (5 mg/kg by mouth; $n = 2$), ibuprofen (10 mg/kg by mouth; $n = 1$), or a second dose of paracetamol (15 mg/kg by mouth; $n = 13$). Four children had an epidural infusion. Ten children had significant pain in the PACU (numeric rating scale $> 3$ at rest or $> 5$ with movement), and they were given a single dose of opioid: fentanyl (1 $\mu$g/kg; $n = 5$) or oxycodone (0.05 mg/kg; $n = 5$) intravenously for rescue analgesia.

DISCUSSION

Our study indicates that paracetamol enters readily through an intact BBB in children. Paracetamol was detected from the earliest CSF samples, and only in the CSF sample taken 5 minutes after the intravenous injection was paracetamol below the lower limit of quantification 1.0 mg/L. The highest CSF-paracetamol concentration, 18 mg/L, was measured 57 minutes after the injection. Thereafter, CSF and plasma concentrations were similar, with CSF/plasma ratios between 0.78 and 2. This relatively rapid CNS penetration enables the fast analgesic and antipyretic onset of intravenous paracetamol observed in clinical studies.2–5

The CNS penetration of paracetamol in children was measured in 2 previous reports, which found that similar peak CSF concentrations are attained with enteral paracetamol doses 2 to 3 times higher than our study using intravenous paracetamol (15 mg/kg). Anderson et al13 administered paracetamol (40 mg/kg) by nasogastric tube to 9 ventilator-dependent children with head trauma or other CNS pathology. In these 9 children, the highest CSF and plasma concentrations (20 and 21 mg/L, respectively) were similar to those detected in the present study (18 and 33 mg/L, respectively). However, the peak CSF paracetamol concentration was attained at 210 minutes in that study in contrast to our study where the peak CSF concentrations were detected 57 minutes after intravenous injection. In another study by Anderson’s group,14 paracetamol (30 mg/kg) was administered rectally to 41 children undergoing insertion or revision of ventriculoperitoneal shunt or insertion of ventricular drain. The highest CSF and plasma paracetamol concentrations observed 2 hours after the paracetamol administration were 21 and 33 mg/L, respectively, which are similar to those observed in our study.

The mechanism by which paracetamol exerts its antinociceptive effects is not established, but recent studies indicate that the analgesic action of paracetamol may be multimodal and that activity in the CNS are essential for its analgesic action. In the CNS, paracetamol may act through several different pathways. First, it was shown that paracetamol attenuates prostaglandin synthesis through a weak cyclooxygenase inhibition,15 and there is evidence to suggest both peripheral16 and central sites17 of action that may involve inhibition of cyclooxygenase. Second, animal studies indicate that paracetamol antinociceptive action may also involve spinal nitric oxide pathways, which are associated with spinal glutamate N-methyl-D-aspartate receptor activation.18 Finally, both

<table>
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<th>TABLE 1 Patient Characteristics</th>
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<tr>
<td>$N = 32$</td>
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<tr>
<td>Median age (range), mo</td>
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<td>Median weight (range), kg</td>
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<td>Median height (range), cm</td>
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animal and human experimental pain models consistently indicate that paracetamol acts at the CNS by serotonergic mechanisms.\(^{10}\)

In previous trials in children, we evaluated the CSF penetration of 2 nonsteroidal antiinflammatory drugs (NSAIDs), indomethacin\(^{19}\) and ketoprofen.\(^{20,21}\) The onset

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**TABLE 2** Paracetamol Concentrations in CSF and Plasma and the CSF to Plasma Concentration Ratio in Each Patient

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sampling Time, min</th>
<th>CSF Concentration, mg/L</th>
<th>Plasma Concentration, mg/L</th>
<th>Concentration Ratio, CSF/Plasma</th>
<th>Gender</th>
<th>Age, mo</th>
<th>Height, cm</th>
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<td>6.2</td>
<td>3.9</td>
<td>1.60</td>
<td>Male</td>
<td>56</td>
<td>111</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>308</td>
<td>4.7</td>
<td>2.4</td>
<td>2.00</td>
<td>Female</td>
<td>99</td>
<td>135</td>
<td>27</td>
</tr>
<tr>
<td>Minimum</td>
<td>5</td>
<td>BLQ</td>
<td>2.4</td>
<td>0.07</td>
<td>—</td>
<td>3</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Maximum</td>
<td>308</td>
<td>18.0</td>
<td>33.0</td>
<td>2.00</td>
<td>—</td>
<td>153</td>
<td>160</td>
<td>69</td>
</tr>
<tr>
<td>Median</td>
<td>57</td>
<td>7.2</td>
<td>14.0</td>
<td>0.80</td>
<td>—</td>
<td>55</td>
<td>107.5</td>
<td>19.5</td>
</tr>
</tbody>
</table>

Patient 1 was given 20 mg/kg of paracetamol, and patient 4 was given 12.5 mg/kg of paracetamol. For patients 26 and 15, the infusion time was 30 and 40 minutes, respectively. BLQ indicates below the limit of quantification.

\(^a\) The CSF sample was blood stained.

---

**FIGURE 1**
Plasma (circles) and CSF (squares) paracetamol concentrations after a single intravenous injection of paracetamol 15 mg/kg. A logarithmic scale is used in the inset.
of analgesic action of these 2 NSAIDs in children is fast, and both also penetrate readily into the CSF, because high CSF concentrations are detected early.\textsuperscript{19–21} After intravenous indomethacin, CSF concentrations are uniform from the first minutes after injection up to 4 hours, which could explain both the rapid analgesic action and the high incidence of CNS adverse effects.

However, there seem to be a major difference in BBB penetration between paracetamol and NSAIDs. Forty-five minutes after intravenous administration, paracetamol concentrations in CSF are similar or higher to those in plasma. On the contrary, because of a high degree of plasma protein binding with indomethacin and ketoprofen, CSF concentrations are \(<0.1\%\) of total plasma concentrations\textsuperscript{19–21} but similar to protein-free plasma concentrations. Thus, although paracetamol activity on cyclooxygenase is weak,\textsuperscript{15} we suggest that the relatively high CSF concentrations are sufficient to inhibit prostaglandin \(E_2\) in the CNS to a degree comparable to NSAIDs.

Our study shows that in children paracetamol may penetrate the BBB more readily than in adults, which may explain the effective analgesic action of paracetamol in pediatric pain management. Bannwarth et al\textsuperscript{11} evaluated CSF penetration of intravenous propacetamol (2 g), a prodrug of paracetamol, in 43 healthy adults having lumbar puncture for myelography. At this dose, corresponding to 1 g of paracetamol (15 mg/kg), peak CSF paracetamol concentration was found at 45 minutes, which is comparable to 57 minutes in our study. However, the peak CSF concentration of 9 mg/L was only half of that observed in children.\textsuperscript{13,14} In our study, 12 of 32 children had CSF-paracetamol concentrations \(>9\) mg/L, which was the highest concentration observed in adults.

In our study, an interesting finding was that girls developed significantly higher CSF paracetamol concentrations than boys. In adults, gender differences in drug response and adverse effects were noted, but it is unclear whether these differences are pharmacokinetic or pharmacodynamic.\textsuperscript{23} The present finding warrants additional studies on gender differences in pharmacokinetics of analgesics in pediatric populations.
In our study, intravenous paracetamol was well tolerated. Six children developed adverse effects. Most common was emergence agitation, which occurred in 3 children. Emergence agitation is common in children after inhalation anesthesia but rarely reported after spinal anesthesia. Paracetamol-related agitation was not reported earlier, and in our present study it was more likely with the associated drugs given for performing the spinal anesthesia (midazolam, thiopental, or propofol). One child experienced shivering in the PACU, and this was probably because of the spinal anesthesia used.

It is considered unethical to recruit healthy volunteers for studies on pediatric pharmacology; furthermore, performing a lumbar puncture involves risks. We collected the CSF samples during an already-indicated lumbar puncture. The volume of the sample (1 mL of CSF) was always less than the volume of injected local anesthetic. Therefore, the study protocol was well incorporated into the standard care in our institution. Spinal anesthesia is routinely used in our department, and all children having surgery are provided nonopioid analgesic. Therefore, the study protocol was well incorporated into the standard care in our institution.

CONCLUSIONS

Our study indicates that paracetamol (acetaminophen) permeates readily into the CSF of healthy children. The relatively fast and extensive CNS permeation enables the rapid CNS analgesic and antipyretic effects of intravenous paracetamol.

REFERENCES

Antifungal Therapy in Children With Invasive Fungal Infections: A Systematic Review

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ABSTRACT

Invasive fungal infections are associated with significant morbidity and mortality. Differences between children and adults are reported, yet few trials of antifungal agents have been performed in pediatric populations. We performed a systematic review of the literature to guide appropriate pediatric treatment recommendations. From available trials that compared antifungal agents in either prolonged febrile neutropenia or invasive candidal or Aspergillus infection, no clear difference in treatment efficacy was demonstrated, although few trials were adequately powered. Differing antifungal pharmacokinetics between children and adults were demonstrated, requiring dose modification. Significant differences in toxicity, particularly nephrotoxicity, were identified between classes of antifungal agents. Therapy needs to be guided by the pathogen or suspected pathogens, the degree of immunosuppression, comorbidities (particularly renal dysfunction), concurrent nephrotoxins, and the expected length of therapy.

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Key Words
antifungal agents, pediatrics, mycoses, candidiasis, aspergillosis, neutropenia

Abbreviations
IFI—invasive fungal infection
CAB—conventional amphotericin B deoxycholate
ABLC—amphotericin B lipid complex
ABCD—amphotericin B colloidal dispersion
RCT—randomized, controlled trial

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PEDiATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics
Invasive Fungal Infection (IFI) is a significant problem in those at risk. Candida and Aspergillus species are the most frequent fungi responsible for invasive infections in children. Worldwide, the incidence is increasing in at-risk populations. Furthermore, the increasing incidence of resistant fungi is creating additional therapeutic challenges.

Despite improvements in supportive care, IFI is still associated with a significant mortality rate and high health care costs. In studies published within the last decade, mortality rates in children with candidemia range from 19% to 31%. Invasive aspergillosis in children is associated with even greater mortality: 68% to 77%. A higher mortality rate is seen in those with greater degrees of immunosuppression, particularly after hematopoietic stem cell transplantation.

Currently, there are 4 classes of drugs for treatment of IFIs: polyenes, triazoles, echinocandins, and nucleoside analogues. The available polyenes include conventional amphotericin B deoxycholate (CAB), liposomal amphotericin B, amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD). Numerous triazoles have been trialled, including fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole. Both groups of drugs target ergosterol, a key component of the fungal cell membrane. Echinocandins (caspofungin, micafungin, and anidulafungin) are a novel class of antifungal agents that interfere with cell wall biosynthesis. Finally, the nucleoside analog flucytosine interferes with nucleotide synthesis.

Differences between children and adults with IFI exist. These differences include predisposing factors, infective organism, and site of infection. Significant pharmacokinetic differences occur between pediatric and adult patients with many antifungal agents. Therefore, there is a need for pediatric-specific data to guide antifungal therapy in children.

METHODS

We performed a systematic review that included all trials in children with IFIs. The aim was to collate evidence for best-practice guidelines. The Medline, Embase, and Cochrane databases were searched from January 1966 to May 2006 for relevant studies. Review of references and conference proceedings led to the identification of additional relevant articles including unpublished data. Pediatrictrialstrialsoftrials with a sufficient number of pediatric subjects were identified and reviewed.

In this review, data on the most frequently encountered clinical problems are presented: antifungal therapy in prolonged fever and neutropenia, candidemia/ invasive candidiasis, and invasive aspergillosis. Relative antifungal toxicities are also compared. When pediatric studies have been judged to be insufficient, adult studies have been used to supplement data. Pediatric comparative trial data are listed in Tables 1 and 2; recommended pediatric and adult dosages of antifungal agents are listed in Table 3.

Empiric Antifungal Therapy in Those at Risk (Prolonged Fever and Neutropenia)

IFIs are an important cause of morbidity and death in patients with neutropenia. In 1982, Pizzo et al conducted an unblinded randomized study in 50 neutropenic children, adolescents, and young adults who remained febrile for 7 days despite broad-spectrum antibiotic treatment. Results demonstrated more rapid fever defervescence and less fungal infections in those who received amphotericin B, but the findings failed to reach significance. Despite the study limitations and those of the European Organisation for Research and Treatment of Cancer trial that followed, it has become standard of care to use antifungal agents in neutropenic subjects who remain febrile despite the use of broad-spectrum antibacterial agents.

Prentice et al conducted the largest pediatric randomized, controlled trial (RCT) to date. In an RCT that included 202 children with 96 hours of fever and neutropenia that were unresponsive to broad-spectrum antibiotics, liposomal amphotericin B (1 or 3 mg/kg per day) was compared with CAB (1 mg/kg per day). Safety was the primary end point. The study also included 134 adults. Treatment success (fever defervescence without additional antifungal therapy) was observed in 51% of children who received CAB, 64% who received 1 mg/kg per day of liposomal amphotericin B, and 63% who received 3 mg/kg per day of liposomal amphotericin B (P = .22). Although the overall analysis (adults and children inclusive) demonstrated a significant difference in treatment success between CAB and the higher dose of liposomal amphotericin B (49% vs 64%; P = .03), the Kaplan-Meier analysis of time to fever defervescence failed to show any significant difference between these treatment arms.

In another small trial, CAB (0.8 mg/kg per day) and ABCD (4 mg/kg per day) therapy were compared in 49 children with prolonged fever and neutropenia. A composite end point was used to assess treatment success: fever defervescence, survival for at least 7 days after drug cessation, no documented or suspected IFI within 7 days of receipt of the study drug, and no toxicities that required cessation of therapy. The difference in treatment success observed between CAB and ABCD approached significance (41% vs 69%; P = .051), yet the time to fever defervescence was similar with both treatments (P = .654).

Other empiric antifungal trials that compared different formulations of amphotericin B have not included children, or pediatric subgroup analysis was not performed. Adult trials have failed to demonstrate a significant difference in treatment success when CAB (0.6–0.8 mg/kg per day) is compared with lipo-
TABLE 1  Data on Efficacy From Comparative Pediatric Trials

<table>
<thead>
<tr>
<th>Trial Author (Year)</th>
<th>Clinical Setting</th>
<th>Method (No. of Children)</th>
<th>Comparators</th>
<th>Outcome</th>
<th>Results (Significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prentice et al 26</td>
<td>Fever and neutropenia</td>
<td>Open-label RCT (n = 202)</td>
<td>CAB (1 mg/kg per d) vs liposomal amphotericin B</td>
<td>Fever defervescence without additional antifungal therapy or breakthrough IFI</td>
<td>51% vs 64% vs 63% (NS [P = .22])</td>
</tr>
<tr>
<td>Sandler et al 27</td>
<td>Fever and neutropenia</td>
<td>Double-blind RCT (n = 49)</td>
<td>CAB (0.8 mg/kg per d) vs ABCD (4 mg/kg per d)</td>
<td></td>
<td>41% vs 69% (NS [P = .051])</td>
</tr>
<tr>
<td>Khayat et al 38</td>
<td>Fever and neutropenia</td>
<td>Retrospective comparison</td>
<td>Liposomal amphotericin B vs caspofungin</td>
<td>Treatment success a</td>
<td>92% vs 92% (NS)</td>
</tr>
<tr>
<td>Lopez Sastre et al 50</td>
<td>Invasive candidiasis (neonatal)</td>
<td>Open-label observational study (n = 110)</td>
<td>Liposomal amphotericin B (mean: 3.8 mg/kg per d) vs ABLC (mean: 4.2 mg/kg per d)</td>
<td>Clinical recovery; normalization of blood count and CRP, with sterilization of infected sites</td>
<td>94% vs 86% (NS)</td>
</tr>
<tr>
<td>Mondal et al 68</td>
<td>Candidemia (ICU)</td>
<td>Double-blind RCT (n = 42)</td>
<td>Fluconazole (10 mg/kg per d) vs itraconazole</td>
<td>Clinical recovery with sterilization of blood cultures</td>
<td>82% vs 81% (NS)</td>
</tr>
</tbody>
</table>

CRP indicates C-reactive protein; NS, not significant.

a Composite end point: fever defervescence, survival for at least 7 days after drug cessation, no documented or suspected IFI during the study or within 7 days, and no toxicities that required cessation of therapy.

TABLE 2  Data on Toxicity From Comparative Pediatric Trials

<table>
<thead>
<tr>
<th>Trial Author (Year)</th>
<th>Clinical Setting</th>
<th>Method (No. of Children)</th>
<th>Comparators</th>
<th>Outcome</th>
<th>Results (Significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prentice et al 26</td>
<td>Fever and neutropenia</td>
<td>Open-label RCT (n = 202)</td>
<td>CAB (1 mg/kg per d) vs liposomal amphotericin B</td>
<td>Nephrotoxicity (serum creatinine ≥ 2.0 × baseline)</td>
<td>21% vs 8% vs 11% (NS [P = .13])</td>
</tr>
<tr>
<td>Sandler et al 27</td>
<td>Fever and neutropenia</td>
<td>Double-blind RCT (n = 49)</td>
<td>CAB (0.8 mg/kg per d) vs ABCD (4 mg/kg per d)</td>
<td>Nephrotoxicity a</td>
<td>52% vs 12% (P &lt; .003)</td>
</tr>
<tr>
<td>White et al 37</td>
<td>Fever and neutropenia</td>
<td>Double-blind RCT (n = 46)</td>
<td>CAB (0.8 mg/kg per d) vs ABCD (4 mg/kg per d)</td>
<td>Nephrotoxicity a</td>
<td>52% vs 12% (P &lt; .01)</td>
</tr>
<tr>
<td>Lopez Sastre et al 50</td>
<td>Invasive candidiasis (neonatal)</td>
<td>Open-label observational study (n = 110)</td>
<td>Liposomal amphotericin B (mean: 3.8 mg/kg per d) vs ABLC (mean: 4.2 mg/kg per d)</td>
<td>Nephrotoxicity (serum creatinine &gt; 1.5 mg/dL)</td>
<td>6% vs 9% (NS)</td>
</tr>
<tr>
<td>Mondal et al 68</td>
<td>Candidemia (ICU)</td>
<td>Double-blind RCT (n = 42)</td>
<td>Fluconazole (10 mg/kg per d) vs itraconazole</td>
<td>Nephrotoxicity (serum creatinine &gt; 88 µmol/L)</td>
<td>17% vs 12% (NS)</td>
</tr>
<tr>
<td>Sandler et al 27</td>
<td>Fever and neutropenia</td>
<td>Double-blind RCT (n = 49)</td>
<td>CAB (0.8 mg/kg per d) vs ABCD (4 mg/kg per d)</td>
<td>Fever</td>
<td>82% vs 74% (NS)</td>
</tr>
<tr>
<td>Prentice et al 26</td>
<td>Fever and neutropenia</td>
<td>Open-label RCT (n = 202)</td>
<td>CAB (1 mg/kg per d) vs liposomal amphotericin B</td>
<td>Chills</td>
<td>50% vs 78% (NS)</td>
</tr>
<tr>
<td>Driessen et al 67</td>
<td>Candidemia (neonatal)</td>
<td>Open-label RCT (n = 21)</td>
<td>CAB (1 mg/kg per d) vs fluconazole (5 mg/kg per d after 10 mg/kg load)</td>
<td>Hepatotoxicity (transaminases ≥ 110 IU/L)</td>
<td>17% vs 17% vs 23% (NS)</td>
</tr>
<tr>
<td>Mondal et al 68</td>
<td>Candidemia (ICU)</td>
<td>Double-blind RCT (n = 42)</td>
<td>Fluconazole (10 mg/kg per d) vs itraconazole</td>
<td>Hepatotoxicity (transaminases &gt; 2 × baseline)</td>
<td>18% vs 8% (NS)</td>
</tr>
</tbody>
</table>

NS indicates not significant.

a Nephrotoxicity was defined as a serum creatinine >2.0 baseline, increase of ≥88 µmol/L (1 mg/dL) in serum creatinine, or ≥50% reduction in creatinine clearance.
TABLE 3  
Recommended Antifungal Dosing for Children and Adults With IFI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Recommended Pediatric Dose</th>
<th>Recommended Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABa</td>
<td>Intravenous preparation</td>
<td>0.6–1.5 mg/kg per d(^{13,157})</td>
<td>0.6–1.5 mg/kg per d</td>
</tr>
<tr>
<td>Lipid preparations(^{a})</td>
<td>Intravenous preparation</td>
<td>1–5 mg/kg per d(^{28,137})</td>
<td>1–5 mg/kg per d</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>Intravenous preparation</td>
<td>3–5 mg/kg per d(^{13,157})</td>
<td>3–5 mg/kg per d</td>
</tr>
<tr>
<td>ABCD</td>
<td>Intravenous preparation</td>
<td>5 mg/kg per d(^{13,157})</td>
<td>5 mg/kg per d</td>
</tr>
<tr>
<td>ABLC</td>
<td>Intravenous preparation</td>
<td>6–12 mg/kg per d(^{101})</td>
<td>400–800 mg/d</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Capsule, suspension, and intravenous preparation</td>
<td>In neonates: 6–12 mg/kg (1–2 wk of age: every 3rd day; 2–4 wk of age: every 2 nd day)</td>
<td></td>
</tr>
<tr>
<td>Itraconazole(^{b})</td>
<td>Capsule, suspension, and intravenous preparation(^{c})</td>
<td>2.5–5 mg/kg twice daily(^{108,109})</td>
<td>200–400 mg/d</td>
</tr>
<tr>
<td>Voriconazole(^{d,11,12})</td>
<td>Tablet, suspension, and intravenous preparation(^{d})</td>
<td>6 mg/kg twice daily for 24 h then 4 mg/kg twice daily(^{104})</td>
<td>6 mg/kg twice daily for 24 h then 3–4 mg/kg twice daily (intravenous)</td>
</tr>
<tr>
<td>Posaconazole(^{e})</td>
<td>Suspension</td>
<td>400–800 mg/d in 2–4 divided doses(^{110})</td>
<td>800 mg/d in 2–4 divided doses</td>
</tr>
<tr>
<td>Caspofungin(^{f})</td>
<td>Intravenous preparation</td>
<td>50 mg/m(^2) daily for children and adolescents(^{106})</td>
<td>70 mg followed by 50 mg daily</td>
</tr>
<tr>
<td>Micafungin</td>
<td>Intravenous preparation</td>
<td>2.5–5 mg/kg twice daily(^{107}) for premature neonates(^{106})</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>Intravenous preparation</td>
<td>1–4 mg/kg per d(^{11,112})</td>
<td>150 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5–3 mg/kg load on d 1 followed by 0.75–1.5 mg/kg per d(^{11})</td>
<td>200 mg followed by 100 mg daily</td>
</tr>
</tbody>
</table>

\(^{a}\) The recommended dose depends on the clinical scenario.

\(^{b}\) Therapeutic drug monitoring is recommended for children with invasive fungal disease given the variable metabolism and limited pharmacokinetic data in children.\(^{104,108,109,157}\)

\(^{c}\) Cyclodextrins are present in the intravenous preparations of itraconazole and voriconazole. Caution should be taken when using both drugs in patients with creatinine clearance of <50 mL/minute.\(^{78,120}\)

\(^{d}\) Dose modification is recommended for adults with cirrhosis (voriconazole) and moderate-to-severe hepatic insufficiency (caspofungin).\(^{156}\) No pharmacokinetic data exist regarding caspofungin use in children with liver disease, although a decreased dose is recommended.\(^{157}\)

\(^{e}\) Posaconazole has been studied in children 8 to 17 years old; no data are available for younger children. It is only licensed for children ≥13 years of age.

Liposomal amphotericin B (3 mg/kg per day) or ABCD (4 mg/kg per day).\(^{29,30}\) Furthermore, a meta-analysis of RCTs that included 1895 patients failed to demonstrate any difference in mortality between CAB and lipid-agent use.\(^{30}\) Fewer breakthrough fungal infections were seen in those receiving liposomal amphotericin B compared with CAB.\(^{30}\) No difference in treatment success was observed when using a composite end point; however, fewer breakthrough fungal infections were seen in those who were receiving voriconazole.

Khayat et al\(^{38}\) retrospectively compared liposomal amphotericin B and caspofungin in 26 febrile and neutropenic children. The duration of neutropenia and treatment were significantly shorter in those receiving caspofungin. No difference in effectiveness was observed (92% in both cohorts). Liposomal amphotericin B and caspofungin were compared in 1095 febrile neutropenic adults. Despite there being a greater number of patients who survived for ≥7 days after completion of the study therapy in the caspofungin group, no overall difference in treatment success was observed.\(^{39}\)

In summary, no clear differences in overall treatment success or mortality have been demonstrated in pediatric or adult trials in which empiric conventional amphotericin B and lipid preparations were compared in subjects with prolonged fever and neutropenia. Fewer breakthrough infections may occur in subjects who receive liposomal amphotericin B. In azole-naive neutropenic subjects, conventional amphotericin B and fluconazole seem equally effective. Furthermore, in febrile neutropenic adults, voriconazole and caspofungin seem to be as effective as liposomal amphotericin B.
Antifungal Therapy in Proven Candidemia or Invasive Candidiasis

In pediatric and neonatal case series, Candida albicans and Candida parapsilosis are the most frequently isolated organisms responsible for invasive disease. Other species such as Candida tropicalis, Candida glabrata, and Candida krusei occur less frequently than in adult cohorts. C tropicalis, C glabrata, C krusei, and Candida guillermontii frequently have reduced susceptibility to fluconazole, and Candida lusitaniae is thought to have variable sensitivity against amphotericin B.

Higher rates of candidemia with nonalbicans species are seen in those who receive systemic antifungal agents. Previous fluconazole therapy is a risk factor for infection with a fluconazole-resistant organism. The association between C parapsilosis and central-line infections has been documented by a number of authors. Numerous antifungal agents have been used in open-label trials in neonates and children with candidemia/invasive candidiasis. Amphotericin B and its lipid preparations, azoles, and echinocandins have all been shown to be effective in neonates with candidal infections. Amphotericin B-based preparations, azoles, and echinocandins have also been shown to be effective in predominantly immunosuppressed pediatric populations. The most frequently used end point is microbiologic clearance of candidemia (CAB: 68%–96%; lipid preparations of amphotericin B: 83%–100%; fluconazole: 72%–97%; itraconazole: 81%; caspofungin: 85%–100%; micafungin: 72%). Comparing trials is difficult given the small numbers, mixed patient populations, and varying comorbidities. Furthermore, newer agents are frequently used as salvage therapy in open-label trials after failure of standard agents.

Two small RCTs have compared antifungal agents in pediatric candidemia. DiRienzo et al compared CAB (1 mg/kg per day) with fluconazole (5 mg/kg per day) in 23 predominantly preterm neonates. Although the trial was significantly underpowered, no significant difference in treatment success or mortality rate was demonstrated. Mondal et al compared enterally administered fluconazole (10 mg/kg per day) and itraconazole (10 mg/kg per day) in 43 pediatric intensive care patients with candidemia. No significant difference in total mortality rate (18.2% vs 9.5%) or attributable mortality rate (4.8% vs 4.5%) was demonstrated. The time to mycological cure (5.6 ± 1.6 vs 5.5 ± 1.9 days) and clinical cure (7.0 ± 2.6 vs 7.9 ± 1.3 days) was similar for both treatment groups.

The therapeutic equivalence of fluconazole and CAB has been demonstrated in predominantly nonneutropenic adolescents and adults with candidemia or invasive candidiasis. Furthermore, the therapeutic equivalence of voriconazole compared with CAB followed by fluconazole was demonstrated in 370 nonneutropenic adolescents and adults. Voriconazole was superior in subjects with C tropicalis sepsis. Therapeutic equivalence of fluconazole and voriconazole was demonstrated for esophageal candidiasis by Ally et al in adult patients with cancer and HIV.

Echinocandins have been compared with CAB and azoles in adults with candidemia and invasive candidal infections. No comparative pediatric trials have been performed. Caspofungin and CAB seem equally effective in adult patients with candidemia and oropharyngeal or esophageal candidiasis. No difference in treatment success has been demonstrated in adults with esophageal candidiasis treated with fluconazole and caspofungin, micafungin, or anidulafungin. Caspofungin has been shown to be effective in treating fluconazole-resistant esophageal candidiasis.

At least 14 days of therapy after the last positive blood-culture result is recommended for children and neonates with candidemia in the absence of disseminated disease. Donowitz and Hendley retrospectively reviewed short-course therapy in 30 neonatal and pediatric patients with candidemia. Clinical and mycological cure was documented in 58% of subjects administered 7 to 14 days of antifungal therapy after bloodstream sterilization. No comparison has been performed with longer courses of antifungal therapy. An intravascular device is the most frequent source of candidemia in children (D. Marriot, MBBS, T. Sorrell, MD, M. Slavin, MBBS, S. Chen, MBBS, PhD, and D. Ellis, PhD, “The Australian Candidaemia Study: A Prospective Population Based Laboratory Surveillance for Candidaemia in Australia Over a Three Year Period,” unpublished work, 2006). Management of intravascular devices is integral in the management of children with candidemia but is beyond the scope of this review (see Nucci and Anaisis). Treatment for deep candidal infection frequently requires prolonged therapy. Treatment recommendations are from open-label and observational studies rather than comparative trials. Pappas et al recommended at least 4 weeks of therapy in candidal meningitis after resolution of symptoms and signs. Combination therapy (ie, amphotericin B derivative and fluconazole) is often recommended. The role of newer antifungal agents has not yet been fully established. Prolonged antifungal therapy (ie, >6 weeks) is frequently required for chronic disseminated candidiasis, endocarditis, endophthalmitis, and osteomyelitis. This prolonged treatment is influenced by the underlying degree of immunosuppression, the presence of prosthetic material, and the response to both medical therapy and surgery where warranted.

In conclusion, no adequately powered comparative trials in pediatric candidemia or invasive candidiasis have been performed. No difference in treatment success has been seen when CAB, azoles, and echinocandins were compared in nonneutropenic adolescents and adults. Previous antifungal therapy may have an impact.
on the infecting *Candida* species and should influence empiric therapy.

**Antifungal Therapy in Proven or Suspected Invasive Aspergillosis**

There is a paucity of comparative data for pediatric aspergillosis. Furthermore, a lack of uniform definitions for diagnosis and treatment response, the relatively small subject numbers in pediatric studies, the lack of pediatric subgroup analysis in larger studies, and differences in the study populations create uncertainty about optimal management.\(^7\) Assessment of open-label pediatric trials indicates that the most frequently used end point has been clinical cure and/or improvement. Treatment response rates have varied markedly (CAB: 32%;\(^9\) ABLC: 39%–78%;\(^6\)\(^6\)\(^3\)\(^6\)\(^8\)\(^5\); voriconazole: 60%;\(^9\) caspofungin: 70%;\(^6\)\(^5\); micafungin: 45%;\(^8\)\(^6\)). Mixed patient populations and the use of antifungal agents as either primary or salvage therapy make interpretation of the data difficult.

The only comparative trial of antifungal therapy in pediatric aspergillosis compared ABCD with CAB. Children and adults who were given ABCD were compared with a historic cohort treated with CAB.\(^7\) ABCD was administered to patients who were intolerant of or refractory to CAB therapy, had preexisting renal impairment, or were enrolled in ABCD dose-escalation trials after hematopoietic stem cell transplantation. Pediatric numbers were small, and no pediatric subgroup analysis was performed. White et al\(^7\) found that treatment success and survival were greater in the ABCD group. Those treated with ABCD were younger and less likely to be neutropenic.

Using comparative data from adult trials, a number of conclusions can be drawn regarding the relative efficacy of different antifungal agents. CAB was compared with lipid preparations in 2 underpowered RCTs: no significant difference in treatment outcome was observed when CAB (1.0–1.5 mg/kg per day) was compared with liposomal amphotericin B (5 mg/kg per day) or ABCD (6 mg/kg per day).\(^8\)\(^6\)\(^9\)

Two randomized trials compared different doses of liposomal amphotericin B in proven or probable aspergillosis. No difference in clinical response was observed between 1 and 4 mg/kg per day of liposomal amphotericin B, although the trial was insufficiently powered.\(^9\) In patients with proven aspergillosis at group assignment, clinical response was seen in 58% of those who received 4 mg/kg per day compared with 37% who received 1 mg/kg per day. Another trial compared 3 and 10 mg/kg per day of liposomal amphotericin B in 339 subjects with filamentous fungal infection (predominantly aspergillosis). No differences in treatment success at 12 weeks (50% vs 48%, respectively) or survival (72% vs 58%, respectively) were observed.\(^9\)

Herbrecht et al\(^9\) compared CAB (1 mg/kg per day) with voriconazole (6 mg/kg twice daily for 24 hours followed by 4 mg/kg twice daily) in 277 adolescents and adults with proven or probable aspergillosis. Voriconazole was superior with regards to treatment success (53% vs 32%, respectively) and survival (71% vs 58%, respectively). Some of the voriconazole treatment success may be attributable to duration of therapy, because it was significantly longer in the voriconazole group (77 vs 10 days, respectively). Other licensed antifungal agents were used less frequently in those who were administered voriconazole compared with CAB (36% vs 80%, respectively).

Caspofungin and micafungin have been shown to be effective in open-label trials in adults with aspergillosis who were intolerant of or refractory to other antifungal agents.\(^9\)\(^3\)\(^9\)\(^5\) No comparative trials have been published to date.

The duration of antifungal therapy required for invasive aspergillosis in children and adults has not been determined. Herbrecht et al\(^9\) clinically and radiologically evaluated subjects after 12 weeks of antifungal therapy. In an open-label study of voriconazole use in children with IFI (predominately aspergillosis), the median duration of therapy was 93 days (range: 1–880).\(^9\) The length of therapy administered needs to be influenced by response to therapy and immunologic recovery.

In summary, pediatric data are insufficient to guide therapy in children with invasive aspergillosis. Adult data suggest that in subjects with invasive aspergillosis, voriconazole is superior to conventional amphotericin B and associated with superior survival. Higher doses of liposomal amphotericin B are not superior to 3 mg/kg per day of liposomal amphotericin B. Echinocandins are effective in aspergillosis, although no comparative trials have been completed.

**Combination Antifungal Therapy**

Given the high morbidity of IFI, the role of combination therapy is frequently considered. To date, no pediatric combination trials have been published, although research is underway. In nonneutropenic adults with candidemia, amphotericin B and fluconazole were compared with amphotericin B alone.\(^9\)\(^8\) Clearance of *Candida* from the bloodstream occurred more frequently with combination therapy; however, no difference in the primary end point or 90-day mortality rate was demonstrated. Combination therapy with voriconazole and caspofungin (n = 16) was retrospectively compared with voriconazole (n = 31) in a population of adults with proven or probable aspergillosis and progression despite treatment with amphotericin B.\(^9\) Three-month survival, estimated with Kaplan-Meier curves, demonstrated a reduced mortality rate with combination therapy (hazard ratio: 0.28; \(P = .011\)).

In summary, there is insufficient evidence currently to support the routine use of combination therapy in
children with candidemia, invasive candidiasis, or aspergillosis. Combination therapy should be reserved for salvage therapy pending additional trial data. Two antifungal agents from different classes should be used for salvage therapy.

Pediatric Antifungal Pharmacokinetics and Drug Interactions

Significant differences between adult and pediatric antifungal pharmacokinetics have been demonstrated with a number of antifungal agents. Pediatric amphotericin B pharmacokinetics differ significantly from adults.99,96–100 Because amphotericin B products do not accumulate in plasma, have large volumes of distribution, and long elimination half-lives, recommended doses are not dissimilar from adult recommendations. Pediatric studies reveal more rapid elimination and larger volumes of distribution in children administered fluconazole compared with adults.101–103 From pharmacokinetic modeling, 12 mg/kg per day of fluconazole is required to achieve comparable plasma concentrations to adults receiving 400 mg/day.101 Neonatal fluconazole elimination is reduced, necessitating less frequent dosing. Voriconazole pharmacokinetics in children are linear compared with the nonlinear pharmacokinetics seen in adults. The area under the curve in children given 4 mg/kg 12-hourly is similar to adults given 3 mg/kg 12-hourly.104 Doses of up to 11 mg/kg twice daily may be required in children to achieve concentrations similar to 4 mg/kg twice daily in adults. Again, pediatric caspofungin pharmacokinetics are different to adults administered the drug. Variations in the pharmacokinetic results with both weight and age suggest that weight-based dosing fails to provide consistent pharmacokinetics across all ages. In children and adolescents, 50 mg/m² best approximates the area under the curve and trough concentration of adults receiving 50 mg/day.105 In premature neonates, 2 mg/kg or 25 mg/m² best approximate adult pharmacokinetic data.106

Adult and pediatric pharmacokinetics seem to be similar for itraconazole,107–109 posaconazole,110 micafungin,111,112 and anidulafungin.113 Additional studies are required to define the correct pediatric dosage for newer antifungal agents including posaconazole, ravuconazole, micafungin, and anidulafungin.110–113 Currently recommended pediatric dose ranges are listed in Table 3.

Competition for cytochrome p450 metabolism is a problem with certain antifungal agents. This is of particular relevance to the interaction of azoles with cyclophosphamide and other immunosuppressants (cyclosporine, tacrolimus, and sirolimus). Dose reduction (cyclosporine or tacrolimus with itraconazole or voriconazole) or avoidance (sirolimus with voriconazole) is recommended.21,114–120 Despite initial concerns about cyclosporine and caspofungin coadministration, a number of observational studies in children and adult subjects who received concomitant therapy have demonstrated the safety of this combination.65,121,122

Antifungal Toxicity in Children

The development of new antifungal agents has been driven by the toxicities that occur with CAB. Azoles, lipid preparations, and echinocandins are all associated with significantly less toxicity. The toxicity of CAB,6,123–135 lipid preparations,54,55,61,62,67,68,102,108,133,134 fluconazole,54,55,61,62,67,68,102,108,133,134 itraconazole,68,108,109 voriconazole,59,104,139,140 caspofungin,56,57,85,105,141 micafungin,94,111 and anidulafungin113 have been determined in a number of pediatric trials, yet there is a paucity of comparative data. Furthermore, a lack of uniform definitions hinders comparison.

Two pediatric randomized trials that compared CAB to ABCD demonstrated a reduced rate of nephrotoxicity with ABCD (52% vs 12% in both studies; P < .01).27,29 Although Prentice et al26 failed to detect a significant difference in the rates of nephrotoxicity when they compared 1 mg/kg per day of CAB and 1 to 3 mg/kg per day of liposomal amphotericin B (21% vs 8%–11%, respectively; P = .10), their definition of nephrotoxicity was less stringent (see Table 2).

These pediatric data are supported by numerous larger trials. Three meta-analyses demonstrated a 49% to 75% reduction in nephrotoxicity with lipid preparations compared with CAB.30,142,143 If nephrotoxicity secondary to a lipid preparation occurs, it occurs after a longer course of therapy.26,29 Both adult and neonatal studies have demonstrated that lipid preparations are safe in subjects with pretreatment nephrotoxicity.46,144,145 No pediatric studies have compared different lipid preparations. In contrast to the findings of Wingard et al,31 a recent meta-analysis demonstrated no significant difference in rates of nephrotoxicity seen with liposomal amphotericin B and ABLC.143

Both azoles and echinocandins cause less nephrotoxicity than CAB and liposomal amphotericin B when compared in adolescents and adults.34,36,37,71,72,92 No trials comparing ABLC or ABCD to azoles and echinocandins exist to date. In children who were given fluconazole and itraconazole, similar rates of nephrotoxicity have been seen.68 When compared with both CAB and liposomal amphotericin B, less nephrotoxicity is seen in adults who are given caspofungin.39,74,76 No difference in the rates of nephrotoxicity have been seen when caspofungin and fluconazole were compared in adults.77

A number of authors have identified specific risk factors for amphotericin B–induced nephrotoxicity. Amphotericin B dose, preexisting renal impairment, hypotension, hypovolemia, and the concurrent use of nephrotoxic medications are associated with an increased risk of amphotericin B nephrotoxicity.28,129,146–151 Age and underlying disease are not associated with increased risk. When nephrotoxic medications are assessed independently, cyclosporine and diuretics increase the
rate of nephrotoxicity, whereas aminoglycosides and vancomycin in isolation seem not to increase the risk. In a study by Walsh et al, the risk of nephrotoxicity more than doubled when ≥2 concurrent nephrotoxins (cyclosporine, aminoglycosides, or foscarnet) were used. Avoidance of nephrotoxins and hypovolemia as well as sodium loading before amphotericin B use may decrease the risk of nephrotoxicity. Wingard et al determined that hematopoietic stem cell recipients were >5 times more likely to require hemodialysis when administered amphotericin B for aspergillosis than solid organ transplant- and nontransplant-related chemotherapy recipients. Dialysis was a significant risk factor for death.

Infusional toxicity (most frequently chills, rigors, fever, nausea, and vomiting) is a frequent complication of amphotericin B treatment in children and adults. Despite premedication and the development of tolerance, infusional toxicities continue to pose a problem. Infusional toxicities are rarely reported in neonates. Comparative trials with adult and pediatric patients have demonstrated that liposomal amphotericin B is the amphotericin B product associated with the least infusional reactions. Newer agents have been compared with both conventional and lipid preparations of amphotericin B. Compared with amphotericin B products, fluconazole, itraconazole, voriconazole, and caspofungin are responsible for less infusional reactions. Furthermore, both voriconazole and caspofungin are associated with less infusional toxicity than liposomal amphotericin B. No difference in infusional toxicity has been seen when fluconazole and micafungin were compared.

Continuous amphotericin B infusions result in less nephrotoxicity and infusional toxicity compared with intermittent infusion. No adult or pediatric trials have compared continuous CAB infusions with lipid preparations. Experimental in vitro and in vivo studies support concentration-dependant killing with a prolonged postantibiotic effect, which suggests that a large daily dose will be most effective and that achieving an optimal peak concentration is important. The limitations of vascular access in children with multiple comorbidities and therapies pose significant problems with continuous infusions.

Hepatotoxicity has been assessed in a number of pediatric and adult trials. No significant difference between CAB and any lipid preparation of amphotericin B has been demonstrated. No significant difference has been detected between azoles and conventional or liposomal amphotericin B. Furthermore, no significant difference has been observed between caspofungin, CAB, and fluconazole.

Rash is seen more frequently in adults who are given fluconazole or voriconazole compared with amphotericin B. Visual disturbance or eye symptoms are reported more frequently in both adults and children taking voriconazole.

In conclusion, pediatric and adult toxicity data demonstrate clear differences when comparing different agents. Lipid preparations of amphotericin B cause less nephrotoxicity than CAB, yet azoles and echinocandins are less nephrotoxic than all amphotericin B preparations. Preexisting renal impairment, concurrent nephrotoxins, or those receiving large cumulative doses have a higher risk of nephrotoxicity. Hematopoietic stem cell recipients are at the greatest risk of needing dialysis. Rates of infusional toxicity also vary widely: liposomal amphotericin B is associated with less infusional toxicity compared with CAB, yet both azoles and echinocandins seem to result in lower rates than all amphotericin B preparations. Rash, visual disturbances (with voriconazole), and drug interactions with azoles create additional complexity when administering antifungal therapy.

CONCLUSIONS

IFIs continue to be associated with significant mortality and morbidity. Despite significant differences in pediatric antifungal pharmacokinetics, few adequately powered pediatric trials have been conducted to compare the efficacy and toxicity of different antifungal agents. Pediatrians often rely on adult data with results extrapolated to children.

No consistent differences in treatment success or mortality rate have been demonstrated in comparative trials in patients with fever with neutropenia, candidemia, and invasive candidiasis. Initial therapy with voriconazole is superior to conventional amphotericin B in aspergillosis, with an associated survival advantage. Numerous differences in antifungal toxicity have been observed in children and adults when conventional amphotericin B is compared with newer antifungal agents. Insufficient evidence is available to recommend routine use of combination therapy for candidemia or aspergillosis.

Additional research on antifungal agents in children to assess pharmacokinetics and toxicity of newer agents, relative efficacy, and cost is needed. Given the difficulties in performing adequately powered efficacy trials in children, in whom the incidence of IFIs is low, the ongoing extrapolation of adult data to pediatric practice is likely to be required.

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ABSTRACT

OBJECTIVE. Despite the recommendation of the American Academy of Pediatrics, just 53 of the ~3500 juvenile justice residential facilities in the United States have received voluntary accreditation for facility health care from the National Commission on Correctional Health Care. This suggests either that facilities do not meet the standards of care or do not seek accreditation. This study describes whether and under what conditions juvenile detention facilities (a narrowly defined subset of all facility types) adhere to some of the standards outlined by the National Commission on Correctional Health Care and promoted by the American Academy of Pediatrics.

METHODS. Data from 2 national censuses of juvenile justice residential facilities (n = 726) were used to describe detention facility performance in terms of 10 types of service provision, ranging from health screening to communicable-disease testing. Multivariate models predicting high levels of service provision were estimated.

RESULTS. Juvenile detention centers partially meet some of the minimum standards. Most services can be garnered at some level; however, they tend to be provided on an ad hoc basis for portions of the population rather than systematically for the whole population. Detention centers most likely to provide a higher tier of services tend to be those that have longer average lengths of stay, are larger, and are government owned. There are also geographic and racial differences in quality and scope of health services.

CONCLUSIONS. Juvenile facilities have been provided a single set of standards for a diverse system with tremendous variation across and within facility types. Detention centers are just one specialized type. Very few detention centers meet a minimum standard of care, which suggests that standards are simply not being met (hence the low levels of accreditation). The findings of this study call into question...
whether detention facilities with little in the way of health care infrastructure can benefit from National Commission on Correctional Health Care standards as they are currently packaged, regardless of whether accreditation is the ultimate goal.

In 2001, the American Academy of Pediatrics (AAP) Committee on Adolescence published a policy statement entitled "Health Care for Children and Adolescents in the Juvenile Correctional Care System."1 Reviewing the ever-growing body of evidence that shows that young people in the juvenile system are at considerably higher risk for health, mental health, social, family, substance abuse, and other problems, the committee provided 7 recommendations for better securing health care for this underserved population. Among its recommendations was a call for pediatricians who serve this population to adopt the standards advanced by the National Commission for Correctional Health Care (NCCHC).

The NCCHC has developed and published "Standards for Health Services in Juvenile Detention and Confinement Facilities" (most recently updated in 2004).2 This 300-page document is sold on the NCCHC Web site and represents the official position of NCCHC in terms of 9 general areas of health services ranging from governance and administration to medical and legal issues. The standards are designed as evaluation tools for juvenile facilities of all sizes and types and are promoted as a means to increase the quality of health services for young people in the juvenile justice system.3

The position adopted by the Committee on Adolescent Health1 implies, and the standards offered by the NCCHC2 state, that health care policy can be applied equally across the spectrum of juvenile justice residential facilities (JJRFs). This may not be a feasible means of designing service delivery. There is tremendous variation within and across JJRF types relevant to a facility's ability to provide health services. Across facility types, JJRFs vary in terms of their fundamental purpose (see Appendix). Facilities also vary substantially within type in terms of structural characteristics (such as ownership, size, length of stay, services offered, and openness to the community), all of which impact their ability to realize a formal system of care.3-5 Therefore, suggesting that a 1-size-fits-all standard of care may be equally applied within and across this vast array of facility types is much the same as suggesting that all hospitals in the United States and the different units found therein should provide the same services at the same standard.

In addition to Pediatrics, publications in other leading medical and public health journals have advocated the targeting of children and adolescents housed in the juvenile justice system for health services.6-10 Yet, there has been no systematic national evaluation of whether facilities are adopting recommended practices or whether the recommended practices have increased the health and well-being of these young people. The most recent attempt to describe facility practices came from an analysis of data derived from a sample of facilities in the late 1980s and early 1990s.11 Those results suggested that just 26% of the facilities in the sample conformed to the service criteria defined in the study. The only contemporary indication available of compliance with suggested standards is whether facilities voluntarily seek and receive accreditation from the NCCHC. Earlier this year, just 53 of the 3500 facilities in the United States were so accredited (accreditation staff at NCCHC, verbal communication, January 18, 2006).

Our study provides a contemporary description of the extent to which JJRFs adhere to the standards published by the NCCHC and identifies predictors of variation in health care provision. Although the NCCHC suggests that their standards be applied equally across the universe of facilities and these census data allow for the description of health care across all facilities, this study focuses on a specific type of juvenile justice facility: detention centers. The basis for this decision is described below: however, in brief, the decision stems from the vast differences within and across facility types that make universal characterizations unwieldy and insensitive to important variations. Ideally, the results of this study will provide a critical context in which to guide correctional health care policy makers and professionals as they prioritize health care–delivery goals in light of the realities of the JJRF system.

**METHODS**

**Participants**

The universe of JJRFs includes everything from group homes and boot camps to residential treatment and long-term secure facilities that resemble adult prison (see Appendix for more description). It is important to recognize that different types of facilities have very different institutional priorities (which range from protecting the community to providing respite and treatment for children in need of services). A gross summary of services across all facilities will mask important differences across facility types. We began our study by evaluating health services in juvenile justice facilities and focused on arguably the most critical stage in the residential system: the detention facilities. Furthermore, by focusing on a single type of facility, we allowed for examination of the within–facility-type variations critical to the successful implementation of health care.

It has been argued that juvenile detention facilities represent an excellent opportunity to intervene with the greatest number of high-risk youth.6 This is because detention centers serve the highest volume of young people and are the gate through which young people enter the JJRF system, thus affording the first (and perhaps only) occasion to provide services in a controlled
setting. Providing health care in detention centers is not without substantial complications. Detention centers tend to have shorter lengths of stay, mostly because their purpose is to house young people who are awaiting either adjudication or postdisposition placement into a different type of facility. Despite the challenges of rapid population turnover, these facilities may represent the only chance to identify health needs and coordinate health care for many high-risk young people, including both the young people who proceed to long-term facilities and those who are released back to the community.12–14

Data
The Office of Juvenile Justice and Delinquency Prevention of the US Department of Justice sponsors 2 censuses of all public and private JJRFs in the United States: the juvenile residential facilities census (JRFC)15 and the census of all public and private JJRFs in the United States: the JRFC.16 To meet the inclusion criteria for these censuses, facilities must house young persons under the age of 21 who have been charged with or adjudicated for an offense and are in the facility because of that offense. The JRFC and CJRP are rotated so that 1 census is conducted every October. The CJRP was introduced in 1997, and the JRFC in 2000. The JRFC collects data on characteristics of the facilities and services provided to young people, including information about health care. The CJRP collects data on each young person housed on a specific reference night in these same facilities (for additional details on the censuses, see refs 3–5 and 12–14).

The health care module of the JRFC was designed, in part, to answer questions about whether and under what conditions basic and specialized health care services are provided to young people. The health care module has been fielded twice, once in 2000 and again in 2004. It provides a unique opportunity to measure whether the policy statements and standards proposed by AAP and NCCHC are practiced. This study uses data from the 2000 and 2004 JRFCs and the 2003 CJRP to describe the scope of health care services.

Methods for the implementation of these censuses are rigorous. Both questionnaires underwent years of iterative pretesting, including cognitive interviewing with facility administrators and service providers and mail-out field testing. Response analyses are conducted on samples of facilities to ensure the ongoing validity of the data. Respondents are guaranteed confidentiality. The census frame is updated yearly. The response rates range from 95% (2003 CJRP) to 96% (2000 and 2004 JRFC).

The universe of facilities in these censuses includes all facility types, ranging from nonsecure group homes to long-term facilities that are secured with razor wire. As discussed above, this study focuses on detention centers (see Appendix for more detail on detention centers). Thus, the data analyzed here represent a census of all juvenile detention centers operating in the United States on the reference days of the census administrations.

Over the 3 census years (2000 JFRC, 2003 CJRP, and 2004 JRFC) there were, on average, 726 juvenile detention facilities that housed ∼36 000 young people on each of the reference days (see Table 1). Put in more global terms, these 726 facilities housed approximately one third of the total daily facility population of 105 000 young people in 3500 facilities. Nearly 50% of all detention centers housed <25 young people. The bulk of facilities were government owned and operated (∼85%). The average length of stay was 37 days, although the average shortest length of stay within these facilities was 1.8 days.

Analysis
Table 2 describes standards promoted in the NCCHC 1999 and 2004 publications that may be measured with JRFC data. There are 9 major sections of the NCCHC standards. For this study we examined key aspects within 4 of those areas, including such basics as health screening and assessment, to more specialized services and first aid. It should be noted that the standards are often lengthy and are not readily operationalized. The corresponding JRFC coverage is also provided in Table 2. The full JRFC questionnaire is available online.15,16

The analyses began by describing each of the measurable services in simple frequencies (Tables 3 through 10). To further describe the provision of health care within detention centers, multivariate models were estimated to identify predictors of the scope of health care services provided. The outcome of interest was operationalized in 3 ways. First, a 9-point index that summed all NCCHC-recommended services measurable with JRFC data (with the measure of nonemergency medical requests dropped because every facility had at least 1 mechanism for youth to secure an appointment and because there is no inherent ranking of the different modes for requesting services) was constructed. Within each service area, a score of 1 was assigned for full compliance, 0.5 was assigned for partial compliance, and a 0 was given for not offering the service. Second, a 3-category ordinal scale was developed on the basis of the distribution of the 9-point service to provide relative rankings of facilities in terms of the numbers of services provided as either low, medium, or high (see Table 11). Finally, the 3-category scale was collapsed into a dichotomous variable that distinguished between high and low/medium rankings. The 3 models were estimated by using ordinary least squares, ordinal probit, and logistic regression, respectively.

Predictor variables were derived from other work on correlates to health care delivery in the JJRF system.17,18 They included the geographic region (the country was divided into 10 regions), facility population size, level of security, ownership status (whether government or pri-
vate), crowding within the facility, length of stay of residents, average age of young people, percentage of the population that is black/African American, the percentage that is Hispanic, the percentage that is male, and the percentage of residents who had been adjudicated or convicted (in other words, found guilty of a crime). All predictor variables in the final models came from measures in the 2004 JRFC, with the exception of the demographic and length-of-stay measures, which came from the 2003 CJRP.

Results across the models were robust, and only the final reduced logistic model predicting high service ranking is presented here, largely because logistic results are most intuitive and because of the fit with underlying assumption of the model parameters. The outcome in the final model is whether the facility was among the high health care service providers. This is defined as falling into the top tier of all facilities on a 9-point index of service. This translates into a score of >5.5 and, in practical terms, means that a facility met the standards for at least 5 of the recommended services.

Limitations
This study provides limited assessment of the multitude of NCCHC standards. However, the types of health services covered are arguably among the most fundamental, and the work represents a first attempt at modeling facility-level provision of services for this area of health care.

The measures in this study should be viewed strictly as indicators of facility practices. Future work is needed on the extent to which policy and stated practices translate into actual implementation. Furthermore, it is critical to gauge whether the implementation reflects evidence-based recommendations for diagnoses and treatment and to assess whether best practices result in measurable improvement in health. An additional limitation is the lack of measures on the individual health needs of the population served by each facility.

RESULTS
Table 3 provides a description of health screening practices. The NCCHC recommends that all young people receive a screening immediately on arrival by a trained health screener. Most facilities (98%) report that all young people are “asked questions or administered a form which asks questions about the current status of their physical health.”15 Contrary to NCCHC recommendations, more than half of the facilities use staff that are not trained in screening techniques and are not health
Nearly all facilities have young people screened within 7 days after arrival. By 2004, the percentage of facilities that screened within 24 hours rose from 68.7% to 75.7%.

A similar analysis of health assessment practices in juvenile detention centers (see Table 4) reveals that far fewer young people receive a health assessment. In 2004, just 51.1% of all facilities had all young people receive a health assessment, and 11.2% did not conduct health assessments. For the purposes of the JRFC, health assessments are defined for the respondent as involving “a nurse, nurse practitioner, doctor or physician assistant examining such things as eyes, ears, nose, throat, blood pressure, and pulse; collecting blood; or taking medical histories.” By 2004 one quarter of all facilities conducted health assessments within 24 hours after arrival.

### TABLE 2: NCCHC Standards That Can Be Measured, in Part, by JRFC Data

<table>
<thead>
<tr>
<th>NCCHC Standard</th>
<th>NCCHC Title</th>
<th>Corresponding JRFC Measure</th>
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<tbody>
<tr>
<td><strong>Section B: managing a safe and healthy environment</strong></td>
<td>Y-13 Y-B-01 Infection-control program and medical isolation</td>
<td>Detection of communicable diseases (e.g., tuberculosis)</td>
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<tr>
<td></td>
<td>Y-14 Y-E-04 Sexually transmitted disease and blood-borne disease detection</td>
<td>Detection of sexually transmitted and blood-borne diseases</td>
</tr>
<tr>
<td><strong>Section C: personnel and training</strong></td>
<td>Y-20 Y-C-03 Continuing education for qualified health care professionals</td>
<td>Ability to provide CPR by qualified or certified staff</td>
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<tr>
<td></td>
<td>Y-C-04 Current CPR training for child care workers who work with juveniles</td>
<td></td>
</tr>
<tr>
<td><strong>Section E: juvenile care and treatment</strong></td>
<td>Y-34 Y-E-02 Receiving screening and medical clearance</td>
<td>When, by whom, and for what population a health status screening is conducted</td>
</tr>
<tr>
<td></td>
<td>Y-35 Y-E-04 Health assessment</td>
<td>When, by whom, and for what population a full health assessment is conducted</td>
</tr>
<tr>
<td></td>
<td>Y-37 Y-E-06 Oral screening and oral health</td>
<td>Gynecologic assessment of girls/young women</td>
</tr>
<tr>
<td></td>
<td>Y-38/Y39 Y-E-07 Daily handling of nonemergency medical requests and sick call</td>
<td>What population receives an examination by a dentist</td>
</tr>
<tr>
<td><strong>Section F: health promotion and disease prevention</strong></td>
<td>Y-42 Y-E-08 Emergency services</td>
<td>Circumstances under which young people may request medical care</td>
</tr>
<tr>
<td></td>
<td>Y-48 Y-F-03 Recreational exercise</td>
<td>Ability to provide first aid&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Appendix.
<sup>b</sup> The 5 sections of NCCHC standards not covered by JRFC data include section A: governance and compliance; section D: health care services and support; section G: special needs and services; section H: health records; and section I: medical-legal issues.


<table>
<thead>
<tr>
<th>By whom the health screening is conducted</th>
<th>2000 (n = 692)</th>
<th>2004 (n = 762)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No health screening</td>
<td>9 (1.3)</td>
<td>14 (2.0)</td>
</tr>
<tr>
<td>Untrained screener</td>
<td>362 (53.2)</td>
<td>390 (54.7)</td>
</tr>
<tr>
<td>Trained screener</td>
<td>206 (30.3)</td>
<td>216 (30.3)</td>
</tr>
<tr>
<td>Health professional</td>
<td>103 (15.1)</td>
<td>93 (13.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time health screening is conducted after arrival at the facility</th>
<th>2000 (n = 692)</th>
<th>2004 (n = 762)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No health screening</td>
<td>9 (1.3)</td>
<td>14 (2.0)</td>
</tr>
<tr>
<td>Some other period</td>
<td>71 (10.4)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>&gt;7 d</td>
<td>8 (1.2)</td>
<td>17 (2.4)</td>
</tr>
<tr>
<td>Within 1 and 7 d</td>
<td>125 (18.1)</td>
<td>139 (19.5)</td>
</tr>
<tr>
<td>Within 24 h</td>
<td>467 (68.7)</td>
<td>540 (75.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scope of population screened</th>
<th>2000 (n = 692)</th>
<th>2004 (n = 762)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No health screening</td>
<td>9 (1.3)</td>
<td>14 (2.0)</td>
</tr>
<tr>
<td>Some young people screened</td>
<td>9 (1.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>All young people screened</td>
<td>662 (97.4)</td>
<td>697 (97.8)</td>
</tr>
</tbody>
</table>
Table 5 shows the extent to which detention facilities were in compliance with NCCHC recommendations on screening and health assessments. Most facilities (58%) were in partial compliance with screening standards, but they largely failed to meet standards on the training of the screener. Another 40% were in full compliance. A noticeable improvement was found between the years 2000 and 2004 on meeting the health assessment standard. However, there was a modest increase in noncompliance.

Table 6 shows the extent to which detention facilities provide specialized services. The NCCHC standards suggest that all young people receive an oral health examination and that all girls/young women receive a gynecologic examination. The NCCHC standards (both 1999 and 2004) make no mention of vision or eye examinations, although they are included among the services covered in Table 6. Few facilities made vision, dental, or gynecologic (in facilities housing female residents) services available to all young people (between 13% and 18% across service areas in 2004). Nearly 30% do not provide a vision examination (by either an ophthalmologist or optometrist), and 18.3% fail to provide any of its female population with a gynecologic examination. A large proportion of facilities providing these services do so outside the facility (i.e., through local providers in the community).

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The NCCHC 2004 standards stated that “All juveniles have the opportunity daily to request health care. Their requests are documented and reviewed for immediacy of need and the intervention required. Sick call and providers’ clinics are conducted on a timely basis and in a clinical setting by qualified health care professionals”2(p72) (emphasis in the original). As shown in Table 7, facilities have a variety of mechanisms in place for young people with medical complaints to request care. All facilities had some means for requesting care. It is difficult to place a value on the type of mechanism available, although most in 2004 had upward of 2 methods for accessing care.

Facilities are encouraged to provide opportunities for “recreational exercise.” Table 8 indicates that 10% of all detention centers do not offer voluntary opportunities for exercise; however, almost 70% require an average of 1 hour of exercise every day of the week. Exercise was defined in the JRFC as large-muscle activity, including group sports, running, aerobics, and weight training.

An evaluation of communicable-disease–detection practices and pregnancy testing is provided in Table 9. The NCCHC has suggested that young people entering juvenile residential facilities be tested for tuberculosis because of the high-risk nature of the correctional envi-
Ten percent provide no testing, and 44% test as necessary.

The NCCHC standards suggest testing for sexually transmitted and blood-borne diseases, most likely in light of the disproportionately high rate of occurrence in this population and the emerging co-occurrence of these diseases. Few facilities test all young people for HIV (4.3%), although more of them claimed to test all young people for various other sexually transmitted diseases (18.5%). A more common practice is to test at the discretion of a health care professional.

Facilities that house girls/young women seem to be encouraged to determine if they are pregnant during the initial health screening. It seems to be more of an inquiry process rather than a pregnancy test that is recommended. Nonetheless, ~18% of facilities that hold girls/young women reported testing all of them for pregnancy. Fifteen (2.4%) facilities that house girls/young women do not provide any pregnancy testing, even when requested by the resident herself.

The NCCHC standards recommend that child care...
workers who work with juveniles be able to provide cardiopulmonary resuscitation (CPR) and for qualified health care professionals to participate in “continuing education programs.” The JRFC data reveal (see Table 10) that 85% of facilities have basic first aid service and CPR-trained staff members available during normal weekday business/operating hours inside the facility, as well as after hours and on weekends. Very few facilities do not have either basic first aid (0.3%) or CPR-trained staff members (1.7%).

Table 11 provides some bivariate analyses of the relationship between some of the independent variables (facility characteristics) and the 3-category collapsed version of the 9-point index of service provision. The results of the final reduced logistic model are presented in Table 12. Recall that the outcome in this model is whether the facility was among the high health care service providers, in other words, they scored >5.5 on the 9-point index.

It is clear that even within the universe of detention facilities, there is variation in the conditions under which relatively high levels of service are provided (see Table 12). First, there is a geographic variation. Compared with those elsewhere in the country, facilities in both New England and the west were 2 times as likely...
to be in the top tier of service levels. The size of the facility also significantly predicted higher service provision. With each 1 person increase in facility population size, the odds of providing high service levels increased by 1%. Similarly, the longer the facility houses young people the more likely it is that higher levels of health care services are provided (odds ratio [OR]: 1.01). Facilities housing higher percentages of black/African American young people were significantly more likely to report higher service provision (OR: 1.02). Finally, privately owned (as compared with government-owned) facilities had significantly lower odds of reporting high service provision (OR: 0.42).

DISCUSSION
This study provides a national description and analysis of basic health care service provision in a subset of juvenile residential facilities: juvenile detention centers. Using some of the minimum standards suggested by the NCCHC and promoted by the AAP as the basis for evaluation, the results of this study can be taken as both good and bad news. Nearly all detention centers are providing at least a minimum amount of health care. This largely comes in the form of some manner of intake health screening and assessment, optional exercise, and CPR availability around the clock. It remains important to note, however, that some facilities do not provide even these fundamental services.

The most notable weaknesses in service provision include the lack of training of the intake health care screener and the strikingly low levels of vision, dental, and gynecologic services. Although most facilities require recreational exercise, 10% of these detention facilities fail to provide any opportunity for voluntary large-muscle exercise (these facilities housed 1903 young people on the reference day).

Perhaps more alarming is the low level of full population testing for infectious and communicable diseases. The majority of facilities report that testing is conducted for some young people as “deemed necessary by a nurse or doctor.” In the general population, testing as recommended by physicians is certainly appropriate, however, in light of the growing evidence of high rates of infection in the correctional population; along with the ease of transmission within facilities and the limited time window for providing health services, testing the entire population may better serve the public health of these young people. It could also benefit the workers within the facility and the population in their home communities. Likewise, it may be best to test all girls/young women to determine if they are pregnant. The follow-up care is certainly problematic and, no doubt, presents significant challenges, especially for those who leave the facility before services can be offered. Rather than offering standards that cannot be met, guidance on how to handle these cases in the form of standards would likely be welcomed.

There are reasonable structural correlates of meeting minimum standards of care. Larger facilities and facilities that hold young people for longer average lengths of stay are more likely to have a broad service portfolio. This reflects the reality that large facilities are more likely to have a health care infrastructure and systematic means of processing health needs, and facilities that hold young people for longer periods of time have more opportunity to provide services. That smaller, shorter-length-of-stay facilities are not meeting minimum standards of care should be worrying. Young people in these facilities are no less in need of basic services and are equally as likely to return to the community with communicable, preventable, and treatable conditions and diseases. It is reasonable to conclude that these facilities are more likely to garner services in a piecemeal fashion. Although this may be the most creative use of available resources, the lack of systematic care should be addressed. Similarly, private facilities are notably less likely to provide fuller ranges of services. Because young people in private detention centers have not been shown to be systematically different from those in public facilities, they should, by definition, require the same level of care.

Although black/African American and Hispanic youth are demonstrably underserved in the larger community, the results from this study reveal a potentially different pattern within detention centers in terms of having access to health care services, at least at the facility level. Facilities with better service portfolios were linked to higher percentages of black/African American young people in their population. Although it cannot be determined with these data that these young people are actually being served within the facilities, it certainly warrants additional investigation, because it is in striking contrast to use of services in the community.* Despite the underrepresentation of female residents and the overrepresentation of Hispanic residents, effects were not found for either of them in terms of the scope of services provided. There is, however, a low level of gynecologic services for facilities that house girls/young women, and this gap in service provision needs to be a priority. Finally, there is significant regional variation. It may be that facilities in different regions offer more services because they are of higher quality; alternatively, it could be attributed to a difference in the quality and availability of health care in the community. Yet again, it could be because of the general health status of the population served by each facility.

*Although the 2001 AAP policy statement (citing Snyder and Sickmund19) reports that black/African American youth make up ~45% of the facility population (and just 15% of the general population), the current analyses find that 38% of the full facility and 36% of the detention population is black/African American.
CONCLUSIONS
This exercise suggests several recommendations. First, the universal standards promul gated by the NCCHC may be more useful if they were to consider the variation in priorities and purpose across and structural variation within the different types of facilities. The findings presented here speak directly to the latter issue: Even within a narrowly defined subset of all facilities, there is significant natural structural variation related to whether health care is provided. It could be argued that this structural variation is unrelated to the need to provide health care and what attitudinal priority facility administrators place on health services. Just as a large emergency department that serves an urban area should have different operational goals than a rural emergency department that serves an elderly population, so too should small and large detention centers.

Second, there is no doubt that young people who enter detention centers are underserved and at greater risk for health problems. The wisdom, however, of trying to provide a full portfolio of care (such as that recommended in the current NCCHC standards) remains debatable in this type of facility. Detention centers are legally required to address urgent health problems and any health services ordered by the court, but beyond this, it is unclear what their obligation should be. From a public health perspective, it would seem to be an ideal place for intervention, if not only because of the sheer volume of high-risk young people served. Health professionals who work with this population and experts in the risks that these young people face need first to reach a consensus on what time-dependent priorities these type of facilities should achieve. Such a consensus must be built within the current parameters of the legal and organizational structures of the juvenile justice system. If standards were developed that reflected time-dependent algorithms of care, perhaps detention centers, particularly those with little or no infrastructure, could have the guidance needed to provide a higher and more effective system of care.

APPENDIX: GLOSSARY OF FACILITY TYPES

- Detention center—the juvenile equivalent to adult jail; tends to be the first facility encountered by young people entering the system; typically houses young people who are awaiting adjudication or postdisposition placement in another JJRF; houses young people charged with all types of offenses, from status (ie, runaway, truant) to murder; highly variable but shorter length of stay than other types of facilities; tends to have higher levels of security (eg, razor wire and multiple locked doors) because of flight risk and uncertainties of population classification; most often owned and operated by local governments, but a substantial proportion are privately owned.

- Reception or diagnostic center—facility designed to diagnose and classify young people who are typically adjudicated delinquent, placed in the legal custody of the state, and are awaiting assignment to a long-term facility pending results of screening and classification; houses young people charged with all types of offenses; short but less-variable length of stay; tends toward higher security levels; most often owned by state governments, although a number are also locally and privately owned and operated.

- Group home/halfway house—small, community-based facility or house with low levels of security designed to house adjudicated young people for longer periods of time, typically to provide transition back to the community; many are privately owned and operated.

- Boot camps/ranch, forestry camp, wilderness or marine program or farm—shorter length-of-stay facility with intense programming for adjudicated youth; most often locally or privately owned and operated; low physical security, high staff security, and often operated in rural, sparsely populated areas.

- Training school/long-term secure facility—the juvenile equivalent to adult prison; facility designed to house large numbers of adjudicated youth who are remanded to state custody for long periods of time in a high-security facility, typically secured with razor wire, multiple locked ports, and high staff security; typically a state-level facility, but many are owned or operated by private companies.

- Residential treatment center—longer-stay facility that provides specialized treatment services (eg, substance abuse, mental health, sex offender therapy, etc) for adjudicated youth; security tends to be lower to midlevel with an emphasis on staff security; most often privately owned and operated, with smaller- to midsize populations.

- Shelter—typically an alternative to detention for court-involved young people with lesser charges or with charges but substantial family and social concerns identified by other agencies; facility also houses young people in child welfare and foster care systems; locally operated and often privately owned; many local jurisdictions do not have this type of facility available or combine these young people with those in detention; low physical security; longer stays than in detention.

REFERENCES
Creation and Development of the Public Service Orphan Drug Human Botulism Immune Globulin

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The author has indicated he has no financial relationships relevant to this article to disclose.

The public service orphan drug Human Botulism Immune Globulin for the treatment of infant botulism would not have come into existence without the federal Orphan Drug Act and the funding mechanism that it provided to conduct pivotal clinical trials. Nonetheless, creating, developing, and achieving licensure of Human Botulism Immune Globulin took approximately 15 years and approximately $10.6 million (2005 dollars) to accomplish. Use of Human Botulism Immune Globulin to treat patients with infant botulism has resulted thus far in more than 30 years of avoided hospital stay and more than $50 million (2005 dollars) of avoided hospital costs. To provide a possible paradigm for others, the circumstances that enabled a state public health department to create, test, license, and distribute an orphan drug are described here.

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Key Words
infant botulism, botulism immune globulin, BabyBIG, botulinum toxin, botulism, orphan drugs, orphan diseases, drug development

Abbreviations
FDA—US Food and Drug Administration
BIG—Botulism Immune Globulin
BIG-IV—Botulism Immune Globulin Intravenous (Human)
CDHS—California Department of Health Services
IND—investigational new drug
OOPD—Office of Orphan Products Development
IRB—institutional review board
CDC—Centers for Disease Control and Prevention
INFANT BOTULISM is the intestinal toxemia form of human botulism that occurs when swallowed spores of Clostridium botulinum (or, rarely, Clostridium butyricum or Clostridium baratii) germinate, temporarily colonize the large intestine, and produce botulinum toxin in it. Botulinum toxin blocks neuromuscular transmission, and the illness usually presents as weakness and hypotonia of bulbar and skeletal musculature. Seven toxin types (A through G) of botulinum toxin exist that are distinguished from each other by the inability of neutralizing antitoxin against 1 toxin type to neutralize any of the other 6 types. Almost all infant botulism in the United States results from either botulinum toxin type A or B.

ORPHAN DISEASES AND ORPHAN DRUGS
Infant botulism causes the hospitalization of ~80 to 110 children in the United States each year and thereby qualifies as an orphan disease, which, by definition, is an illness or condition that affects fewer than 200 000 persons in the United States. This definition was chosen in part because this disease prevalence had historically provided insufficient market incentives to stimulate development of new therapeutics by the pharmaceutical industry. However, ~6000 such orphan diseases are believed to exist that collectively affect ~25 million US residents. Thus, the large population of patients with orphan disease (~8% of the US population) who had been left without medicines constituted a major societal lapse and public health problem that was remedied partially by passage of the Orphan Drug Act in 1982. The act (Pub L No. 97-414, as amended) enabled the US Food and Drug Administration (FDA) to support pivotal (phase III) clinical trials, as this requirement had been identified as the major obstacle to licensure of potential products for orphan diseases. The act also provided financial incentives (research credits and a period of market exclusivity) to orphan-drug sponsors. From 1995 to 2005, Congress provided between ~11.3 and ~14.4 million annually to the FDA for pivotal orphan-drug and -device trials. In the 22 years 1983–2005, a total of 256 orphan drugs and devices have been licensed, in contrast to fewer than 10 in the 10 years preceding 1982. The Orphan Drug Act also authorized academic, governmental, and other not-for-profit institutions to sponsor the development of orphan drugs.

THE PRODUCT
Botulism Immune Globulin Intravenous (Human) (BIG-IV) was created by the California Department of Health Services (CDHS) in 1991 to treat infant botulism caused by type A or B botulinum toxin. BIG-IV was produced from high-titer immune plasma that was donated by CDHS volunteers and others who had been immunized with pentavalent (A–E) botulinum toxoid for occupational safety and then boosted before plasmapheresis. The product was made and licensed in accord with all FDA requirements, which included careful screening of donors and testing of plasma for viral (eg, HIV) and other illnesses. BIG-IV is a lyophilized, 5% immunoglobulin G powder that is stabilized with 1% human albumin and 5% sucrose and contains ≥15 IU of anti-A and ≥4 IU of anti-B neutralizing antibody per 50 mg. BIG-IV was evaluated for safety and efficacy in a randomized, controlled pivotal trial in California in 1992–1997 and in a subsequent nationwide open-label study in 1998–2003. The primary efficacy end point of the pivotal trial was a significant reduction of mean hospital stay, while the safety evaluation was a comparison of the occurrence of adverse events in the treatment and placebo (commercial normal human immune globulin) arms of the study.

In brief, in the pivotal statewide clinical trial, treatment with BIG-IV shortened the mean hospital stay from 5.7 to 2.6 weeks (P < .001) and reduced mean hospital charges by $88 600 (2004 dollars) per patient (P < .001). The mean duration of intensive care was shortened by 3.2 weeks (P < .001), mean duration of mechanical ventilation was reduced by 2.6 weeks (P = .01), and mean duration of tube or intravenous feeding was shortened by 6.4 weeks (P < .001). All these primary and secondary outcome measures were also reduced significantly when stratified by toxin type (A or B) of illness. There were no serious adverse events attributable to treatment. In the nationwide open-label study, the mean hospital stay was further reduced to 2.2 weeks, and early treatment with BIG-IV shortened hospital stay significantly more than did later treatment. Since introduction of BIG-IV, its use to treat patients with infant botulism has resulted thus far in more than 30 years of avoided hospital stay and more than $50 million (2005 dollars) of avoided hospital costs.

CHRONOLOGY
The need for a human botulism immune globulin to treat patients with infant botulism became evident with initial recognition of the disease in California in 1976. The existing equine botulism antitoxin was known to have substantial serious adverse effects (eg, allergic reactions, serum sickness, anaphylaxis) and a short 5- to 7-day half-life. Efforts in 1977–1978 by the CDHS and the University of Wisconsin to initiate civilian development of a human botulism immune globulin to be sponsored by the US Department of Health, Education, and Welfare (predecessor to the Department of Health and Human Services) were unsuccessful. However, in 1978 the US Army began to collect hyperimmune botulism immune plasma, from which it eventually made a BIG investigational new drug (IND) product.

The request of the CDHS in 1982 for a small amount of the IND Army BIG with which to treat patients with infant botulism was fulfilled some years later after passage of the 1986 Federal Technology Transfer Act pro-
vided the Army with needed authority to make its research products available to the civilian sector. The now-available Army product enabled the CDHS in December 1988 to apply to the FDA Office of Orphan Products Development (OOPD) for funds with which to carry out a pivotal clinical trial of BIG for the treatment of infant botulism. At the time, California was the only locale in the world that could conduct such a trial because its high endemic incidence of this rare disease provided an adequate number of patients and its established state health department infant botulism program provided disease expertise and statewide laboratory diagnostic services. The OOPD officially designated BIG an orphan drug in early 1989.

With OOPD approval of its randomized, placebo-controlled, double-masked, pivotal clinical trial design and funding application, the CDHS proceeded to organize the study by recruiting participating physicians and hospitals and obtaining institutional review board (IRB) approval from each one. California’s large size, together with the rarity of the disease and the unpredictability of its occurrence, necessitated recruitment of all hospitals that had treated at least 1 patient with infant botulism in the previous 5 years. Organizational efforts, arranging hospital and local investigator participation, and obtaining the needed 59 hospital IRB approvals took ~1 year to complete. IRB approval times for the identical protocol ranged from 2.5 weeks to 10.5 months.

In August 1990, as the pivotal-trial organizational efforts neared completion, Iraq invaded Kuwait. In consequence, the US Army redirected its entire supply of BIG to anticipated military needs in the Persian Gulf. Although the CDHS and the California pediatric community were ready to begin the pivotal clinical trial, there was no product to evaluate.

This setback was overcome by creating a new product that the FDA formally named Botulism Immune Globulin Intravenous (Human) (BIG-IV). Because of its ongoing botulism research and diagnostic activities, the CDHS had in 1990 a relatively large number of individuals who had been immunized for occupational safety with a still-investigational (after 30 years) botulinum toxoid product that was distributed by the Centers for Disease Control and Prevention (CDC). These people, together with others similarly immunized, volunteered to donate their immune plasma so that the antitoxin toxin antibodies in it could be used to make the new BIG-IV to replace the Army’s diverted product. The FDA Orphan Drug Office provided supplementary funding for collection of plasma, and a licensed manufacturer of human immune globulin products (the Massachusetts Public Health Biologic Laboratories) fractionated the immune plasma into BIG-IV lot 1 at no charge because the prospect of a public service orphan drug harmonized with its institutional activities and goals. Approvals from the IRBs of the 59 participating hospitals then had to be obtained to substitute BIG-IV lot 1 for the original Army BIG product.

The pivotal clinical trial of BIG-IV finally opened for patient enrollment in February 1992. Five years later, the planned 120th patient with laboratory-confirmed infant botulism was entered into the study. In the interim, at the urging of parents of patients with infant botulism, the California legislature and governor had approved a measure that aligned the CDHS activities with the requirements of the federal Orphan Drug Act. The unanimously passed legislation provided for ongoing production and national distribution of BIG-IV as a not-for-profit, self-supporting state activity if the pivotal clinical trial demonstrated safety and efficacy of the product.

In May 1997, after obtaining the advance approval of FDA statisticians and regulators with whom the study statisticians had previously and privately reviewed the results, a semipublic data-unveiling meeting was held in Berkeley, California. At this meeting, the study investigators and representatives of the FDA, the CDC, CHDS administrative leadership, parents of patients, donors of BIG-IV source plasma, and interested colleagues all learned for the first time that the pivotal clinical trial had succeeded in meeting its primary and secondary end points. A few days later, the FDA authorized open-label distribution of BIG-IV in California under compassionate use and emergency IND status because hospital IRB approval of the product already existed here.

In June 1998, while licensure efforts continued, the FDA authorized nationwide open-label distribution of BIG-IV under treatment IND status because the pivotal clinical trial had been completed and the product treated a life-threatening condition for which no alternative therapy existed.10 Open-label treatment IND distribution of BIG-IV enabled confirmation and extension of the safety and efficacy results of the pivotal clinical trial with a much larger number of treated patients; such follow-up confirmation was later recommended generally for orphan-drug studies.11 Open-label treatment IND distribution also permitted limited ($1.8 million [2005 dollars]) recovery of the prelicensure CDHS developmental expenses for BIG-IV that are specified in federal regulations as not to exceed “the costs of manufacture, research, development and handling of the investigational drug.”12 The FDA recently proposed new regulations that further limit cost recovery for investigational drugs.13

A principal remaining licensure requirement was the production of a second lot of BIG-IV, an ~3-year endeavor that was completed in 2000. Because plasma donors were then being boosted with the investigational (ie, unlicensed) botulinum toxoid for nonoccupational safety reasons, additional IRB (CDHS and CDC) and FDA approvals were required. Later in 2000, the CDHS and the FDA met for prelicensure application discussions, and in 2001 the CDHS submitted the biologics license
application for BIG-IV as a preapproved “fast-track” submission. In June 2002, the FDA returned a comprehensive review of the biologics license application that conveyed additional licensure requirements, to which the CDHS was able to respond in April 2003. The responses were satisfactory, and exactly 6 months later on October 23, 2003, in accord with fast-track procedures, the FDA licensed BIG-IV to the CDHS as BabyBIG for the treatment of infant botulism types A and B.

**COMPARATIVE COSTS AND REGULATORY APPROVAL TIMES**

Creating, testing, and obtaining licensure for BIG-IV cost approximately $10.6 million (2005 dollars) in cash expenditures. The FDA OOPD provided approximately $1.9 million (17.9%), FDA-approved precollection cost-recovery fees provided $1.8 million (17.0%), and the State of California provided $6.9 million (65.1%) through “in-kind” contributions and interest-bearing loans from the state’s general fund (a not-uncommon method of launching eventually self-supporting “at-cost” public health programs) (all in 2005 dollars). In comparison, as determined by the Tufts Center for the Study of Drug Development, the median “out-of-pocket” developmental costs (comparing only phase II and III costs because BIG-IV had negligible phase I costs) for 24 newly approved (1983–1994) small-molecule and biological products were $110.2 million (2000 dollars). Although the Tufts Center methodology has been questioned, it determined that the total out-of-pocket developmental costs for these and other products averaged $403 million (2000 dollars).

The mean time from initiation of clinical testing to licensure for the 24 products analyzed by the Tufts Center was 14.0 years (a duration that includes the “interphase” times between phase I–III studies and submission of the license application). The equivalent interval for BIG-IV was 11.7 years. Total development time for BIG-IV from submission of the study protocol and initial funding application to licensure was 14.8 years.

Recent calls for improvement in the drug-approval process reflect in part the shortcomings of the present pathway in expeditiously providing new medicines, particularly new molecular entities, to patients. This deficiency is highlighted by the fact that in the mean interval between the start of clinical testing and new product licensure (14.0 years), Marco Polo in the 13th century could have traveled over land and sea from Venice, Italy, to Beijing, China, and back to Venice approximately twice (2 × 7.8 years). Other comparative multiples of noteworthy feats of exploration and discovery accomplished under similarly arduous circumstances during the ensuing 700 years are substantially higher (Table 1).

**CONCLUSION**

BIG-IV came into existence through a variety of special circumstances. The high incidence of this rare illness in California enabled a randomized, controlled, pivotal treatment trial to be conducted here. The federal Orphan Drug Act provided a mechanism for funding the trial. The availability in northern California of potential donors immunized with investigational botulinum toxoid permitted collection of the botulism immune plasma that was needed to make sufficient BIG-IV to carry out the clinical trials. The California legislature and governor supported the project with legislation and loans, which enabled the medicine eventually to become licensed. The developmental costs of BIG-IV were substantially lower than those of most new pharmaceutical products, and its time to licensure was less than average. The humanitarian and societal benefits of BIG-IV have been established by the more than 30 years of avoided hospital stay and by the more than $50 million of avoided hospital costs that have been achieved thus far through use of the medicine. In 2004 the National Museum of American History (a part of the Smithsonian Institution) requested and received an exemplary vial of BabyBIG for its permanent medicines collection.

**TABLE 1** Comparative Times of Terrestrial Exploration Achievements and Modern Drug Licensure

<table>
<thead>
<tr>
<th>Explorer/Leader</th>
<th>Destination</th>
<th>Departure Date, Location</th>
<th>Arrival Date, Location</th>
<th>Elapsed Time, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marco Polo16</td>
<td>China</td>
<td>Spring 1271, Venice, Italy</td>
<td>Summer 1275, Beijing, China</td>
<td>4.3</td>
</tr>
<tr>
<td>Columbus19</td>
<td>East Indian islands</td>
<td>Spring 1292, Zayton, China</td>
<td>Winter 1295, Venice</td>
<td>3.5</td>
</tr>
<tr>
<td>Magellan20</td>
<td>Philippine and “Spice” Islands</td>
<td>August 1519, Seville, Spain</td>
<td>May 2011, London</td>
<td>2.6</td>
</tr>
<tr>
<td>Cook21</td>
<td>“Great South Land” (Antarctica) and Pacific Ocean exploration</td>
<td>July 1772, Plymouth, UK</td>
<td>July 1775, Plymouth</td>
<td>2.4</td>
</tr>
<tr>
<td>Lewis and Clark22</td>
<td>Pacific Ocean overland</td>
<td>May 1859, St Louis, MO</td>
<td>September 1860, St Louis</td>
<td>2.6</td>
</tr>
<tr>
<td>Burton23</td>
<td>Headwaters of the Nile</td>
<td>October 1586, London, UK</td>
<td>May 1589, London</td>
<td>1.8</td>
</tr>
<tr>
<td>Amundsen24</td>
<td>South Pole</td>
<td>June 1910, Norway</td>
<td>March 1912, Tasmania, Australia</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* In Antarctica January 1911 to January 1912, Amundsen did not immediately return to Norway but instead proceeded to a lecture tour in Australia.

* Mean time from start of phase I clinical testing to licensure, including mean interphase times (data are from Table 3 in ref 14).
ACKNOWLEDGMENTS
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Executive Summary of the Workshop on Oxygen in Neonatal Therapies: Controversies and Opportunities for Research

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ABSTRACT

One of the most complex areas in perinatal/neonatal medicine is the use of oxygen in neonatal therapies. To address the knowledge gaps that preclude optimal, evidence-based care in this critical field of perinatal medicine, the National Institute of Child Health and Human Development organized a workshop, Oxygen in Neonatal Therapies: Controversies and Opportunities for Research, in August 2005. The information presented at the workshop included basic and translational oxygen research; a review of completed, ongoing, and planned clinical trials; oxygen administration for neonatal resuscitation; and a review of the collaborative home infant monitoring evaluation study. This article provides a summary of the discussions, focusing on major knowledge gaps, with prioritized suggestions for studies in this area.
In the 1890s, Thomas Morgan Rotch, a pioneer US pediatrician, administered oxygen to premature infants in small doses as a stimulant, often combining it with brandy as a second stimulant.1 By the middle 1930s, “routine” oxygen therapy piped into incubators had become common. After 8 decades of regular use, however, large knowledge gaps remain concerning oxygen therapy for newborn infants. Even the definition of “appropriate oxygenation” is not clear. New concerns have emerged about the use of supplemental oxygen for resuscitation. The proper concentration of administered oxygen, especially for extremely preterm infants, remains to be established. Therefore, although we know many short- and long-term risks of hypoxia, the goal of using oxygen safely to combat hypoxia remains to be achieved. To complicate matters, the evolution and course of disorders such as retinopathy of prematurity (ROP), bronchopulmonary dysplasia, and persistent pulmonary hypertension of the newborn may be influenced both by deficiency and excess of administered oxygen and by systemic hypoxia and hyperoxia.

To address the complex issues related to oxygen therapy, the National Institute of Child Health and Human Development organized a workshop in 2005, Oxygen in Neonatal Therapies: Controversies and Opportunities for Research. The invited experts reviewed the current evidence for care practices and identified knowledge gaps. They addressed the biological features of oxygen therapy, the consequences of deficient and excess oxygen, data from the collaborative home infant monitoring evaluation (CHIME) study, and practical aspects of oxygen use for newborns. This meeting summary may help future investigators plan for innovative research and clinicians develop evidence-based practice strategies, while appreciating the limits of our current knowledge on this complex topic.

### Biological Features of Oxygen: Basic and Translational Oxygen Research

Blood flow and oxygen content are integrated intimately to meet the metabolic needs of tissues. Hypoxia refers to low oxygen content or partial pressure in the blood or in inspired air. Hyperoxia is defined as an excess of oxygen content in the blood or inspired air. Just as lack of blood flow or hypoxia, on either an acute or chronic basis, can lead to poor tissue oxygenation and injury, acute or chronic hyperoxia can lead to oxygen-induced cellular and tissue injury. The following is a summary of the research discussed. The gaps in knowledge and opportunities for basic and translational research identified by the participants are summarized in Table 1.

Several investigators are attempting to characterize the nature of tolerance and susceptibility to low and high concentrations of oxygen. Haddad2 showed that *Drosophila melanogaster* flies can sustain complete anoxia for up to 5 hours without morphologic abnormalities and continue to engage in complex behavior, such as mating, flying, and seeing. Phenotypic evaluation of anoxia-sensitive *D melanogaster* by using behavioral and physiologic assays and genomic markers or elements of the reactive oxygen species (ROS) systems were used in the model. For evaluation of the effects of long-term chronic hypoxia, exposure to lower ambient oxygen levels can occur over several generations of *D melanogaster*, for assessment of offspring under conditions of hypoxia or demonstration of genes whose expression is increased or decreased under conditions of chronic hypoxia. Three genes have been found to be downregulated by 5% oxygen, namely, ubiquitin ligasease, peptidase,3 and oxidase.4 Trehalose-6-phosphate synthase synthesizes trehalose, a disaccharide found to be protective against oxidative stress, including lipid peroxidation, DNA oxidation products, glutathione, and pentane.

### Table 1 Gaps in Knowledge and Opportunities for Research

<table>
<thead>
<tr>
<th>Basic science</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypoxia and hyperoxia tolerance, biochemical and genetic bases</td>
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<tr>
<td>2. Hypoxia and hyperoxia susceptibility, biochemical and genetic bases</td>
</tr>
<tr>
<td>3. Reoxygenation injury, biochemical, physiologic, and genetic bases</td>
</tr>
<tr>
<td>4. Oxidative injury, changes in ROS, and different organ effects</td>
</tr>
<tr>
<td>5. Markers of oxidative stress, including lipid peroxidation, DNA oxidation products, glutathione, and pentane</td>
</tr>
<tr>
<td>6. Localized antioxidants and sympathetic processes. What are the interactions?</td>
</tr>
<tr>
<td>7. Interaction of hypocapnea and hypercapnea with hypoxia and hyperoxia</td>
</tr>
</tbody>
</table>

### Translational science

1. Oxygen delivery versus oxygen consumption
2. Measurement of oxygen saturation at tissue level
3. How do placental function/pathologic features affect oxygenation in the fetus?

### Clinical science

1. Minimization of oxygen saturation variability
2. What is the optimal saturation target and for whom? Are there differences at different gestational ages? Does postnatal age affect the optimal saturation level?
3. How low can saturations be set before causing harm?
4. Is it still acceptable/appropriate to use 100% oxygen for resuscitation? What is the ideal amount of supplemental oxygen to use for resuscitation? Are there differences based on gestational age? What effects do perinatal events have on oxygenation at the time of delivery?
5. What is the therapeutic range of inspired oxygen? What is the toxic range of inspired oxygen? What explains the variability in toxicity? How do specific disease processes affect toxicity?
6. What variables are important in designing studies to examine the optimal inspired concentration and blood oxygen saturation for clinical trials?
   a. Survival
   b. Neurodevelopmental impairment
   c. Visual function
   d. Growth
   e. Pulmonary outcomes
   f. Days of oxygen therapy

### Technology needs

1. Measurement of oxygenation at tissue level
2. Feedback devices to keep oxygenation constant, closed-loop oxygen controllers or oxygen delivery systems with pulse oximetry regulation
much work needs to be done to translate these findings into clinical applications in higher species and to develop therapeutic modalities for oxidant-related diseases (Table 1).

ROS can have profound effects on lung tissues. ROS can lead to protein modification, DNA base modification, and strand scission. Increased proliferation of type II pneumocytes and fibroblasts, alterations in the surfactant system (synthesis, function, and clearance), and stimulation of inflammatory cells and cytokines are attributable to ROS. Lung hyperoxia can lead to increased collagen deposition, endothelial cell damage, and apoptotic cell death. Elevation of growth factors (transforming growth factor-β, fibroblast growth factor, and insulin-like growth factor) and increased matrix metalloproteinases have been observed in the presence of ROS. In vivo experiments have demonstrated that ROS cause decreased cell proliferation and alveolarization in neonatal animals and decreased microvascular density. Research gaps and opportunities are listed in Table 1.

Newborn animals have better tolerance to hyperoxia than adults because of their ability to increase antioxidant defense mechanisms when exposed to oxygen. The activity of antioxidant enzymes and other antioxidant mechanisms is generally lower in premature animals and humans than in their term counterparts. Maturation of the antioxidant system parallels maturation of the surfactant system. Prenatal glucocorticoid therapy also increases antioxidant enzyme responses and survival rates for oxygen-exposed premature animals.

Premature infants are more vulnerable to oxygen toxicity because of decreased levels of antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and catalase. Premature infants have decreased levels of antioxidant vitamins A, E, and C and decreased amounts of the trace elements zinc, copper, and iron. Strategies that have been proposed to decrease oxygen toxicity in premature infants include reduction of oxygen exposure, antioxidants (including vitamin A, vitamin E, glutathione, trace elements, lipids, and inositol), and antioxidant enzymes. Identified gaps and opportunities are listed in Table 1.

Hyperoxia and hypoxia have been implicated in retinal injury in preterm infants. Preterm birth results in exposure of the infant to a higher ambient oxygen concentration ex utero, as opposed to in utero. This relative hyperoxia after preterm birth results in slowing, cessation, and sometimes regression of retinal vasculature development. Over time, the retina grows in thickness without concurrent blood vessel growth. Ultimately, hypoxia occurs at the tissue level, causing an increase in the release of angiogenic growth factors (such as vascular endothelial growth factor) and resulting in an overgrowth of vessels or ROP.

It has been long recognized that acute hypoxia is a powerful stimulus for cerebral vasodilation. However, the responses of fetal and neonatal cerebral circulation seem to be considerably different from those seen in older age groups. Some factors that seem to affect cerebral vascular responses include the severity and acuteness of hypoxia, speed of acclimatization, maturation and postnatal age, and systemic blood pressure and cardiac output. Acute hypoxia promotes adenosine release, leading to a dual effect. Through adenosine’s action on neuronal A1 receptors, fetal cerebral oxygen consumption is depressed; at the same time, through activation of A2 receptors on cerebral arteries, vasodilation is achieved. The latter accounts for approximately one half of the vasodilation observed in response to hypoxia in the fetus. Much of the adenosine-independent vasodilatory response to hypoxia is mediated through the release of nitric oxide and opioids, and a small fraction of the vasodilatory effect is attributable to the direct effect of hypoxia on cerebral arteries, through a vascular endothelial effect. During acclimatization to chronic hypoxia, fetal cerebral blood flow tends to normalize, especially if cardiac output is not compromised. However, severe, prolonged, uncompensated chronic hypoxia (lack of oxygen over time, without mechanisms to offset the process) in the fetus can produce significant changes in brain structure and function, increased incidence of intracranial hemorrhage, and periventricular leukomalacia. Pearce and colleagues showed that fetal cerebrovascular adaptations to chronic hypoxia seem prioritized to conserve energy while preserving basic contractility. More research is needed in the areas listed in Table 1. Similar to hypoxia, hyperoxia can lead to a complex set of responses in the brain. Increased minute ventilation, leading to a decrease in PCO2, leads to reductions in cerebral blood flow. Therefore, a combination of hyperoxia and hypocapnea has been shown to increase the risk of brain injury after intrapartum asphyxia. Vanucci et al showed that, in a hypoxic/ischemic encephalopathy rat model, mild hypercapnia could be neuroprotective. Systemic effects of hyperoxia can produce increased plasma insulin levels, increased glucagon levels, diminished myocardial contractility, and reduced myocardial relaxation. These effects may be mediated by central neural actions on sympathetic and hypothalamic hormonal regulation, rather than just peripheral actions of oxygen. Hyperoxia results in responses from forebrain, limbic, and cerebellar sites, which have the potential to modify autonomic and hormonal output (Table 1).

Hypoxia combined with anemia can affect oxygen content profoundly and thus reduce levels of oxygen delivered to the tissues, which in turn can affect growth. Severe anemia has been shown to cause neonatal growth failure. Although fetal growth occurs optimally at PaO2 levels of 35 to 40 mm Hg (levels much lower than those seen postnatally), there are important differ-
ences in oxygen physiologic features between fetal and postnatal life. Some of these differences include higher hemoglobin concentrations, greater proportions of fetal hemoglobin having steeper oxygen dissociation characteristics (enabling uptake of more oxygen from the placenta and release of more oxygen at the tissues), differences in oxygen consumption, and fetal levels of activity. There are also differences in placental transfer of nutrients, compared with the postnatal period. The complexities of oxygen physiologic features in the transition from fetal life through the newborn period highlight the need for more research, as outlined in Table 1.

**PRACTICAL ASPECTS OF OXYGEN THERAPY: CLINICAL TRIALS**

Oxygen is used widely in neonatal care. Many issues regarding its use represent outstanding gaps in knowledge and research questions to optimize clinical care. Table 1 summarizes major questions regarding the clinical use of oxygen.

Clinical trials that have been conducted to test the role of supplemental oxygen for ROP include the Supplemental Therapy With Oxygen to Prevent ROP Trial (BOOST). The Supplemental Therapy With Oxygen to Prevent ROP Trial tested the hypothesis that, among premature infants with prethreshold ROP in ≥1 eye, supplemental oxygen given to maintain 96% to 99% saturation (determined through pulse oximetry), in contrast to conventional levels of 89% to 94% saturation, would reduce the rate of progression to threshold ROP. A secondary hypothesis was that supplemental oxygen would also improve the infants’ growth. Six hundred forty-nine children were enrolled, with an average gestational age at birth of 25.4 weeks and an average postmenstrual age of 35.4 ± 2.5 weeks (range: 30–48 weeks). The progression of ROP from prethreshold to threshold disease was not reduced by supplemental oxygen. A posthoc subgroup analysis showed that infants with no plus disease, defined as posterior pole dilation/tortuosity, at the time of enrollment had less progression to threshold with supplemental oxygen. There were no differences with respect to infant growth in the 2 groups. Supplemental oxygen increased adverse pulmonary events during treatment and during follow-up monitoring through a corrected age of 3 months.

BOOST was designed to determine whether 1 of 2 oxygen saturation target ranges (pulse oximetry saturation of 91%–95% or 95%–98%) begun at postmenstrual age of 32 weeks would improve growth and development at a corrected age of 1 year. A total of 358 infants were enrolled. There were no differences in outcomes between the 2 target saturation groups, with respect to growth (assessed as weight, height, and head circumference) or major developmental abnormalities. Analysis of secondary outcomes showed an increased number of oxygen days and older postmenstrual age at oxygen discontinuation for the higher target saturation group (target saturation of 95%–98%). The authors stated that the optimal oxygen saturation range for preterm infants soon after birth should be determined with a large trial.

Existing gaps in the area of oxygen administration, oxygen saturation, and toxicity are summarized in Table 1. Trials to determine target saturation ranges are ongoing and under development. The following trials have the same design for the oxygen saturation arm. The Supplemental Therapy With Oxygen to Prevent ROP Trial is being conducted in the National Institute of Child Health and Human Development Neonatal Research Network. A factorial design has been developed to enroll infants to 4 possible strategies, as shown in Table 2.

The hypotheses being tested are that early continuous positive airway pressure and permissive ventilation can increase survival rates without an increase in bronchopulmonary dysplasia rates and that lower saturation targets (85%–89%) can increase survival rates without severe ROP (threshold disease or disease requiring surgical intervention). Infants between 24½ weeks and 27½ weeks of gestation are eligible for enrollment by 2 hours of age. As of April 30, 2006, 276 of the needed 1300 infants had been enrolled.

Funded by the National Health and Medical Research Council in Australia, BOOST II is a randomized, double-blind trial that will evaluate 2 ranges of oxygen saturation (85%–90% and 91%–95%) to determine whether development, vision, and health assessment are affected at 2 years of age. The primary study outcomes include severe ROP (stage III or higher), major disability, and death. Children will be enrolled by 24 hours of life and be of gestational age of <28 weeks. At the time of this writing, BOOST II has begun enrollment.

The US Pulse Oximetry Saturation Trial for Prevention of ROP under development will enroll children by 24 hours of age into 2 saturation arms (85%–89% and 91%–95%). The study will enroll 1525 children by 24 hours of age at <28 weeks of gestation. The primary study outcomes are ROP, pulmonary morbidity, severe disability at 24 months, and death. The hypothesis of this study is that children assigned randomly to the lower saturation arm should have less severe ROP and less pulmonary morbidity with no increase in the combined outcome of death or severe disability at a corrected age.

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**TABLE 2** Design for Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial

<table>
<thead>
<tr>
<th>Randomized Intervention</th>
<th>Low Saturation (85%–89%)</th>
<th>High Saturation (91%–95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early CPAP with permissive ventilation*</td>
<td>Strategy 1</td>
<td>Strategy 2</td>
</tr>
<tr>
<td>Intubation with prophylactic surfactant</td>
<td>Strategy 3</td>
<td>Strategy 4</td>
</tr>
</tbody>
</table>

CPAP indicates continuous positive airway pressure.

*Permissive ventilation is defined by the protocol as PCO2 of >65 mm Hg for intubation.
of 24 months. A prospective meta-analysis has been proposed to combine the resultant data from the Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial, BOOST II, and the Pulse Oximetry Saturation Trial for Prevention of ROP to examine moderate but important effects that may be detected with the large number of patients.

RESUSCITATION AND OXYGEN
Immediate use of oxygen for resuscitation in the neonatal period has been a long-standing practice. A recent Cochrane review evaluated air versus oxygen at birth for infants. The value of routine use of high inspired oxygen concentrations for resuscitation has been questioned recently, and many scientists have suggested that room air can be as effective as and perhaps safer than higher concentrations of oxygen during resuscitation. The rationale in favor of the use of room air use for resuscitation is that infants resuscitated with room air have earlier spontaneous respiration and 100% oxygen exposure can increase oxidative injury. Furthermore, a study of the surviving infants in the Collaborative Perinatal Project suggested a weak association between exposure to higher concentrations of oxygen for >3 minutes during resuscitation and later childhood cancer. Because of major limitations, such as selection bias and early death as a competing outcome, the conclusions of this study should be considered speculative. However, on the basis of a systematic review of 5 studies that compared room air versus oxygen for resuscitation of term infants, the authors concluded that resuscitation using room air resulted in a reduction in the neonatal mortality rate (8% vs 13%), higher 5-minute Apgar scores (6.6 vs 6.45), faster heart rate at 90 seconds of age (116 vs 111 beats per minute), and faster time to first breath (1.8 vs 2.3 minutes).

Despite the optimistic conclusion regarding the value of room air for resuscitation based on the meta-analyses, some limitations of the latter should be noted, including a lack of blinding in many studies, exclusion of apparent stillbirths, leading to lower prevalence of infants with severe asphyxia, and lack of validation of these studies in diverse intensive care settings around the world. Issues involving the use of oxygen for neonatal resuscitation are summarized in Table 1.

It should be noted that oxygen use in neonatal resuscitation has garnered much interest in commentaries. The expert panel at the workshop discussed the advantages and disadvantages of resuscitation using room air versus oxygen. The International Liaison Committee on Resuscitation recommendations for pediatric and neonatal advanced life support have since been published and state the following.

There is insufficient information to recommend for or against the use of any specific inspired oxygen concentration during and immediately after resuscitation from cardiac arrest. Until additional evidence is published, we support health care providers’ use of 100% oxygen during resuscitation (when available). Once circulation is restored, providers should monitor oxygen saturation and wean inspired oxygen while ensuring adequate oxygen delivery.

Additional International Liaison Committee on Resuscitation recommendations for neonatal resuscitation state the following.

There is currently insufficient evidence to specify the concentration of oxygen to be used at the initiation of resuscitation. Once adequate ventilation is established, if the heart rate remains low, there is no evidence to support or refute a change in the oxygen concentration that was initiated. Supplementary oxygen should be considered for infants with persistent central cyanosis. Some have advocated adjusting the oxygen supply according to pulse oximetry measurements to avoid hyperoxia, but there is insufficient evidence to determine the appropriate oximetry goal because observations are confounded by the gradual increase in oxygen saturation that normally occurs following birth.

In summary, appropriate use of oxygen during resuscitation is an area in need of additional study (Table 1). The CHIME study was set up to determine whether preterm infants, infants with sibling sudden infant death syndrome, and infants who have had a life-threatening event are at greater risk for cardiorespiratory events than healthy term infants. Extreme events (defined as apnea for ≥30 seconds, heart rate of <60 beats per minute for ≥10 seconds at postconceptional age of ≤44 weeks’ postconceptional age, or heart rate of <50 beats per minutes at postconceptional age of >44 weeks) were common for preterm infants. The increased risk for these events among preterm infants diminished by postconceptional age of 43 weeks, and it was concluded that these events are not likely to be immediate precursors to sudden infant death syndrome. The CHIME study also collected information on oxygen saturation levels, as measured with pulse oximetry. Among the two thirds of extreme events with high-quality pulse oximetry recordings, the degree of hypoxemia increased with increasing duration of apnea or bradycardia. In addition to storing waveforms associated with cardiorespiratory events, the CHIME monitor automatically stored 3 minutes of recordings every hour. Oxygen saturations ranged from 97% to 100% during periods of regular breathing. There were, however, well-documented periods of saturation decreases to <90% for 66% of the infants in the first 5 weeks of life. These decreases in saturation were usually brief (<5 seconds) but could last for >10 seconds (7% of events). Acute decreases in saturation occurred for 50% of infants. Most of these events (79%) were associated with periodic breathing and were more likely to occur during side or supine sleeping.
Areas identified throughout the meeting as opportunities to advance technology for oxygen monitoring are summarized in Table 1. Measurements of oxygenation at the tissue level, oxygen feedback systems, and feedback systems from pulse oximeters to maintain constant oxygenation were identified as areas for technology development.

CONCLUSIONS
A significant number of gaps and opportunities for research were identified (Table 1). The workshop participants observed that presently there is a lack of information on the effects of varying oxygen levels on organ development as a whole. They also noted that there is a need for data on interventions to prevent and to treat hypoxic and hyperoxic injury. Studies are needed to provide evidence-based information to assist clinicians in using oxygen appropriately for newborn infants. Critical areas in need of urgent study include the use of oxygen during resuscitation and appropriately targeting oxygen saturations for a wide variety of newborn infants. In addition, it is important to obtain more information on the short- and long-term outcomes related to oxygen therapy.

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The Intimidation of British Pediatricians
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Financial Disclosure: Dr Jenny was retained as an expert witness by the Crown Prosecution Service in the case of R v Harris, Rock, Cherry, and Faulder, Court of Appeal of England and Wales, 2005.

ABSTRACT

British pediatricians who diagnose and treat child abuse cases have come under attack by the British press and by parents who have been investigated for possible abuse. Now the General Medical Council also is intimidating these pediatricians. The General Medical Council is the licensing authority for physicians in the United Kingdom. This has resulted in fewer pediatricians being willing to care for abused children or to testify in child abuse cases. In the United States, the recent recognition of the pediatric subspecialty of child abuse pediatrics should help set standards for child abuse medical evaluation and testimony.

Key Words
child abuse, General Medical Council, child abuse pediatricians

Abbreviation
GMC—General Medical Council

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Some of the physicians who diagnose and treat child abuse cases have come under persistent attack in Great Britain. The most notorious example occurred when the General Medical Council (GMC) (the organization that licenses physicians in the United Kingdom) struck a respected child abuse pediatrician, Sir Roy Meadow, “off the register,” withdrawing his license to practice medicine. The reason for this extreme action on the part of the GMC was that, while testifying as an expert witness in a criminal trial, Dr Meadow quoted a controversial statistic about the likelihood of sudden infant death syndrome occurring twice in the same family. In the June 2006 issue of Pediatrics, Chadwick et al. published a defense of Dr Meadow. Dr Meadow appealed the GMC ruling in the High Court of Justice of England and Wales. A court decision in February 2006 reversed the ruling against Dr Meadow and reinstated him on the Registry of Medical Practitioners.2

Another distinguished British child abuse pediatrician, Dr David Southall, was brought before the GMC after he contacted the child protection division of the police department about a child abuse case in which he had not been involved professionally. In 2004, the GMC ruled that he could not be involved in any child protection work for 3 years.3

Complaints about child abuse pediatricians are not uncommon. In this month’s issue of Pediatrics, Williams et al. quote a disturbing survey of pediatricians involved in child abuse cases, performed by the Royal College of Pediatrics and Child Health in the United Kingdom. In 2004, 14% of those pediatricians had been subject to a formal complaint regarding child protection. Eighty-six of those complaints went to the GMC for review.

The attacks on child abuse pediatricians come in other forms as well. The British press attacks these doctors constantly. When complaints are filed, the physicians are hounded and insulted by the press. Several “theories” of child abuse are attacked. As in the cases of Drs Meadow and Southall, the concept of Munchausen syndrome by proxy (in which children are abused by the medical care system because caretakers report falsely, exaggerate, or even induce illness in their children) is discredited in the press as false and overdiagnosed. This occurs despite the number of well-documented cases in the literature. A Web site maintained by Mothers Against Munchausen Allegations (www.msbp.com) keeps an ongoing record of such press articles.

Many reporters in the British press have attacked the validity of shaken infant syndrome, basing their position on the opinions of a few nonpediatric physicians and convicted perpetrators who question the existence of this entity. I testified before the Court of Appeal in England during a review of abusive head trauma cases in 2005. The newspapers and magazines presented a highly slanted view of the proceedings, publishing stories of evidence presented by the convicted appellants and ignoring evidence presented by the Crown Prosecution Service. The press justifies its antagonism to shaken infant syndrome and abusive head trauma by emphasizing the work of researchers with “novel hypotheses” about how otherwise normal, healthy infants experience subdural hematomas and severe retinal hemorrhage. The most notable example is the “unified hypothesis” of Geddes et al.5 Geddes et al.5 published an article saying that trauma was not necessarily needed to cause subdural and retinal hemorrhage in infants with no identifiable medical illness. Instead, they proposed that cerebral vessels “leaked” because of hypoxia, brain swelling, and increased central venous pressure. They said this could occur after an apneic or choking episode, despite the absence of any scientific or clinical data linking subdural hematomas or retinal hemorrhage to such events.

Geddes’ theory led to the review of many abusive head trauma convictions in England, and 4 cases were sent to the Court of Appeal for review. This received much press attention. During the trials, however, Dr Geddes retracted her theory. In the court transcript, the following exchange occurred.

Question: “Dr Geddes, cases up and down the country are taking part where Geddes [her article on the unified hypothesis] is cited by the defense time and time again as the reason why the established theory is wrong.”

Answer: “That I am very sorry about. It is not fact; it is hypothesis. But, as I have already said, so is the traditional explanation. I have never said—that I would be very unhappy to think that cases were being thrown out on the basis that my theory was fact.”6

The fact that Dr Geddes and her colleagues no longer endorse this theory was not noted by the London daily newspapers in their reporting of the trial. In addition, little attention was given to the judges’ decision in the appeals cases. Lord Justice William Gage stated in the appeals decision, “...the unified hypothesis can no longer be regarded as a credible or alternative cause of the triad of injuries” (subdural hemorrhage, retinal hemorrhage, and encephalopathy).7 Now a new campaign is being waged to discredit metaphyseal fractures as a sign of child abuse. James Le Fanu, a medical columnist for the London newspaper The Telegraph, mischaracterizes the work of Boston radiologist Paul Kleinman to suggest that metaphyseal fractures are “normal variants.”8 This is despite the meticulous work of Dr Kleinman and colleagues9,10 demonstrating the pathologic features of metaphyseal fractures in child abuse cases.

In the article by Williams et al.,5 53 pediatricians, 1 senior lawyer, and 1 senior social worker report that one third of the child protection posts for physicians in the United Kingdom National Health Service are unfilled.4 They also quote a survey showing that 62% of pediatric trainees do not want to deal with child protection cases. The authors say that the decisions of the GMC intimidate pediatricians di-
agnosing child abuse. The decisions of the GMC are re-
ported to have had a chilling effect on young physicians,
discouraging them from becoming involved in child pro-
tection cases and affecting their willingness to testify.

What about child abuse pediatricians in the United
States? In some areas, similar pressure is being exerted
on pediatricians through lawsuits or press attacks. A
1999 survey documented stressors for pediatricians diag-
nosing child abuse, especially the stress involved in court
appearances.11 Two factors, however, make our system
better. First, all 50 states have “mandated reporting” laws,
whereby physicians are required to report child abuse to
authorities and are protected from liability if they report in
good faith. Mandatory child abuse reporting is not codified
in Great Britain. Second, we have formalized training for
child abuse pediatricians here, with many successful fel-
lowships producing well-recognized expert physicians.12,13
Recently, the American Board of Pediatrics approved child
abuse pediatrics as a newly recognized subspecialty.14
This will provide credibility and standards for child protection
practice. We must be careful, however, to see that the
public and the press are educated responsibly about the
realities of the diagnosis of child maltreatment.

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SPECIAL ARTICLE

United Kingdom General Medical Council Fails Child Protection

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ABSTRACT

To protect children, pediatricians must be willing to raise the possibility of abuse and not be intimidated by the consequences. We consider that the United Kingdom General Medical Council does not understand child protection matters and has no system for dealing adequately with complaints submitted by parents who claim false allegations of abuse. The actions of the General Medical Council in the recent cases of Drs Roy Meadow and David Southall conflict with current child protection laws and guidance for professionals. By deterring doctors from raising concerns about a child’s safety and giving opinions on child deaths, the General Medical Council may be increasing the risk of serious child abuse. Although the rate of registrations by child protection authorities decreased by 28% between 1995 and 2005 (ie, there are fewer multiagency child protection plans), the number of criminal convictions for cruelty to or neglect of a child increased by 247% between 1998 and 2005. It is unacceptable that to date the General Medical Council has refused training in child protection offered by the Royal College of Paediatrics and Child Health.
We agree with the conclusions of the article by Chadwick et al\(^1\) and offer the following as additional evidence in support of their conclusion that the actions of our medical regulatory body, the General Medical Council (GMC), conflict with current child protection laws and guidance for professionals and already might have contributed to the reduction in the willingness with which doctors raise child protection concerns.

In 2004, the Royal College of Pediatrics and Child Health in the United Kingdom performed a survey of members; 14% of 3853 pediatricians had been subject to a formal complaint about child protection.\(^2\) This had increased from <20 cases in 1995 to >100 cases in 2003. Of those doctors, 29% were less willing to participate in child protection work. Doctors have also witnessed the GMC censure of Drs Roy Meadow and David Southall, who have been central to the identification of life-threatening child abuse. These factors have probably increased the proportion of doctors unwilling to take part in child protection work. One third of child protection posts for designated doctors in child protection are unfilled,\(^3\) and 62% of trainees in North West England do not wish to deal with child protection cases.\(^4\)

The actions of the GMC have been accompanied by an effective campaign led by a group of parents accused of abuse and supported by some influential journalists. One aim, among others, is to deny the existence of certain types of life-threatening child abuse. This has resulted in politicians stating in the Houses of Parliament how fabricated and induced illness is a “pernicious and ill-founded theory,” “a theory without science,” “based on the assertions of its inventor Professor Meadow,” and “has now been discredited.”\(^5\)

Our own analysis of the GMC transcripts in Dr Southall’s case indicated that the GMC failed to understand the obligations placed on all clinicians by the Children Act of 1989, failed to understand the multidisciplinary context in which judgments are reached in child protection work, and failed to recognize the conflict of interest that could have affected the views of its only expert witness. The GMC also paid inadequate attention to the experience of and evidence base underpinning Dr Southall’s opinion and failed to give attention to its own expert’s view that there was no evidence for a medical cause for the nose-bleeding incident and the expert’s support for Dr Southall’s opinion that such bleeding, if attributable to suffocation, would occur immediately (the mother, who had been convicted previously for causing the infants’ deaths, was not present at the time the nose bleeding began). The GMC’s expert had in fact considered that the father could not be implicated, although the GMC heard how third-party checks on his whereabouts at the time of the first infant’s death had not been made. Therefore, the GMC judged Dr Southall’s allegation to be false without appropriate expertise or investigation to make such a judgment. The GMC contravened natural justice in other ways, as outlined by Chadwick et al,\(^1\) and thus denied Dr Southall a fair hearing and an impartial judgment.

Article 10 of the European Convention for the Protection of Human Rights and Fundamental Freedoms states specifically that citizens are entitled to voice their concerns and are limited only by the law of defamation. Furthermore, the House of Lords ruled in 2005 that “when considering that something does not feel ‘quite right,’ a doctor must be able to act single-mindedly in the interests of the child.”\(^6\) The views of the GMC were contrary to current child protection guidance, which treats the child’s safety as paramount, that is, “the doctor is charged with the protection of the child, not with the protection of the parent.”\(^6\) We do not consider that the reporting of genuine concerns about the safety of a child to responsible authorities, within the confidentiality of established processes, brings the medical profession into disrepute, but the GMC did because it failed to understand the medical responsibilities in child protection.

Regardless of whether the medical opinion is supported or rejected by the court, doctors must feel safe in sharing genuinely held concerns about the welfare of children without fear of sanctions. However, the GMC’s view that Dr Southall brought the profession into disrepute by acting precipitately in contacting child protection services and by giving an opinion “based on a theory . . . as underpinned by your own research . . . without any evidence to support those theories at all”\(^7\) is likely to deter many pediatricians from prompt action. Some of us have tried to publish our analysis of this case and Dr Southall’s reasoned opinion in United Kingdom journals but have been unsuccessful, largely because lawyers considered that this has the risk of precipitating an unaffordable libel trial.

In the case of Dr Meadow, the GMC removed his name from the medical register for failing in the criminal court to qualify his quotation from a government publication on the risks of 2 sudden infant deaths. However, a Court of Appeal judge had ruled previously that Dr Meadow’s “opinion was based on his expert assessment of the medical and circumstantial evidence, not on the statistical material.”\(^8\) Dr Meadow had never held himself out as having expertise in statistics, and the court and lawyers had copies of his resume and did not object to his answers in court.

The High Court judge who reinstated Dr Meadow on the medical register confirmed the position on witness immunity, that is, “the possibility of disciplinary proceedings based on a complaint by someone affected by the evidence given has a serious deterrent effect.”\(^9\) The judge described the GMC’s opinion as follows: “to say his [Dr Meadow’s] conduct was ‘fundamentally incompatible with what is expected by the public from a medical practitioner’ approaches the irrational.”\(^9\) Drs Southall and Meadow had both given their opinions in good faith.
that the infant deaths were unnatural, a view contested by the parents, as so often occurs in child protection work.

To protect children, pediatricians must be willing to raise the possibility of abuse and must not be intimidated by the consequences. We consider that the GMC does not understand child protection matters and has no system for dealing adequately with complaints submitted by parents who claim false allegations of abuse. The GMC’s actions are not in accordance with current child protection guidance and, by deterring doctors from raising concerns about children’s safety and giving opinions in child deaths, they may be increasing the risk of serious child abuse. Although the rate of registrations by child protection authorities decreased by 28% between 1995 and 2005 (ie, there are fewer multiagency child protection plans), the number of criminal convictions for cruelty to or neglect of a child increased by 247% between 1998 and 2005. It is unacceptable that to date the GMC has refused training in child protection offered by the Royal College of Paediatrics and Child Health. Furthermore, their failure to understand the pediatricians’ responsibilities in child protection matters is compounded by their unjust process. Having spent 3 weeks in November 2006 hearing further complaints against Dr Southall relating to child protection cases from up to 20 years ago, they have now postponed the completion of the hearing until November 2007. Justice delayed is justice denied—to both complainants and doctors.

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B RONCHOPULMONARY DYSPLASIA (BPD) is a serious health problem associated with mortality and high morbidity among graduates of the NICU. The cost of BPD is tremendous. It is associated with prolonged hospitalization of the preterm infant, multiple rehospitalizations during the first few years of life, and survival with developmental delay and/or cerebral palsy. It becomes, therefore, a major goal for the neonatal community to prevent or at least partially control the incidence of BPD.

In an effort to scientifically ameliorate the incidence of BPD, Walsh et al examined the 3 best-performing NICUs among the 17 units of the National Institute of Child Health and Human Development Neonatal Network. The study team determined some practices in these 3 units that they could adopt in a clinical trial. They then initiated a cluster-randomized, controlled trial among the remaining 14 units; 7 of these units changed their practices accordingly, and the other 7 units continued their routine care. Early administration of surfactant, use of vitamin A, and maintaining lower oxygen saturation were among the adopted practices in this randomized trial. Early nasal continuous positive airway pressure (CPAP) was not one of the targeted practices to change, because there was “insufficient evidence” to support its use. In fact, when compared with the control group, the 7 NICUs in the intervention group used more endotracheal intubation (77% vs 66%) and less CPAP (16% vs 27%) in the delivery room. During the first week of life, mechanical ventilation was more prolonged in the intervention-group infants (4 vs 3.5 days). Despite the overtly scientific approach and the tedious efforts and resources spent to ensure quality of care and compliance with policies, the incidence of BPD did not change in the 4095 recruited infants.

BPD is caused by an inflammatory process that results in either airway injury and parenchymal fibrosis of the lung alternating with emphysema (classical BPD) or cessation of alveolar septum formation (the new BPD). This inflammation is driven by the use of mechanical ventilation and oxygen. The liberal use of oxygen has been shown to induce lung injury and produce BPD. For decades, not only has mechanical ventilation alone been shown to damage healthy lungs and even lead to death in animal studies, but the use of elective ventilation for even a few breaths also clearly causes significant damage to premature animal lungs. In addition, mechanical ventilation by itself poses an independent risk for cerebral palsy and learning disability in premature infants. Therefore, to control BPD, it is imperative to avoid ventilator injury.

Despite the clear cause-and-effect relationship between the ventilator and lung injury, studies have not been designed to avoid intubation and instead have been conducted to test every possible strategy for reducing lung injury in already-intubated and -ventilated infants. In addition, even more desperate efforts are spent trying different drugs on ventilated infants: glucocorticoids, vitamin A, superoxide dismutase, or even inhaled nitric oxide.
oxide. A simple search at the National Library of Medicine can identify at least 800 well-designed trials that were performed mostly on ventilated premature lungs. Injury starts immediately after the first few mechanical breaths in the delivery room, so it is puzzling to find that such continued efforts against BPD are still concentrating on those already-intubated infants.

Logically, more studies should be performed with the aim of avoiding lung injury in the first place, but such simple logic has not gained ground because it is not “evidence based.” In fact, evidence-based critical thinking should urge us to explore whether the practice of elective intubation in the delivery room has any supportive biological or physiologic proof compared with CPAP use.

With this frustration of not having a “silver bullet” to prevent or control BPD, an increasing number of NICUs are reporting their experience of less BPD when using CPAP. In 1985, Avery et al\(^1\) reported less BPD (4%) at Columbia University (in New York) when compared with 8 other centers. Columbia University is known for its strategy of early use of CPAP. A later comparison conducted at Columbia University confirmed the decreased incidence of BPD.\(^2\) NICUs in and outside the United States have reported their experiences with lower incidence of BPD using CPAP when compared with their own historical outcomes or current national benchmark values.\(^2,3,4\) The strength of evidence of these reports is not adequate, because they were not originally designed as randomized, controlled trials. However, it is important to remember that the absence of evidence is not evidence of absence.

In an effort to validate such CPAP claims, Finer et al\(^5\) conducted a randomized trial and proved the feasibility of the application of CPAP in the delivery room even with the lowest birth weight categories (<1000 g). In that pilot trial, the overall majority of these infants ended up being intubated shortly after birth. On the basis of these reports, it is fair to conclude that the use of CPAP in the delivery room is possible but requires tedious training and bedside nursing experience to ensure its success.

A collaborative effort to achieve satisfactory levels of training and experience might have made CPAP clinical trials more meaningful. A randomized, controlled trial without adequate CPAP training might seem to demonstrate the absence of efficacy of CPAP in the prevention of BPD but would not differentiate whether the failure occurred with CPAP itself as a “tool” or was a result of lack of experience in the hands of the “carpenter.” However, this does not explain why units experienced with CPAP have a much lower incidence of BPD than the national average.

I strongly believe that we need to collaborate to decrease the incidence of BPD. Units that have used CPAP successfully should step forward and share their experiences with other units that are willing to use CPAP for a scientific trial or as a standard of practice. The ability to reproduce CPAP experience in different units would be the best proof of its effectiveness and should be a prerequisite before any meaningful trials can start.

Eight years ago, the incidence of BPD at the George Washington University (GWU) had been steady at 33% in infants <1500 g. The early use of CPAP in the delivery room was initially associated with an unfavorable trend during the first year of its application. The incidence of BPD has been declining steadily for 8 consecutive years (Fig 1). A favorable trend has also been established in infants <1000 g.\(^6\) To control BPD and ensure safer management of preterm infants everywhere, we need to share our resources and experiences. We have been contacted by several units that are eager to reproduce a successful CPAP experience. This interest led us to start a health initiative called “the CPAP rescue team” at GWU that aims to share experiences and teach hands-on care to nurses and physicians, which allows interested NICUs to reproduce their own successful experience. We envision this move to be in the right direction; it will transform debates into actions and skepticism into hands-on care. We invite NICU advocates to move forward and join with us to stop the suffering of those we are caring for.

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Male Circumcision for Prevention of HIV and Other Sexually Transmitted Diseases

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A recent commentary in Pediatrics reviewed the documented medical benefits of newborn male circumcision, including protection against balanoposthitis, phimosis, infections of the urinary tract in male infants, and protection against human papillomavirus–associated genital cancers and HIV and Chlamydia infection in adolescents and adults.1 Low rates of minor surgical complications (0.2%–0.6%) and safety and efficacy of local anesthesia were noted. The ability of newborn circumcision to protect against sexually transmitted diseases (STDs) was also shown in a recently published cohort study from New Zealand.2 Recent large randomized clinical trials in South Africa, Kenya, and Uganda demonstrated reduction of HIV-acquisition risk by male circumcision performed outside the newborn period, showing the role of adult male circumcision in prevention of STDs in adolescents and adults.3,4

An association between lack of male circumcision and acquisition of HIV infection was first noted in 1986.5 Over the next 10 years, more than 35 studies including ecologic, cross-sectional, case-control, and cohort studies in general and high-risk populations throughout the world evaluated the possible protective effect of male circumcision against HIV acquisition.6-8 A systematic review summarized the studies from sub-Saharan Africa and showed an estimate of the adjusted relative risk of HIV acquisition of 0.42 (95% confidence interval [CI]: 0.34–0.54; protection of 58%) in circumcised compared with uncircumcised male subjects.7 The impact of male circumcision on prevention of HIV acquisition was greater in high-risk groups than in the general population.6 A cohort study has also suggested that transmission of HIV to female partners of men with HIV may be lower when the male partner is circumcised.9-11

To define more accurately the potential role of male circumcision in prevention of HIV acquisition, investigators have undertaken 3 large randomized clinical trials in southern and eastern Africa. The results of the first of these trials were published in 2005.5 In that study, 3274 uncircumcised men in South Africa were randomly assigned to either be circumcised immediately after randomization (intervention group) or at the end of the study (control group). The trial was stopped early, after a mean follow-up of 18 months, when the results of an interim intention-to-treat analysis revealed a significant protective effect of circumcision of 60% (95% CI: 32%–76%). When the data were analyzed to take into account men who were actually circumcised in the control group or not circumcised in the intervention group, the protective benefit of circumcision was 76% (95% CI: 56%–86%). Similar protection was demonstrated by the other 2 large trials, which were stopped early when results of an interim analysis showed that circumcision of adult men has protective efficacy of 53% (in the Kenya study) or 48% (in the Uganda study).4

Male circumcision may act directly to reduce the risk

Abbreviations: STD, sexually transmitted disease; CI, confidence interval

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of HIV acquisition by reducing the ability of the virus to attach to and enter cells. The inner mucosal surface of the foreskin contains a higher density of Langerhans cells (a target cell for HIV infection) than stratified squamous epithelium (which is on the surface of the penis) and is more susceptible to HIV infection in vitro. The foreskin is also more susceptible to trauma, which may increase susceptibility to HIV infection during sexual activity. Alternatively, the effect of circumcision on prevention of HIV acquisition may be indirect. Infections with ulcerative STDs including syphilis, chancroid, and herpes are reduced in men who have had a circumcision. Because these ulcerative STDs are associated with increased HIV-acquisition risk, reduction in other STDs may partially explain the reduced HIV-acquisition risk associated with male circumcision.

Newborn circumcision may be preferable to circumcision at an older age because of its enhanced safety. Questions remain about the possibility that circumcised men may practice riskier sex because of presumed protection. The protective effect of circumcision on reducing HIV transmission found in Africa, where HIV is predominantly heterosexually transmitted and HIV prevalence is high, may not be directly applicable in the United States, where HIV in men is predominantly transmitted by male-to-male sex and HIV prevalence is lower. However, newborn circumcision has been shown to prevent later acquisition of STDs in young adult men in New Zealand, which suggests that the protective effect is not confined to developing countries.

Since 1999, 16 states have eliminated Medicaid payments for circumcisions that were deemed “not medically necessary,” justifying that decision in part on the basis of the American Academy of Pediatrics statement that “potential medical benefits . . . are not sufficient to recommend routine neonatal circumcision.” Data now demonstrate the benefit of male circumcision as an intervention for the prevention of STDs including HIV and genital cancers. Therefore, if parents choose circumcision for their newborn male child, or if an adolescent decides that circumcision might be appropriate to reduce risk of STD acquisition, it is a medically rational choice that should be included in government health or private insurance benefits. Circumcision, like vaccination, may be an effective intervention for disease prevention in the United States as well as in other countries. Advisory groups in the United States need to carefully consider how recent data on the preventive efficacy of adult male circumcision might change current recommendations for care of newborns and adolescents in the United States.


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The State Children’s Health Insurance Program (SCHIP) was passed by Congress in the Balanced Budget Act of 1997 during the Clinton presidency. The legislation appropriated approximately $40 billion for 10 years, 1998–2007. By 2003, 4.4 million children were enrolled in separate SCHIPs, and an additional 1.6 million were enrolled in SCHIP-financed Medicaid expansions. As of 2006, 7 states (Vermont, New Jersey, Connecticut, Maryland, New Hampshire, West Virginia, and Massachusetts) had expanded their SCHIP eligibility to families who are earning at least 300% of the federal poverty level (FPL), which will make almost all uninsured children who are US citizens eligible for public programs. The governors of California, Pennsylvania, Oregon, and Wisconsin have also introduced initiatives that include SCHIP expansions to substantially reduce the number of uninsured children in their states. In 2007, SCHIP must be reauthorized by Congress with a new appropriation of funds to continue to function in 2008. Because SCHIP is a block grant or capped-grant program, a number of states that established programs having higher income-eligibility thresholds, better outreach and marketing, and more streamlined enrollment procedures are projected to have a shortfall in federal support in 2007. For fiscal years 1998 through 2001, the annual appropriation was slightly over $4.2 billion. The appropriation dropped to under $3.2 billion from 2002 through 2004 but then increased to $4.1 billion for 2005 and 2006 and $5.0 billion in 2007. Because of greater than anticipated enrollment and per capita expenditures, the states’ total spending of federal SCHIP funds has exceeded the annual appropriations since 2002. The shortfalls of federal SCHIP funds after 2002 were covered by redistributing unspent federal funds allocated to states for the years prior to 2002. However, as states expanded their SCHIP programs during the past several years, the amount of unspent federal funds available for redistribution has diminished. As a result, Congress appropriated an additional $283 million in the Deficit Reduction Act of 2005 for projected shortfall states. In addition, The National Institutes of Health Reform Act of 2006 contained SCHIP provisions requiring an early redistribution of unspent 2004 and 2005 federal allocations to states with federal shortfalls in 2007. However, the original budgeting approach leaves SCHIP future funding vulnerable because significant additional funds over the 2007 allocation, between 12 and 14 billion dollars according to an American Academy of Pediatrics estimate, will be needed during the next 5 years just to allow states to maintain their existing SCHIP programs. Expanding existing state programs will require funds in addition to the 12 to 14 billion dollars. Therefore, consideration of state-based strategies for reducing the number of uninsured children that include expanding SCHIP must depend on the federal SCHIP reauthorization.

Although it seems certain that SCHIP will be reauthorized because of its broad base of congressional support among both Republicans and Democrats, it is less clear...
how much new funding will be appropriated and whether any changes will be made to promote enrollment, improve quality of care, and facilitate additional expansions in coverage. The authorization could create a financial incentive for states to enroll a higher percentage of their eligible children, which would encourage states to improve their outreach and marketing and implement more streamlined enrollment procedures. Modifying or waiving the onerous citizenship-verification requirements would also assist states in streamlining the enrollment process. The reauthorization could also fund the development, distribution, and evaluation of pediatric quality measures similar to what Medicare is doing in quality for adult care.

There are several incremental options for expanding coverage with SCHIP to reduce the number of uninsured children. The reauthorization could increase the age of eligibility, because 19- to 25-year-olds have the highest rates of being uninsured. It could give states the option to cover legal immigrant children during their first 5 years living in the country and the option to cover pregnant women during their prenatal, delivery, and postpartum periods. The reauthorization could also make it easier for states to use SCHIP funds to help families purchase family employer-sponsored insurance coverage and to help small employers pay for employee children who are enrolled in Medicaid or SCHIP.

The most comprehensive and far-reaching option would establish a new federal mandate that states expand SCHIP coverage and/or create a strong financial incentive for states to expand coverage to families who are earning 250% or 300% of the FPL. The financial incentive could include changing the federal match rate or federal-state financing structure to benefit states. An example of how federal-state financing structure could be changed is illustrated by the “Kids Come First Act,” a federal legislative proposal introduced in 2005 but not passed.4 In this bill, SCHIP coverage would be expanded to all children under age 21 who live in families with incomes ≤300% of the FPL. Although the program would impose a mandate on the states, the joint financing of SCHIP/Medicaid would be restructured to reduce state expenditures for children enrolled in Medicaid. The federal government would take full financial responsibility for Medicaid coverage and outreach costs for children who live with families who earn ≤100% of the FPL, while states would continue to pay the enhanced SCHIP match rate (an average of 36%) for higher-income children up to 300% of the FPL. This approach would save states money and reduce the state-to-state variability in the proportion of children who lack health insurance coverage. This state-to-state variability is substantial for a wide range of child outcomes beyond the number of uninsured. Petit recently published a book entitled Homeland Insecurity: American Children at Risk,5 which used US Bureau of Census data and other official sources to show that children do much better overall if they live in so-called blue states, where there are higher levels of taxation and investments in children, than if they live in red states, where both taxes and social investments have been low.

Realistically, reauthorization of an expanded SCHIP provides the only current federal opportunity to significantly reduce the number of the nation’s uninsured children by providing a pathway to affordable or reasonably priced coverage. However, expanding SCHIP alone will not guarantee universal coverage for children. SCHIP does not provide children with an entitlement to health care, and if cost increases are greater than projections or if states experience budgetary difficulties, program enrollment freezes or cutbacks could be implemented. In addition, although raising the income-eligibility thresholds for SCHIP would cover most uninsured children who do not have private or public coverage, both a parental mandate and streamlining the enrollment process are needed to ensure full participation. Currently, ~70% of the nation’s uninsured children are already eligible for enrollment in public programs.6 Many parents are unaware that their children would qualify for public programs, and others have difficulty navigating complex enrollment procedures.6,7

However, the road to universal health insurance has been difficult and frustrating to travel. Mayes has written an excellent book entitled Universal Coverage: The Elusive Quest for National Health Insurance,8 in which he describes the lost opportunities dating back to 1935 and failed attempts by Presidents Roosevelt, Truman, Nixon, and Clinton. Whenever the time seems right to pass universal-coverage legislation, an insurmountable political obstacle arises—a recession, a war, a flawed process, or an unwillingness of key stakeholders to compromise. I believe it is unlikely that the US Congress will seriously consider any federal universal-coverage legislation for children or everyone before the 2008 presidential election. Will the nation’s huge budget deficit and ongoing war in Iraq make it difficult to appropriate the new federal funds needed to at least maintain the states’ existing SCHIPs, if not expand the program to reduce the number of uninsured children? Yes, it will be difficult, but child advocates must speak out in support of efforts to ensure that SCHIP reauthorization becomes a vehicle that gets us closer to (not farther from) the goal of universal coverage for America’s children.

REFERENCES


Mycoplasma pneumoniae and Atypical Stevens-Johnson Syndrome: A Case Series

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ABSTRACT
Mycoplasma pneumoniae is a common cause of community-acquired respiratory illness in the adolescent population. Stevens-Johnson syndrome is an extrapulmonary manifestation that has been associated with M pneumoniae infections. Three adolescent males presented within a 1-month period with M pneumoniae respiratory illnesses and severe mucositis but without the classic rash typical of Stevens-Johnson. Diagnosis was facilitated by the use of a polymerase chain reaction–based assay. This case series highlights the potential for M pneumoniae–associated Stevens-Johnson syndrome to occur without rash and supports the use of polymerase chain reaction for early diagnosis.

Mycoplasma pneumoniae is a well-recognized cause of community-acquired pneumonia. Most cases are mild and can be managed on an ambulatory basis. However, some M pneumoniae infections can be complicated by extrapulmonary disease. These manifestations occur in <10% of cases and include hemolytic anemia, hepatitis, arthritis, meningitis, and Stevens-Johnson syndrome (SJS).1 In children, M pneumoniae is the most commonly identified infectious cause of SJS.2 The classic rash and mucosal involvement of SJS typically accompany the signs and symptoms of an M pneumoniae respiratory infection. However, in recent literature, sporadic cases of M pneumoniae pneumonia with mucositis but lacking the typical target lesions and blisters of SJS have been described.3-4 In the following case series is described a cluster of 3 cases of SJS associated with M pneumoniae infection in which the classic rash was absent. All 3 cases were confirmed with polymerase chain reaction (PCR) technology, which facilitated rapid diagnosis and treatment of M pneumoniae.

CASE REPORTS

CASE 1. In December, an 11-year-old previously healthy boy returned from Boy Scout camp with complaints of a sore throat and low-grade fever. He was seen by his primary care provider (PCP), given a diagnosis of streptococcal pharyngitis by rapid antigen testing, and treated with penicillin. The fever persisted, and he developed a cough with shortness of breath over the next few days. On the day before admission, he was noted to have an urticarial rash on his trunk. Because of concern for a drug allergy, he was given diphenhydramine, and treatment was changed to azithromycin. On the following day he developed a fever of 103°F, red eyes, swelling, and peeling of his lips and was admitted to the hospital. He was found to be hypoxic, with an oxygen saturation of 85% on room air, and hypotensive, with diastolic blood pressure measurements (mm Hg) in the 50s in the emergency department. He was admitted to the PICU.

On physical examination, his oral temperature was 38.2°C, heart rate was 135 beats/minute, blood pressure was 100/66 mm Hg, and respiratory rate was 40 breaths/minute. He had bilateral subconjunctival hemorrhages, cracked erythematous lips with friable, erythematous mucosa, shotty anterior cervical adenopathy, and coarse crackles and wheezes bilaterally on auscultation. There were several small, erythematous macules on his shoul-
ders. His laboratory workup results included an erythrocyte sedimentation rate of 47 mm/hour and a C-reactive protein level of 9.8 mg/dL. His chest radiograph showed bilateral infiltrates. He was diagnosed with mucositis and pneumonia.

He received fluid resuscitation, epinephrine, steroids, and oxygen supplementation by face mask. He was initially started on ceftriaxone and clindamycin, in addition to azithromycin, for treatment of the pneumonia, and erythromycin ophthalmic ointment was prescribed for the conjunctivitis. His antibiotic regimen was changed to levofloxacin on day 3 of hospitalization. Throat-swab results for *M pneumoniae* PCR collected at that time were positive. He was discharged on the fifth hospital day to complete a 14-day course of levofloxacin.

**CASE 2.** A 14-year-old previously healthy boy developed a fever of 102.6°F and myalgias thought to be caused by influenza virus in January. Approximately 1 week later, he began to have cough and congestion. A prescription for amoxicillin-clavulanate was telephoned in for him by his PCP. At a follow-up visit with his PCP 2 days later, he was found to have continued fever, worsening cough, and ulcerations of his oral mucosa. A chest radiograph showed a left lower lobe infiltrate, and his antibiotic was changed to clarithromycin. He was admitted to the general pediatric floor later that day because of an episode of hematemesis.

On physical examination, his axillary temperature was 38.1°C, heart rate was 111 beats/minute, respiratory rate was 22 breaths/minute, and blood pressure was 117/66 mm Hg, and his oxygen saturation was 94% on room air. His physical examination showed bilateral injected conjunctiva, friable, erythematous lesions on his lips and soft palate, decreased breath sounds at the left base on auscultation, and an erythematous, ulcerated lesion on the penile meatus. His laboratory workup included a white blood cell count of 12.0/mm³, normal liver-function test results, and negative heterophile antibody test and urinalysis results. He was given a diagnosis of mucositis and pneumonia (see Fig 1).

The patient was started on acyclovir, because of concerns for possible herpes simplex virus (HSV), in addition to azithromycin and cefuroxime. Results of swabs from his mouth and penis, collected for viral cultures, were negative. Throat-swab results for *M pneumoniae* PCR collected on the day of admission were positive. He improved clinically and was discharged on hospital day 3 to complete a 5-day course of azithromycin.

**CASE 3.** A 16-year-old previously healthy boy developed a sore throat and erythematous conjunctiva in January. He was seen by his PCP and had a negative rapid antigen detection test result for group A streptococcus. Polymyxin B and trimethoprim ophthalmic drops were prescribed for his conjunctivitis. Four days later, he was noted to have ulcerations of his oral mucosa, and oral acyclovir was prescribed. The following day, his sore throat worsened, and clarithromycin was prescribed. His fever increased to 103°F, and he was evaluated by an otolaryngologist. The patient was then referred to the emergency department for hydration and management of suspected HSV gingivostomatitis.

His physical examination showed a heart rate of 120 beats/minute and blood pressure of 96/53 mm Hg, bilateral conjunctivitis, swollen, erythematous lips, diffuse friable oral mucosa, and an ulceration of the penile meatus. A chest radiograph showed a right middle lobe infiltrate. He was diagnosed with mucositis and pneumonia. Results of a rapid HSV-antigen test on his oral mucosa were negative, and he was started on ceftriaxone and azithromycin for treatment of the pneumonia. Throat-swab results for *M pneumoniae* PCR collected on the day of admission were positive. The patient subsequently required placement of a percutaneous intravenous central catheter line for parenteral nutrition and patient-controlled analgesia with morphine because of continued severe mouth and pharyngeal pain. He was discharged on hospital day 13 after improvement of his symptoms and completion of 5 days of treatment with ceftriaxone and azithromycin.

**DIAGNOSIS WITH *M pneumoniae* PCR**

Throat-swab specimens were obtained from each of the 3 patients and tested for *M pneumoniae* by a multiplex PCR-based assay as described previously. Throat-swab specimens from each of the patients included in this series were tested positive for both *M pneumoniae* DNA targets in duplicate reactions, and there was no evidence of PCR inhibition. Positive and negative controls also yielded expected results (see Fig 2).
SJS AND M pneumoniae

In a 1-month period of time, 3 adolescent boys were hospitalized at Children’s Hospital of Pittsburgh with M pneumoniae pneumonia associated with SJS but lacking the classic rash. Making the diagnosis of SJS in the absence of the classic rash is clinically challenging, given that a number of other disease processes can manifest with mucosal changes, including infections, autoimmune diseases, and drug reactions. The exact pathophysiology of SJS is unclear but most likely involves immunologic response to reactive drug metabolites or infectious pathogens.7 The earliest histologic finding in skin lesions is a perivasculitis of superficial dermal vessels associated with an inflammatory cell infiltrate.7 Identification and withdrawal of the precipitating agent of SJS is important in management of the disease and may prevent additional episodes.8

In children, infections are the most commonly identified cause of SJS, with M pneumoniae implicated most frequently.2,3 Other associated infections include HSV, Mycobacterium tuberculosis, group A streptococci, hepatitis B virus, Epstein-Barr virus, enteroviruses, Verruca enterocolitica, Histoplasma capsulatum, and Coccidioides immitis.6 HSV has been shown to have a stronger relationship with erythema multiforme minor than with SJS.6 Drugs are also an important cause of SJS and include penicillins, tetracyclines, cephalosporins, aspirin, and nonsteroidal antiinflammatory drugs. Systemic diseases such as inflammatory bowel disease may also precipitate SJS.3,7

Clinical features of SJS usually occur 1 to 3 weeks after the drug or infectious exposure. Patients present with mucosal erosions, skin lesions, and, occasionally, constitutional symptoms. Mucosal erosions typically occur at 2 or more sites such as oral, ocular, or genitourinary. Proximal target lesions followed by skin detachment are the dominant clinical findings.7 Typical target lesions have 3 rings (a bright-pink or red inner ring, a lighter-pink outer ring, and a darker-pink outermost ring) and characteristically occur symmetrically on the extensor surfaces of the extremities and the gluteal area; the trunk and flexor surfaces are less likely to be involved.3,7 Small blisters or purpuric macules may occur, and the skin lesions are frequently pruritic and painful.9 Respiratory or gastrointestinal lesions occur in 10% to 30% of cases. Painful erosions may extend into the esophagus and cause difficulty with swallowing. Ocular complications can include keratitis and corneal scarring.

The adolescents described in this case series had unusual presentations of SJS. Although they all had severe oral mucositis, they lacked typical skin manifestations. The patient in the first case initially had a rash, but it never progressed to blisters or target lesions and quickly resolved. In this case, other etiologies of illness were initially considered, including streptococcal toxic shock syndrome and atypical Kawasaki disease. However, the patient’s symptoms persisted despite appropriate antibiotic therapy for streptococcal disease, and he did not meet the criteria for diagnosis of Kawasaki disease. In addition, the finding of bilateral infiltrates on his chest radiograph was suggestive of atypical bacterial pneumonia as the cause of his illness.

A retrospective review of cases of SJS at Children’s Hospital in Bordeaux, France, demonstrated that M pneumoniae infection was identified in 5 of 17 cases of SJS and strongly suspected in another 5 cases.5 There have also been sporadic reports in the literature of cases of severe mucositis without accompanying skin lesions associated with M pneumoniae infection.3,4 In 2005, Letko et al.7 published a comprehensive review of the literature on SJS in which they demonstrated that, historically, there has been little agreement on diagnostic criteria; however, a majority of the case reports included a description of target lesions. In addition, a number of authors consider SJS to fall within a spectrum of diseases that affect the skin and mucous membranes, including erythema multiforme minor, erythema multiforme major (a term sometimes used interchangeably with SJS), and toxic epidermal necrolysis.7

Mycoplasmas are among the smallest, free-living microorganisms. After an incubation period of 1 to 4 weeks, infection typically presents with cough, coryza, fever, and malaise, which may progress to pneumonia in ~10% of patients.10 The rate of M pneumoniae pneumonia has been shown to be highest in school-aged children between 5 and 14 years of age.10 Extrapulmonary manifestations of M pneumoniae infection are unusual and include mucocutaneous eruptions, nervous system disease, hemolytic anemia, and arthritis.11

Mycoplasmas lack a cell wall and are slow-growing in culture, requiring 10 to 14 days of incubation, a characteristic that has made rapid diagnosis challenging.10 The association of serum cold hemagglutinin titer of ≥1:32 in ~50% to 75% of patients with M pneumoniae pneumonia has been used to assist with diagnosis.11,12 The test is more specific when serologic titers are higher.
In addition, a variety of other respiratory tract pathogens can also cause a modest increase in cold hemagglutinin titers.\(^1\) Immunofluorescence and enzyme immunoassay tests detect immunoglobulin M and G antibodies specific for \textit{M pneumoniae}.\(^10\) After infection, immunoglobulin M antibodies can remain elevated for a period of weeks to months. Consequently, although they can confirm recent infection, they may not signify current infection.\(^12\)

PCR is a rapid, specific, and sensitive method of diagnosis of \textit{M pneumoniae} infections.\(^5,6\) Although previously used mainly in research settings, PCR for \textit{M pneumoniae} detection is now more widely available. The multiplex PCR assay used by our laboratory is specific and considerably more rapid than culture or serology. The assay can detect a single copy of \textit{M pneumoniae} DNA in a PCR. Recent studies have validated the PCR technique, and results compare favorably to culture and serologic testing.\(^13,14\) Sensitivity and specificity of PCR-based assays have been shown to range from 78% to 100%.\(^10,15\) The sensitivity of serology on a single specimen is much less, ranging from 50% to 66%.\(^16\) Although the sensitivity of serology improves when paired sera samples are examined, this lengthens the time to confirmed diagnosis considerably.

**CONCLUSIONS**

Mucositis, with or without accompanying skin lesions, is a recognized extrapulmonary manifestation of infection with \textit{M pneumoniae}. Accordingly, cases of severe mucositis, within the context of respiratory illness, should prompt testing for \textit{M pneumoniae} as a potential causative agent. The use of real-time and multiplex PCR enables a rapid diagnosis, reducing the need for additional laboratory testing, and facilitates early initiation of treatment, thereby potentially decreasing the duration of illness in these patients.

**REFERENCES**

Clinical Mimics of Infant Botulism

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

Since 1992, Human Botulism Immune Globulin has been provided by the California Department of Health Services to infants with probable infant botulism, the intestinal toxemia form of human botulism. Human Botulism Immune Globulin became available in California in 1992–1997 within a randomized, controlled, double-blinded, pivotal clinical trial and subsequently became available nationwide in 1998–2003 in an open-label study until its licensure in October 2003 as BabyBIG. Thereafter, Human Botulism Immune Globulin remained available nationwide as an approved orphan-drug product. To achieve prompt neutralization of circulating botulinum toxin, the decision to treat with Human Botulism Immune Globulin has been based on clinical criteria that include a consistent history and physical findings of bulbar palsies, hypotonia, and weakness. After licensure, the charts of patients who did not have laboratory-confirmed infant botulism were reviewed to identify their actual diagnoses. The ~5% of 681 patients treated with Human Botulism Immune Globulin who did not have infant botulism fell into 5 categories: spinal muscular atrophy, metabolic disorders, other infectious diseases, miscellaneous, and probable infant botulism lacking laboratory confirmation.

I
NFANT BOTULISM IS the infectious intestinal toxemia form of human botulism that results when ingested spores of Clostridium botulinum (or, rarely, neurotoxigenic Clostridium butyricum or Clostridium baratii) colonize the large intestine and then produce botulinum toxin in its lumen. Botulinum toxin blocks the release of acetylcholine at the neuromuscular junction and other peripheral cholinergic synapses, which results in constipation, lethargy, poor feeding, generalized weakness, decreased head control, hypotonia, diminished deep tendon reflexes, hypoventilation, and cranial nerve palsies. Symmetrical bulbar nerve palsies (eg, ptosis, sluggish pupillary response to light, ophthalmoplegia, poor suck, decreased gag reflex, difficulty swallowing, expressionless face) are cardinal features of infant botulism that help distinguish it from other causes of subacute- to acute-onset generalized weakness.

After an ~15-year development period that included 2 clinical trials, the US Food and Drug Administration licensed Botulism Immune Globulin Intravenous (Human) (BIG-IV) as BabyBIG to the California Department of Health Services (CDHS) in October 2003. Because BIG-IV is the only specific treatment for infant botulism, it became the standard of care for infants who presented with the clinical picture of infant botulism. Treatment with BIG-IV should be given as early as possible in the illness to neutralize botulinum toxemia and thereby shorten hospital stay maximally. Approximately 5% of the 681 patients since 1992 who were treated with BIG-IV (or placebo during the randomized, controlled clinical trial) were found not to have infant botulism, and in most of these cases an alternative diagnosis was established. The tabulation of those conditions that so closely mimicked infant botulism that the attending physicians and the consulting
physicians at the Infant Botulism Treatment and Prevention Program concurred that the patient should be treated with BIG-IV may serve as a bedside aid in the correct diagnosis of suspected infant botulism cases.

**METHODS**
Assessment of eligibility for treatment with BIG-IV differed between the 1992–1997 California randomized, controlled trial (RCT), the 1998–2003 nationwide open-label study (OLS), and the subsequent nationwide licensed distribution of BIG-IV. In the RCT, after notification of a possible case of infant botulism, 1 of 2 physician-investigators from CDHS traveled to the bedside to evaluate the patient together with the attending physician; the decision to treat was made jointly, with informed consent obtained from the parents. In the OLS and after licensure, 1 of the CDHS physician-investigators was contacted by telephone by the attending physician, who communicated the medical history, clinical findings, and standard laboratory testing results. If the CHDS physician-investigator concluded that the clinical findings made infant botulism the likely diagnosis, he arranged for shipment of BIG-IV to the hospital, where the attending physician obtained informed consent and administered BIG-IV to the patient. In both the RCT and the OLS and after licensure, definitive laboratory testing of stool or enema for the presence of *C botulinum* toxin and organisms was expected to be performed after treatment with BIG-IV, with due recognition that testing might take several days to be completed.

We collected medical charts of all suspected infant botulism cases treated with BIG-IV (or placebo) since use of it began in 1992 for which the diagnosis of infant botulism was not laboratory confirmed. We defined the actual diagnoses of these cases as “clinical mimics” of infant botulism and reviewed the medical charts to identify them.

**RESULTS**
Between February 24, 1992, and June 30, 2005, a total of 681 infants were treated with BIG-IV or placebo. Thirty-two patients (4.7%) were identified who did not have laboratory-confirmed infant botulism. These 32 patients could be divided into 5 diagnostic categories: spinal muscular atrophy (SMA) type I (*n* = 5); metabolic disorders (*n* = 8); infectious diseases (*n* = 3); miscellaneous (*n* = 7); and probable infant botulism (*n* = 9) (Table 1).

The 5 patients with SMA type I ranged in age from 1½ to 3 months. Four (80%) of the 5 patients with SMA were treated with BIG-IV during the RCT, and 7 (88%) of the 8 patients with metabolic disorders were treated with BIG-IV during the OLS or licensed-distribution periods. Four of the patients with metabolic disorders had MRI of the brain. The patient with glutaric aciduria type I and 2 patients with unknown types of mitochondrial disorders had the similar MRI finding of bilateral basal ganglia infarcts. The patient with Leigh’s syndrome had abnormal computed tomography of the head results that showed decreased attenuation in the basal ganglia consistent with infarcts. The patient with maple syrup urine disease had normal cranial MRI results.

Three patients had an infectious etiology identified. One patient with enterovirus encephalitis had normal cerebrospinal fluid (CSF) at the time of referral; the actual diagnosis was later established by a positive CSF enterovirus polymerase chain reaction test. A second patient who was eventually diagnosed as having respiratory syncytial virus (RSV) bronchiolitis did not have symptoms typical of RSV present at admission. A third patient was thought to have a nonspecific viral syndrome because neurologic status returned to normal within 5 days of admission and laboratory study results were normal.

Seven patients had a variety of final diagnoses. The patient with the Miller Fisher variant of Guillain-Barré syndrome was 365 days old at onset and initially had normal CSF. However, subsequent examination of CSF found a significantly elevated protein concentration (100 mg/dL), and electromyography (EMG) identified a demyelinating neuropathy. At referral, the patient with stage III neuroblastoma had normal laboratory study results and a pulmonary infiltrate.

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**TABLE 1 Clinical Mimics of Infant Botulism That Resulted in Treatment With BIG-IV**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable infant botulisma</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Glutaric aciduria type I</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Leigh’s syndrome</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Succinic semialdehyde dehydrogenase deficiency</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Mitochondrial disorder (n = 4)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>SMA type I</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Enterovirus encephalitis</td>
<td>3 (9)</td>
</tr>
<tr>
<td>RSV bronchiolitis</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Central demyelinating diseaseb</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Total</td>
<td>32 (100)</td>
</tr>
</tbody>
</table>

a Laboratory diagnosis was not established because of difficulty in obtaining or correctly submitting stool or enema specimens.

b The condition was considered idiopathic.
and the infiltrate persisted despite antibiotic therapy. A computed tomography scan found a large mass that extended from the right hilum to the thoracic outlet, which biopsy identified as neuroblastoma. However, antibody associated with either Lambert-Eaton or other paraneoplastic neuromuscular syndromes was not detected in the patient’s serum.

Nine patients had a final diagnosis of “probable infant botulism” because the laboratory studies needed to establish the diagnosis were either not requested or not performed. EMG of 5 of these patients identified a presynaptic transmission defect at the neuromuscular junction consistent with infant botulism.

**DISCUSSION**

SMA type I and metabolic disorders are the 2 most common diagnoses that mimic infant botulism. Patients with SMA type I have a longer history of generalized weakness than do patients with infant botulism, in whom the weakness is subacute to acute in onset. Also, patients with infant botulism typically have ophthalmoplegia and decreased anal sphincter tone, whereas SMA type I typically spares the extraocular muscles and sphincters. Metabolic disorders are best diagnosed by the appropriate laboratory studies.

Although cranial nerve palsies occur in both infant botulism and in the Miller Fisher variant of Guillain-Barré syndrome, these diagnoses may be distinguished by CSF analysis, nerve conduction studies, and EMG. The age of the patient may also aid in differentiation, in that 95% of laboratory-confirmed cases of infant botulism occur in patients who are <6 months old, whereas Guillain-Barré syndrome typically occurs in older children. In infant botulism, EMG may reveal a characteristic but not diagnostic pattern of brief-duration, small-amplitude, overly abundant motor-unit action potentials termed BSAPs (shown as Figure 1 in ref 7). However, absence of BSAPs does not exclude the diagnosis of infant botulism. Paraneoplastic syndromes with neuromuscular junction involvement may also mimic infant botulism. The diagnosis of infant botulism could not be established for 9 (28%) patients because of the failure to obtain or correctly submit a stool or enema specimen for testing.

A careful history and neurologic examination remain the best bases for distinguishing infant botulism from its clinical mimics. The presence of multiple cranial nerve palsies is an essential part of identifying infant botulism, and in this context, a feeble cry, poor suck, weak gag, difficulty swallowing (drooling), and expressionless face should be viewed to be bulbar in origin. Posis may not be evident unless the patient is held in a sitting position (often requiring head support because of neck weakness), while disconjugate gaze and fatigability of the pupillary light reflex may require sustained examination (see Table 153–2 in ref 1). Fatigability with repetitive muscle activity (eg, feeding, breathing, pupillary constriction) is the clinical hallmark of botulism.

The conditions listed in Table 1 constitute a working list of alternative diagnoses for use with patients who present with signs and symptoms suggestive of infant botulism but then lack laboratory confirmation of diagnosis after adequate collection and submission of stool or enema specimens. Consideration of these “clinical mimic” conditions at admission of the hypotonic infant with bulbar palsies may result in earlier correct diagnosis and in appropriately targeted use of BIG-IV.

**CONCLUSION**

Treatment with BIG-IV should be initiated promptly (and not delayed for laboratory confirmation of diagnosis) because prompt treatment ends further progression of the illness. BIG-IV immediately neutralizes all circulating botulinum toxin and remains present in neutralizing amounts in the circulation for ~6 months, thereby allowing regeneration of nerve endings to proceed. Early treatment with BIG-IV within 0 to 3 days of admission shortens hospital stay by ~1 week more than does later treatment at 4 to 7 days and also significantly reduces the associated costs of hospitalization.

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Family-Centered Bedside Rounds: A New Approach to Patient Care and Teaching

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ABSTRACT

The importance of patient-centered care and the role of families in decision-making are becoming more recognized. Starting with a single acute care unit, a multidisciplinary improvement team at Cincinnati Children’s Hospital developed and implemented a new process that allows families to decide if they want to be part of attending-physician rounds. Family involvement seems to improve communication, shares decision-making, and offers new learning for residents and students. Despite initial concerns of staff members, family-centered rounds has been widely accepted and spread throughout the institution. Here we report our experiences as a potential model to improve family-centered care and teaching.

The commonly accepted view of patients as passive recipients of health care is changing. The Institute of Medicine highlighted the importance of patient-centered care in Crossing the Quality Chasm: A New Health System for the 21st Century. In a joint policy statement, the American Academy of Pediatrics and the Institute for Family-Centered Care noted that children’s and family’s perspectives are important in clinical decision-making and encouraged hospitals to make conducting attending-physician rounds in patients’ rooms, with the family present, standard practice. They further noted that the process would make a lasting impression on students and housestaff. The Accreditation Council for Graduate Medical Education has declared that residents must be able to provide family-centered patient care that is culturally effective, developmentally and age appropriate, compassionate, and effective as part of their core competencies.

However, many institutions are concerned that including patients and families in rounds will significantly increase the time spent rounding and disrupt the usual workflow. There are also concerns that rounds may not be the best avenue to convey information and solicit family input in decision-making. Families, unfamiliar with the process, may be too intimidated by the large group or their own lack of medical training, to actively participate. Conversely, there is a fear that the presence of parents might inhibit open discussion among staff. Residents and medical students may fear appearing ignorant in front of patients and families.

Until 2002, our institution conducted traditional attending rounds, usually in conference rooms or hallways. Families were either not included or only briefly involved. Support staff usually carried on their work while physicians conducted rounds. Physicians communicated with staff after rounds via written orders, telephone calls, conversations, or notes in the patient’s charts. Attending physicians communicated separately with families after rounds. Questions and concerns regarding the plan developed on rounds were dealt with later in the day and often involved the nurse paging a physician. Families were not witnesses to the decision-making process and rarely were active participants.

Teaching on rounds focused on developing a care plan and medical information relevant to each patient’s condition. There were few opportunities for faculty or attending physicians to witness or model patient interaction. Patients had little opportunity to make clari-

Key Words: family-centered, teaching rounds, discharge delay

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fications or present their point of view while the care plan was developed. This marked discrepancy between recommendations in the American Academy of Pediatrics/Institute for Family-Centered Care policy statement2 and our own practice led us to test and then implement a new type of attending teaching rounds.

CASE REPORT
Cincinnati Children’s Hospital Medical Center is an academic teaching hospital with 475 registered beds and nearly 24,000 admissions per year. Approximately 300 residents and medical students receive general pediatric training. Faculty and staff hospitalists have a large teaching role. In 2001, Cincinnati Children’s Hospital Medical Center became involved in the Pursuing Perfection initiative,13 which is funded by the Robert Wood Johnson Foundation. As part of that project, a multidisciplinary team, including parents, was formed to redesign the care system for children with acute conditions, with a focus on family-centered and evidence-based outcomes.

The team used the “model for improvement” as a framework for developing and testing rapid changes.14 The model has 4 key elements: aim, measurement, ideas for change, and tests of change. The first 3 elements are exemplified by 3 key questions: (1) What are we trying to accomplish? (2) How will we know that a change is an improvement? (3) What changes can we make that will result in an improvement? The final element is a disciplined approach to rapid testing and learning from change called the plan-do-study-act cycle. Large-scale improvement projects can be broken down into manageable pieces and addressed through a series of small-scale plan-do-study-act cycles.

Family representatives on the team were the first to suggest involving parents in attending teaching rounds to improve communication between staff and families. The team started with small changes and learned from its experiences. Initially, 1 physician with 1 group of residents tried the new approach for 2 weeks. Families were interviewed daily regarding their experiences, and there was near-unanimous support for the effort. This was particularly true for families who had experience with the old rounding method. Nurses, particularly those with years of experience, immediately sensed the improved communication. Residents were initially reluctant to make the change, but after gaining experience and confidence over the 2-week test, they expressed greater support. The rounding process evolved on the basis of feedback from parents, housestaff, nurses, and attending physicians. Additional attending physicians adopted the method and, after just 1 year, family-centered teaching rounds were considered standard procedure on an entire general pediatric unit. Since then, this approach has spread and fundamentally changed the way we provide patient care and teach throughout the hospital.

COMPONENTS OF THE NEW ROUNDING PROCESS

- The family decides how rounds are conducted. At admission, staff members explain the rounding process and how families can participate. They may choose to have the team enter the room during rounds, or the family may come into the hallway. They also may choose not to participate but have physicians and nurses meet with them later in the day. Concerns about confidentiality are addressed, and the family’s preference is marked on a card that is posted outside the patient’s door. Approximately 85% of our families choose to be actively involved in rounds.
- The choice card also identifies whether the family wishes to be awakened for rounds. The intern or medical student responsible for the patient enters the room first to wake the family and reconfirm their wish to participate.
- Introduction is a key component to improving communication and making families feel they are truly partners in the care-giving process. How those introductions are handled is left up to each team. In general, if the team is small, all members are introduced. However, to save time and to keep from overwhelming families, if the team is large, only 4 or 5 key members are introduced. The team forms a circle that is inclusive of the family.
- Team efficiency is important to allow time for family involvement. Team members are assigned roles and complete their work during rounds, including orders, discharge summaries, home health care plans, and prescriptions.
- The intern or student assigned to the patient briefly clarifies the purpose of rounds and welcomes family involvement. Families have helped to identify phrases that promote participation, such as “I’m going to tell his story, but if there is anything you feel is inaccurate, please speak up” or “We are not speaking at you; we want to talk with you. We are the medical experts, but you are the experts on your child; together we can do a better job.” Students and residents are encouraged to begin with these phrases.
- The intern summarizes medical status and treatment options using both medical terminology and lay language. All test results and information are shared openly. Eye contact is made with both the team and family members. The family is then invited to participate in developing a plan for the day, including discharge goals. Family involvement in setting discharge goals decreases the likelihood of delay and confusion at discharge.
- Efficiency is further increased by the presence of nurses and other key ancillary staff who contribute valuable information regarding the patient’s condition.
in the last 24 hours and progress made toward meet-
ing discharge goals.

- Families are active participants in decisions made on rounds. By the time the team leaves, everyone is aware of and comfortable with the treatment plan. Therefore, orders can be conducted in a timely manner with less risk of confusion or change later in the day.

- Throughout rounds, the teaching attending witnesses the intern’s understanding of the patient’s condition and the family’s and staff’s level of comfort. For example, a look of concern could indicate a nurse’s discomfort with part of the care plan, or a tearful parent may be afraid of caring for a child at home. Although young learners may not yet know how to read these verbal and nonverbal cues and nuances, an experienced teaching attending can sense and immediately diffuse any concerns or communication complications.

- The teacher can also model appropriate behaviors so that residents and students learn how to engage fam-
ilies (asking questions, making eye contact, nodding, leaning forward), address any fears, anger, confusion, or misunderstanding, and develop their confidence and expertise.

- Senior residents and teaching attendants ask families for permission to conduct additional teaching in the room. Most parents welcome this additional teaching and find it very helpful. This is also an opportunity to involve parents in teaching, particularly regarding unusual conditions or experiences. These encounters with families can later serve as discussion and teaching points.

DISCUSSION

When considering family-centered rounds, 3 common concerns arise. The first is teaching. Our residents and students initially believed that teaching would be pushed aside if the rounding team focused on the family. Although not all teaching can occur with families, residents now believe that teaching is better and that they are learning in ways that were not possible in the conference room or lecture hall. Of course, teaching styles need to be adapted, and participants must be willing to observe and be observed during crucial patient interactions. Direct observation is a valuable tool in teaching communication skills and is required by the Accredita-
tion Council for Graduate Medical Education outcomes project. Participants must also be confident in their ability to deal with uncertainty. In our experience, physi-
cians who are particularly uncomfortable with uncer-
tainty are also uncomfortable with family-centered rounds.

The second concern is time. All staff members worried that family-centered rounds would take more time and be difficult to carry out in an already-busy day. We have found that family-centered rounds take ~20% longer than traditional rounds. However, all participants believe that their time is used more efficiently and that family-centered rounds saves time later in the day. Nurses have described a marked decrease in the need to page residents to clarify orders. They also report that families are less likely to question the care plan. Of great significance is the improvement in discharge timeliness. Because of the focus on discharge goals, families are aware of the probable time for discharge and are more confident in the decision to go home, and staff are able to complete preparations. On units using family-cen-
tered rounds, we have seen a significant increase in the percentage of children discharged during the first shift (7 AM to 3 PM), which allows the entire hospital staff to prepare for and concentrate on new admissions later in the day (Fig 1).

The third concern is confidentiality. We now have a particular advantage at our hospital in that almost all rooms are private, but the change began on a unit with shared rooms. It is crucial to explain confidentiality is-
issues to the family and be sure they understand that conversations may be overheard. Aware of risks, families choose how to be involved. By respecting their choice, concerns over confidentiality are allayed. Concerns over spreading infection and patient fear and modesty should also be addressed by allowing families to choose how to be involved.

As we have discussed this new method with visitors from other hospitals and at national meetings and other institutions, we have met with healthy skepticism. This improvement project was not conducted as a controlled study, and outcomes and processes were not systemati-
cally evaluated. By reporting our experience, we hope other institutions will conduct their own studies to evaluate family involvement in rounds.

Meanwhile, at our institution, the experience has been dramatic. We believe it is very significant that ~85% of families request involvement in rounds when given the option. All our pediatric hospitalists have enthu-
usiastically adopted this rounding method, and it is now being adapted for children with complex and chronic conditions, with the focus at rounds expanded to include discussion of both daily goals and discharge goals. It is also being tailored for use in our outpatient clinics. This spread has been assisted by the development of a training program with video vignettes to address the most common questions and concerns of attending physicians (information is available at www.cincinnatichildrens. org/family-centered-rounds).
CONCLUSIONS
As an academic institution, we are committed to teaching residents and medical students the core attitudes of respect and interest in the concerns and opinions of patients and parents and the relationship skills that foster partnerships with them. We believe that these techniques cannot be adequately taught by using just a lecture or discussion format. We have noticed that any reluctance to family-centered rounds among residents has all but disappeared. Many residents now praise the process when promoting their program to future residents.

We look forward to other institutions building on our initial experience. In addition to documenting improvements in efficiency and satisfaction, we believe that family-centered rounds increases the potential for more significant improvement for patient safety and improved clinical outcomes.

ACKNOWLEDGMENT
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Enhancing the Diversity of the Pediatrician Workforce

Committee on Pediatric Workforce

ABSTRACT
This policy statement describes the key issues related to diversity within the pediatrician and health care workforce to identify barriers to enhancing diversity and offer policy recommendations to overcome these barriers in the future. The statement addresses topics such as health disparities, affirmative action, recent policy developments and reports on workforce diversity, and research on patient and provider diversity. It also broadens the discussion of diversity beyond the traditional realms of race and ethnicity to include cultural attributes that may have an effect on the quality of health care. Although workforce diversity is related to the provision of culturally effective pediatric care, it is a discrete issue that merits separate discussion and policy formulation. At the heart of this policy-driven action are multiorganizational and multispecialty collaborations designed to address substantive educational, financial, organizational, and other barriers to improved workforce diversity.

A LONG-STANDING COMMITMENT TO WORKFORCE DIVERSITY
The American Academy of Pediatrics (AAP) has a distinguished history of promoting diversity within the pediatrician workforce. Of particular note is the Report of the AAP Task Force on Minority Children’s Access to Pediatric Care,1 which promulgated 66 recommendations covering a wide range of topics, from the health status of minority children to barriers to accessing pediatric care and workforce needs. Racial and ethnic diversity was also a major issue addressed by the report of the Task Force on the Future of Pediatric Education II (FOPE II),2 which called for increases in the percentage of underrepresented minority pediatricians in practice and academic medicine to meet the needs of the ever-growing population of minority children. Recognizing the need for a more comprehensive policy to address the interrelated topics of patient and workforce diversity, the AAP also published 2 companion policy statements: “Ensuring Culturally Effective Pediatric Care: Implications for Education and Health Policy”3 (revision of a previous policy statement4) and “Enhancing the Racial and Ethnic Diversity of the Pediatric Workforce.”5 Over time, however, the focus of public policy discussions about patient and provider diversity has expanded beyond the traditional domains of race and ethnicity to include other attributes such as language, religion, health literacy, and sexual orientation.6 Unfortunately, few data on these other attributes exist, which limits the evidence that can be applied to policy analyses, such as this one, that examine the relationship between workforce diversity and the quality of health care services.

AAP policy statements and task force reports have been used to articulate the

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Key Words
diversity, race, ethnicity, culturally effective care, workforce

Abbreviations
AAP—American Academy of Pediatrics
COGME—Council on Graduate Medical Education
AAMC—Association of American Medical Colleges
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support of the AAP for increasing workforce diversity to a wide range of stakeholders in the health care community. This community includes, but is not limited to, legislators, policy makers, medical and specialty organizations, educators, payers, and patients. At the national level, the AAP has worked with federal bodies, such as the Council on Graduate Medical Education (COGME) and the Advisory Committee on Training in Primary Care Medicine and Dentistry, as well as national medical and specialty societies, including the American Medical Association, the Association of American Medical Colleges (AAMC), the American Academy of Family Physicians, the National Hispanic Medical Association, and the National Medical Association. AAP policy has been the basis of testimony, official communiqués, and collaboration with these and other national organizations, AAP state chapters, state legislators, and state medical societies. The AAP particularly values its work on the Health Professionals for Diversity Coalition, the AAMC revision of its definition of underrepresented minorities, and the amicus brief in support of the University of Michigan’s affirmative-action policies.

THE CASE FOR WORKFORCE DIVERSITY

Recent literature in support of the Supreme Court decisions related to the University of Michigan’s affirmative-action policies have strongly stated the case for diversity at all levels of medical education. A more diverse faculty and student body is viewed as an indispensable component of quality medical education. It will also increase the cultural exposure of all faculty and students, which will help to dispel stereotypes and improve cultural competence by virtue of everyday interactions. A more diverse workforce will likely lead to a more diverse medical research agenda for improving health and the delivery of health care services among racial, ethnic, and cultural minority patients. Creating such a workforce, it is posited, begins with the diversity of those admitted to MD and PhD educational programs. Indeed, in a modern multicultural society, promoting diversity within the medical profession to better reflect the diversity of the patient population while maintaining the high quality of the health care workforce is in keeping with the societal and the amicus brief in support of the University of Michigan’s affirmative-action policies.

THE CASE FOR A BROAD DEFINITION OF DIVERSITY

Since the publication of the previous edition of this policy statement in 2000, the discussion of patient diversity by the medical community has increasingly expanded beyond the traditional attributes of race and ethnicity to include cultural characteristics such as language, national origin, religion, sexual orientation, and physical disability. A broader and more inclusive definition of patient diversity, consequently, requires an expansion of diversity beyond race and ethnicity within the pediatrician workforce as well. The AAP believes that it is important for the organization to take a leading role in applying this expanded definition to the health care workforce to influence future policy deliberations on workforce diversity.

The arguments in the previous section that linked enhanced workforce diversity to higher patient satisfaction and trust and increased care to racial and ethnic minority patients seem to pertain also to the case of cultural minority patients. Although research is less robust in this area, data suggest that cultural minority patients are likely to have better health outcomes when cared for by physicians and health care providers who share their cultural attributes. For example, the medical
literature has shown that problems in communication and trust arising from differences between the physician’s and the patient’s language, religious norms, and cultural understandings of health and medical treatment can have an adverse effect on patient-care outcomes.12-14 These data highlight the importance of expanding data systems to collect workforce data for other cultural minority groups to track minority-recruitment efforts, workforce supply, and the effect of enhanced workforce diversity on patient-care outcomes for these groups.

Despite the dearth of data related to cultural minorities, data on racial and ethnic minorities clearly indicate that the number of individuals from these minority groups entering the physician workforce continues to be small despite the efforts of medical associations and others committed to enhancing the diversity of the physician workforce. According to the American Medical Association Masterfile in 2003, only 12.3% of physicians whose race or ethnicity is known belong to an underrepresented racial or ethnic minority group (black, American Indian, and Hispanic).15 This percentage is approximately half the rate projected by the US Census Bureau for the general population in 2005, which is currently 25.8% for these groups and is projected to grow considerably in the years ahead.16 Therefore, even minority physicians who share some personal attributes with their patients in underserved areas will likely care for an increasingly diverse patient population, including members of other minority groups.17

RECENT POLICY DEVELOPMENTS RELATED TO HEALTH CARE WORKFORCE DIVERSITY

In recent years, affirmative-action policies in the United States, especially in higher education, have experienced legal and judicial threats. Indeed, research has demonstrated that the reversal of affirmative-action policies in California, Texas, Mississippi, and Louisiana led to a decrease in minority medical school enrollment in those states.18 The adverse repercussions of regressive affirmative-action policy on minority physician supply received attention in the mid-1990s as part of the landmark cases of Grutter v Bollinger et al (1997) and Gratz et al v Bollinger et al (1995). The US Supreme Court ruled on June 23, 2003, that the University of Michigan’s affirmative-action admissions policies for its law school and undergraduate school were permissible, as had been argued in the amicus brief issued by the AAMC and supported by the AAP. The court argued in its opinion that the benefits resulting from a diverse student body may constitute a compelling interest to justify admissions policies that are race and ethnicity conscious. The scope of the ruling was clearly understood to apply to medical schools and other public and private institutions of higher learning that receive federal funds.19

Proponents of affirmative action and workforce diversity heralded the Supreme Court’s judgment in the 2 University of Michigan cases as an important step forward. Enhancing the diversity of the health care workforce, however, continues to be a formidable challenge, despite this legal victory and increased attention by the medical community and policy makers. Indeed, concerns about the difficulty of recruiting underrepresented minority students into medicine have generated a number of recent policy reports and initiatives that merit brief discussion. In 2004, the COGME conducted an evaluation of health care workforce diversity20 to determine what progress had occurred since the publication of its twelfth report, *Minorities in Medicine,*21 in 1998. The COGME concluded that continued low rates of high school completion and failure to enroll in and graduate from college are the most significant barriers to the entry of underrepresented minority students into medicine. Among its many recommendations, the COGME report focused on addressing barriers related to low family income of underrepresented minority students and lack of success in early education.20

Many of the COGME’s concerns were also shared by the Institute of Medicine, which issued its own report in 2004 on workforce diversity, *In the Nation’s Compelling Interest: Ensuring Diversity in the Health Care Workforce.* Unlike the COGME report, which identified problems in early education as the key barrier to workforce diversity, the Institute of Medicine report emphasized the importance of making changes within health-profession–education programs and institutions to improve diversity. These changes include incorporating the concept of diversity into institutional accreditation criteria, recruitment of minority faculty for admissions committees, faculty-development programming, research and data collection, and outcomes evaluation.22

The Sullivan Commission on Diversity in the Health-care Workforce, named for former US Secretary of Health and Human Services Louis W. Sullivan, MD, was a “blue-ribbon” panel of leaders in health, business, higher education, law, and other fields. The commission held regional public hearings, commissioned studies, and compiled a landmark report in 2004. Their report, *Missing Persons: Minorities in the Health Professions*, made policy recommendations to bring about systemic change that would address the scarcity of minorities in the health professions. The Sullivan Commission identified 3 major principles that are essential to achieving greater diversity: (1) the culture of health-professions schools must change in response to changing demographics; (2) new and nontraditional paths to the health professions should be explored; (3) and commitments to diversity must be at the highest levels. Expanding on the third principle, the report stressed the need for accountability and stated that “increasing diversity and cultural competency requires leadership, vision, political will, and a clear institutional mandate.”23
ACHIEVING WORKFORCE DIVERSITY: BARRIERS AND OPPORTUNITIES

These reports, as well as many other policy statements, have several features in common that have informed the development of this AAP policy statement. First is the need to pursue active recruitment of minority candidates for health-professions—education programs. To increase the small number of minority individuals entering pediatrics without a negative effect on the number entering other specialties, we must first increase the numbers of minority individuals entering medical school. Social, educational, financial, and other barriers act as disincentives to minority students who might otherwise be interested in careers in the health professions. As the Sullivan Commission observed:

“Even talented minority students who do succeed at primary, secondary, and collegiate levels, and who are committed to pursuing a career in one of the health professions, often find it difficult to gain admission to a health professions school. The barriers they encounter include an over-reliance on standardized testing in the admissions process, unsupportive institutional cultures, insufficient funding sources, and leadership without a demonstrated commitment to diversity.”

Another approach to increasing the recruitment of minority students into the health professions is to focus on reaching out to individuals in earlier educational stages, such as elementary school and high school. To maximize the effectiveness of these programs, appropriate support structures for these individuals within their communities, schools, postsecondary institutions, health care organizations, medical societies, and other entities need to be established. These support structures include financial incentives, mentoring and shadowing programs, adequate staffing for diversity programs, and educational and other initiatives related to cultural effectiveness and diversity.

A focus of many reports has been the expansion of financial incentives to encourage underrepresented minority students to enter medical training. These incentives, including loan forgiveness/repayment and tuition reimbursement, will help to address many of the financial barriers such as low family income and educational debt. These reports also articulate the importance of minority faculty serving as mentors to minority students, serving on admissions committees, overseeing diversity initiatives, and serving in leadership positions at all levels. To support all of these activities, there must be a commitment to increasing diversity at the highest organizational and institutional levels.

Finally, sponsors of diversity initiatives must likewise be able to track their progress in reaching specific targets and goals through research and data-driven outcome measures. It is difficult to improve what we cannot measure. Limited data on cultural minorities in medicine hamper the ability of the profession to evaluate the current status of diversity, implement activities to enhance it, and measure the outcomes of these activities. More research on and better tracking of attributes other than race and ethnicity must be conducted to measure progress in improving diversity within medicine and pediatrics.

CONCLUSIONS

The medical community has made very little progress in diversifying its workforce, a fact that serves as the impetus for this policy statement’s focused recommendations on process, programmatic, and outcomes issues. Indeed, improving diversity within the pediatrician workforce will require proactive leadership from the medical community in a number of areas, including include recruitment, mentoring, education, organizational support systems, and financial incentives. Success will also depend on the collaboration and cooperation of stakeholders, including the AAP, on initiatives designed to promote diversity within the health professions.

RECOMMENDATIONS

The AAP is committed to working in collaboration with federal bodies, policy makers, medical and specialty societies, national minority organizations, AAP chapters, and other groups to achieve greater diversity in medicine, the health professions, and especially the pediatrician workforce and to implement the goals articulated in this policy statement. The following recommendations serve as guiding principles in this endeavor.

1. Affirmative-action programs should be designed to promote the entry of racial and ethnic minority students into medical school and, ultimately, into pediatrics.

2. Recruitment activities should support and advocate for the full spectrum of racial, ethnic, and cultural diversity, including language, national origin, religion, sexual orientation, physical disability, and other attributes, within the medical profession. These activities should maintain the high quality of the health care workforce and encourage individuals from all backgrounds to enter careers in pediatrics.

3. Recruitment and academic preparation of underrepresented minority students should begin in elementary school and continue through the entire scope of their education and professional formation. Efforts to recruit minority students into medical school and pediatrics should be targeted appropriately to each educational level.

4. Financial incentives should be increased to minority students, including federal funding for diversity programs, Title VII funding, loan-forgiveness/repayment programs, and tuition reimbursement.

5. Enhancing diversity within the pediatrician workforce will require a commitment at the highest levels. To put this commitment into practice, educational
and health care institutions, medical organizations, and other relevant bodies should hire staff who are responsible solely for the implementation, management, and evaluation of diversity programs and who are accountable to the organizational leadership. These programs should be integrated into the organization’s operations and provided with an infrastructure adequate to implement and measure the effectiveness of their activities.

6. Institutional commitments to improve workforce diversity must include a formal program or mechanism to ensure that racial, ethnic, and cultural minority individuals rise to leadership positions at all levels. Approaches to increasing the diversity of the workforce in areas such as religion or sexual orientation are likely to require different approaches than those suggested for race.

7. Organizations with a stake in enhancing workforce diversity should implement systems to track data and information on race, ethnicity, and other cultural attributes.

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REFERENCES
Increasing Antiretroviral Drug Access for Children With HIV Infection

Committee on Pediatric AIDS, Section on International Child Health

ABSTRACT

Although there have been great gains in the prevention of pediatric HIV infection and provision of antiretroviral therapy for children with HIV infection in resource-rich countries, many barriers remain to scaling up HIV prevention and treatment for children in resource-limited areas of the world. Appropriate testing technologies need to be made more widely available to identify HIV infection in infants. Training of practitioners in the skills required to care for children with HIV infection is required to increase the number of children receiving antiretroviral therapy. Lack of availability of appropriate antiretroviral drug formulations that are easily usable and inexpensive is a major impediment to optimal care for children with HIV. The time and energy spent trying to develop liquid antiretroviral formulations might be better used in the manufacture of smaller pill sizes or crushable tablets, which are easier to dispense, transport, store, and administer to children.

INTRODUCTION

Background

It is estimated that 540,000 (420,000–670,000) children younger than 15 years were infected with HIV in 2006, mostly through mother-to-child transmission during pregnancy, delivery, or breastfeeding. Effective prevention services, including prenatal HIV testing, perinatal antiretroviral (ARV) prophylaxis, and safe alternatives to breastfeeding, are offered to fewer than 10% of pregnant women worldwide. Because of this global failure in prevention of HIV in children, by the end of 2005 an estimated 2.3 million (1.7–3.5 million) children were living with HIV infection globally; of these children, 2.0 million reside in sub-Saharan Africa.1

In the absence of treatment, most infants and children younger than 5 years with perinatally acquired HIV infection experience rapid progression to severe symptomatic disease and death, particularly in resource-limited countries. In a study of almost 3500 children enrolled in 7 perinatal trials in Africa, 35% of infected children had died by 1 year of age, and 53% had died by 2 years of age.2 In older African children with perinatally acquired HIV infection, most already suffer severe symptoms at the time of diagnosis, including profound growth retardation, and few live to reach adulthood.3

In sharp contrast, most children with perinatally acquired HIV infection in resource-rich countries are treated early with highly active ARV therapy (ART).4,5 Such ART, consisting of a combination of 3 or more potent ARV drugs, has been shown to dramatically modify the course of HIV infection in children, reducing...
mortality by fivefold or more and resulting in high survival rates (>90%) into adulthood.6–8

There are now intensive efforts by governments as well as multilateral and nongovernmental organizations to increase the number of people being treated with ART in resource-limited parts of the world (eg, the Global Fund, the US government–sponsored President’s Emergency Plan for AIDS Relief [PEPFAR], the World Health Organization [WHO]– and United Nations–led “3 by 5 Initiative” and Universal Access, the Clinton Foundation). It is estimated that children accounted for approximately 15% of the 5 million new HIV infections that occurred globally in 2005. The rapid progression to death disproportionately decreases the number of children living with HIV to approximately 6% of the total infected population. In 2005, it was estimated that at least 660 000 children were in need of ART.1 Of those, 90% live in sub-Saharan Africa. However, fewer than 5% of those who receive ART through the WHO 3 by 5 Initiative are children,1 and through March 2005 only an estimated 9500 children living in PEPFAR “focus countries” were treated under PEPFAR funding.

Initial WHO guidelines on ART in 2002 (updated in 2003) included only one chapter on ARV management for HIV-infected children.9 These guidelines have been updated as a pediatric-dedicated guideline document,10 driven by the recognition that children have lagged severely behind adults in receiving ART and that there are numerous barriers to delivery of ART to children in resource-limited settings.1,11

Providing all pregnant women with the most effective prevention services possible within local settings, including prenatal care, HIV diagnosis, ARV prophylaxis, and appropriate feeding options, is important for minimizing the risk of HIV infection for their child. For children infected with HIV, overcoming barriers that limit access to ART is critical, and the enormous scale of the problem makes this an issue of worldwide concern. These issues have been addressed by organizations that are actively involved in prevention of mother-to-child transmission of HIV, deliver ART to children worldwide, and train practitioners in the appropriate use of ART. These organizations include the WHO, the Baylor International Pediatric AIDS Initiative,12 the Elizabeth Glaser Pediatric AIDS Foundation (see “What About Us” at www.pedaids.org/News/Publications/Other/Childrens%20Battle%20to%20Access%20AI.aspx), Medecins Sans Frontieres, the Children’s HIV Association of UK and Ireland, the Forum for Collaborative HIV Research (www.hivforum.org/projects/Pediatric%20Formulations.htm), and the Clinton Foundation.

This statement lists these barriers and potential ways to overcome them and provides strong support for the critical and urgent need for provision of ART to HIV-infected children globally. Multiple pediatric organizations throughout the world have endorsed this statement (see “Organizations That Endorsed This Statement”).

Barrier 1: HIV Diagnostic Testing

Barriers to testing infants and children for HIV infection lead to a delay in diagnosis, and many infants and young children die before HIV is diagnosed or therapy can be given. Most pediatric HIV infections worldwide are attributable to mother-to-child transmission, with transmission occurring during pregnancy, around the time of birth, or through breastfeeding. Special tests are needed to diagnose HIV infection in infants and young children.

For adults and children older than 18 months, diagnosis of HIV infection is made by identification of antibodies to HIV in serum. However, because of the passive transplacental transfer of maternal HIV antibodies to the infant, newborn infants and children younger than 18 months will often test positive for the presence of anti-HIV antibodies even in the absence of true infection. Therefore, definitive diagnosis of HIV infection among infants and children younger than 18 months often requires the use of HIV-specific RNA or DNA nucleic acid tests to detect the virus itself,13 instead of the inexpensive and readily available serologic assays that can be used in adults and children older than 18 months. These HIV-specific RNA or DNA assays are more expensive and more complex to perform and are not available in many areas of the world in which the risk of HIV infection in infancy is highest. In such settings, HIV antibody testing may be used to exclude HIV infection in nonbreastfed infants older than 9 to 12 months, because loss of passively transmitted maternal HIV antibody (seroreversion) occurs by 12 months of age in 95% of HIV-exposed but uninfected infants.14

Appropriate use of these nucleic acid tests requires that exposure of the infant or young child to HIV be identified by determination of maternal HIV-infection status. Ideally, this would occur before or during pregnancy. However, communication of maternal HIV-infection status from the mother’s health care professional to the child’s health care professional often does not occur. The linking of infant exposure to maternal infection will require system changes to optimize infant testing. The lack of appropriate testing in the youngest age group with the highest risk of HIV-related death prevents ART from being used in the very infants and young children who could potentially benefit the most from treatment with ARV drugs. To allow for early identification of HIV-infected infants and young children younger than 18 months, appropriate virologic testing technologies must be made available in resource-limited settings.

Psychological barriers to testing infants also may lead to a delay in diagnosis. The social stigma of the diagnosis for mother and child15 and lack of treatment availability16 may keep women from testing themselves to learn their
own HIV status and testing their children for HIV. Community-wide fear of discussing HIV infection in children may compound the effect of this barrier.

**Barrier 2: Clinicians to Provide Care for Children With HIV**

Even where appropriate HIV diagnostic testing is available and drugs for treatment of HIV infection and prophylaxis for HIV-associated infections are accessible, lack of personnel trained in treatment of children with HIV severely limits access to treatment for large numbers of children. In many areas of the world, medical care is provided by physicians, nurses, and other clinicians with training and experience in the management of adult, but not pediatric, patients. Even the best programs for training health care professionals in the principles of HIV care for children offer little practical exposure to treating pediatric patients, which is time- and resource-intensive. Some programs send health care professionals from resource-rich areas of the world to resource-limited areas to train local practitioners (eg, Medecins Sans Frontieres, the Baylor Pediatric AIDS Corps, the Clinton Foundation, the Children’s HIV Association of UK and Ireland, UK/Kwazulu-Natal, the South Africa Collaboration). Additional efforts are needed to expand the availability of clinicians who are skilled in pediatric HIV care in resource-limited areas of the world, including integrating pediatric HIV care into existing comprehensive child health programs, expanding local networks of experienced health care professionals, and linking local clinicians with local, regional, and international experts.

**Barrier 3: ARV-Drug Formulations**

Assuming that appropriate HIV diagnostic testing is available and the necessary clinical personnel are available to provide care and treatment to HIV-infected children, appropriate formulations of ARV agents for children are also necessary. Lack of availability of appropriate ARV formulations that are inexpensive and easily usable is a major impediment to access to economical health care for children with HIV. As of September 2005, 21 ARV agents were approved by the US Food and Drug Administration (FDA) for use in HIV-infected adults and adolescents older than 16 to 18 years in the United States, but only 13 were approved for children and adolescents younger than 16 to 18 years, and only 11 have pediatric formulations available (see www.aidsinfo.nih.gov/other/cbrochure/english/13_en.pdf for a complete listing of HIV medications available in oral [liquid, capsule, and tablet] and intravenous formulations).

Because of the lack of appropriate pediatric formulations for certain drugs, caregivers of pediatric HIV patients may break or crush tablets meant for an adult patient in an attempt to produce child-size doses. With tablets that are asymmetric or not scored, this may lead to administration of erratic and inappropriate doses. Even with symmetrical tablets scored in the middle, the large quantity of medication in pills meant for adult use could mean that accurately breaking a scored tablet in half might not allow administration of a dosage small enough for an infant or young child, nor will it allow the incremental increases in doses required as the child grows. This problem can be addressed by developing products that contain smaller drug amounts per tablet or tablets that are scored to allow division accurately into halves or quarters. For regulatory purposes, bioequivalence studies may need to be performed by using the divided pills. Drug companies that are currently developing such drug formulations are to be commended.

Even when liquid formulations are available, special requirements and characteristics of such formulations may preclude their widespread use. For example, liquid drug formulations often require special storage such as refrigeration. The large volume of liquid formulations dispensed to allow ART to continue uninterrupted between clinic visits may make use of such drugs difficult in settings where transportation and storage are a challenge. For example, a 10-kg child who is being treated with standard doses of stavudine, lamivudine, and nevirapine, for whom a 3-month supply of drugs is dispensed at a clinic visit, would require 18 bottles of liquid that weigh almost half as much as the child (4.3 kg). For a rural family who may have walked a long distance to reach the clinical center, this is a significant issue. One commonly used ARV agent (zidovudine) requires high volumes of liquid and storage in brown glass bottles, which adds difficulty to treatment efforts.

Another problem with liquid formulations is the taste. When liquid formulations are developed, the taste is often so unpleasant that they may be practically unusable. Bad-tasting drugs are a well-recognized factor in treatment failures in children and lead practitioners to try many approaches to improve palatability of ARV drugs for children. When these attempts fail, some practitioners in resource-rich countries sometimes resort to insertion of gastrostomy tubes for medication administration.

Finally, liquid formulations may contain excipients (additives to maintain the drug in solution) that could be harmful to children. For example, the oral solution of amprenavir has a high content of propylene glycol and vitamin E and should not be used in children younger than 4 years; other liquid formulations may contain high amounts of alcohol. Liquid formulations may contain high concentrations of sugar, which can be detrimental to dental health—a particular problem for children with HIV, many of whom have severely decayed teeth.

Although pharmaceutical companies may spend time and resources attempting to formulate different ARV medications into liquid formulations, this approach may not enable widespread, global access to ART for children. Such time and resources might be better used in the development of formulations that are more acceptable to
children and families than some of the liquid formulations that are currently available. Specifically, in addition to production of appropriate liquid formulations, development of the following should be strongly considered: (1) smaller tablets; (2) tablets in which active drug is uniformly distributed and in shapes that can be easily and accurately divided into halves or quarters to administer smaller doses; (3) capsule sprinkle formulations that can be opened and mixed with food; or (4) tablets that can be crushed, dissolved in water, or chewed.

**Barrier 4: Appropriate Dosing of ARV Drugs in Children**

Even when appropriate formulations of ARV agents are available for children, pharmacokinetic data may be insufficient to appropriately guide drug dosing, especially in the youngest children, who metabolize these drugs differently, but also in adolescents, who may need higher doses than the “maximum adult dose” for adequate drug exposure. For many available drugs, dosage recommendations made by European or US guideline-writing groups on the basis of pharmacokinetic and clinical studies in children may differ from doses approved by the FDA and European Medicines Agency. The variability of drug exposure achieved by administration of “standard doses” of ARV drugs to children results in wide differences in plasma concentrations for many drugs, and some suggest the need for monitoring drug plasma concentrations in children to improve therapeutic outcomes; this is clearly not practical in resource-limited settings.

Completion of the appropriate studies of new ARV agents for use in children younger than 13 years lags behind those in adults. Although it may be appropriate to perform initial phase 1 or 2 studies in adults for initial determination of drug safety, pharmacokinetic studies in children need to follow along quickly to ensure that when the drugs are approved and available for use in adults, information is already available to define appropriate use in children. When new formulations are developed to allow once-daily dosing in adults, these formulations need to be appropriately tested in children, and regulatory approval needs to be gained through the FDA or European Medicines Agency to ensure that the advantages of once-daily dosing become more widely available to children and younger adolescents 13 to 18 years of age. This is particularly critical for life-threatening diseases such as HIV. Government regulations need to be tightened to enforce this approach to pediatric drug development and approval. International cooperation is crucial for successful completion of pharmacokinetic studies of ARV medications in children.

Earlier evaluation of ARV-drug safety and pharmacokinetics in children is needed so that when new ARV formulations are approved for use in adults, there are also preparations available for children; enough information about drug pharmacokinetics in children is available to allow rational dosing recommendations.

Appropriate dosing of drugs in pediatric patients requires measurement of weight and height and the complex calculation of body surface area. The requirement for different doses according to age, weight, and body surface area may put accurate prescribing and sale dispensing of ART and other drugs to pediatric patients beyond the reach of many of the front-line health care professionals who manage children with HIV. Dosing by weight band (recommending a specific dose for an all-inclusive range of weights, so that complex dosing calculations are not needed) has been recommended (see http://bayloraids.org/resources/DosingGuide.pdf), and studies of this approach have shown safety and efficacy for patients as well as acceptability to practitioners. Additional work on this approach is needed, including educating practitioners in its safety and effectiveness. Simplified dosing guides have been developed by the WHO and are readily available to clinicians who care for children and adolescents with HIV infection in resource-limited settings (see www.who.int/hiv/paediatric/en/index.html). These guides will increase the accuracy of dosing and dispensing ARV medications to these patients.

**Barrier 5: Other Issues Related to ARV Drugs for Infants, Children, and Adolescents With HIV Infection**

Many drugs are now being coformulated into tablets that contain 2 or 3 different ARV agents. These fixed-dose combinations (FDCs) are easier to prescribe and dispense, which minimizes errors. A lower pill burden may enhance patient adherence to therapy. Many FDCs have been developed as generic drugs and are offered in resource-constrained settings at reduced prices, thus improving availability of ARV medications for adults in many areas of the world.

FDCs for adults cannot just be cut or directly scaled down for children without appropriate pharmacokinetic studies, because the component medications may be required in different proportions for children than adults. Moreover, if the tablets are not formulated in equal layers, breaking the tablet may result in unequal doses being administered. FDCs are not currently available for children. Developing FDCs that are appropriately formulated for children should be a high priority for pharmaceutical companies. In addition, development of pediatric FDCs as generic drugs, which are more affordable, will enhance availability of FDCs for use in children as it has in adults. However, with generic formulations being manufactured in many countries, formulations need to be standardized to minimize prescribing errors that might occur if pills are supplied in nonstandard sizes.

Drug administration to children is more complex than it is to adults. Finding the best way to get liquids out of a bottle and measured appropriately while avoiding spillage and fully using all of the medication in a bottle is not necessarily straightforward. Syringes enhance dos-
ing accuracy, but without the use of special bottle tops, there may be wastage of liquid left in the bottom of a bottle or spillage when trying to get to the liquid at the bottom. Dividing or crushing tablets takes time and may diminish adherence if it is too difficult. These issues of ease and accuracy of drug administration need to be considered in the effort to increase access to ART for children.

SUMMARY AND RECOMMENDATIONS
To increase the availability and appropriateness of the use of ARV medications for children, the following are suggested ways of overcoming the aforementioned barriers.

Barrier 1: HIV Diagnostic Testing
- Enhance early identification of infants with HIV infection by making appropriate virologic testing technologies available throughout the world.
- Support political, religious, and other community leaders in their endorsement of the value of HIV testing linked to treatment and prevention. Cultural leaders need to demonstrate acceptance and community support of HIV-infected individuals.

Barrier 2: Clinicians to Provide Care for Children With HIV Infection
- Work to expand education of practitioners in the care of children with HIV and expand the number of such practitioners in resource-limited areas of the world.
- Integrate pediatric HIV care into comprehensive child health programs.
- Facilitate collaboration among experts to build capacity and expand expertise in areas of need.

Barrier 3: ARV-Drug Formulations
- Produce pill formulations in smaller milligram amounts and smaller pill sizes.
- Configure tablets so they can be divided easily. This requires that thought be given to production of scored tablets of symmetrical shape with uniform dispersal of active drugs within the tablet, which can be divided accurately and then easily crushed or dissolved.
- In addition to production of liquid formulations, consider production of other formulations for pediatric use, including tablets for dispersal, chewable tablets, or sprinkle formulations.
- Consider best-possible attributes of liquid formulations, including taste, color, consistency, and the highest concentration possible, but recognize that the extra time and expense needed to develop a liquid formulation may be at too high of a cost if it delays availability of medications that are appropriately formulated for infants and children.
- Expedite the availability of new drugs for use in children by requiring that pediatric formulations (liquids and/or appropriate tablet dosage forms and sizes) be available at the time of country approval of the use of the drug in adults unless there is a biological imperative not to develop the drug for use in children.
- Develop formulations and perform necessary studies to allow once-daily dosing in children at the same time as planned for adults.

Barrier 4: Appropriate Dosing of ARV Drugs in Children
- Require studies of drug pharmacokinetics in infants, children, and adolescents at the time that phase 2 and 3 studies are being conducted in adults so that when drugs are approved for use in adults, there is adequate information to allow their appropriate dosing in each of those specific age groups.
- Provide dosing tables for pediatric formulations, preferably weight-band-based tables, to increase the accuracy of dosing and dispensing ART to children.

Barrier 5: Other Issues Related to ARV Agents for HIV-Infected Infants, Children, and Adolescents
- Increase the availability of FDCs for pediatric use.
- Make pediatric formulations affordable in the manner that adult formulations have been made more affordable in many countries.
- Provide drug-administration devices and tools with medications (eg, syringes, bottle tops for use with syringes, medicine spoons, tablet cutters, tablet crushers) and devices to aid adherence, including pill boxes that can accommodate a month’s worth of pills or calendars with medications attached.

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British HIV Pharmacy Association (HIVPA)
British Pediatric Allergy, Immunity and Infection Group (United Kingdom)
Canadian Paediatric Society
Children’s HIV Association of the UK and Ireland (CHIVA)
Elizabeth Glaser Pediatric AIDS Foundation
Pediatric European Network for Treatment of AIDS (PENTA)
Pediatric Infectious Diseases Society
Indian Academy of Pediatrics
International Pediatric Association
Latin American Pediatric Association (ALAPE)
Pediatric Association of Jamaica
Pediatric Society of Thailand
Royal College of Pediatrics and Child Health (United Kingdom)
South African Pediatric Association (SAPA)
Southern African HIV Clinicians Society
Union of National African Pediatric Societies and Associations (UNAPSA)
World Health Organization (WHO)

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www.anecca.org
Baylor International Pediatric AIDS Initiative
http://bayloraids.org
Children’s HIV Association of the UK and Ireland (CHIVA)
www.bhiva.org/chiva
Clinton Foundation
www.clintonfoundation.org/cf-pgm-hs-ai-home.htm
Elizabeth Glaser Pediatric AIDS Foundation
www.pedaids.org
Forum for Collaborative HIV Research
www.hivforum.org
Global Fund to Fight AIDS, Tuberculosis and Malaria
www.theglobalfund.org/en
Medecins Sans Frontieres (MSF)
www.msf.org
Pediatric European Network for Treatment of AIDS
www.pentatrials.org
President’s Emergency Plan for AIDS Relief (PEPFAR)
United Nations: Joint United Nations Program on HIV/AIDS (UNAIDS)
www.unaids.org/en
World Health Organization (WHO)
www.who.int/en

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The following people were instrumental in arranging to have their respective organizations sign on in support of this document. The American Academy of Pediatrics appreciates their help with this endeavor and especially appreciates their ongoing efforts in care of children with HIV.
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REFERENCES


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exposed infants in Johannesburg, South Africa. Health Care Women Int. 2005;26:387–397


Prevention of Influenza: Recommendations for Influenza Immunization of Children, 2006–2007

Committee on Infectious Diseases

ABSTRACT

The purpose of this statement is to update recommendations for routine use of influenza vaccine in children for the 2006–2007 influenza season. The American Academy of Pediatrics recommends annual influenza immunization for (1) children with high-risk conditions who are 6 months and older; (2) healthy children 6 through 59 months of age; (3) household contacts and out-of-home caregivers of children with high-risk conditions and all healthy children younger than 5 years; and (4) health care professionals. Other children, adolescents, and adults can be immunized to decrease the impact of influenza as indicated in the Red Book: 2006 Report of the Committee on Infectious Diseases.

KEY POINTS RELEVANT FOR THE 2006–2007 INFLUENZA SEASON

1. The recommended age range of children for annual influenza immunization has been expanded to include all healthy children 6 through 59 months of age. Studies indicate that healthy children younger than 24 months of age and children of all ages with chronic heart and lung conditions are hospitalized for influenza infection and its complications at rates similar to those experienced by the elderly. This recommendation was extended to include healthy children 24 through 59 months of age, in part, on the basis of documentation of the significant morbidity in this age group, which results in additional office and emergency department visits and increased use of antimicrobial agents. This preschool-aged cohort is also an important potential source of transmission of influenza to household members and others in the community.

2. Household contacts and out-of-home caregivers of either high-risk children and adolescents or all healthy children younger than 5 years should also receive influenza vaccine each year. To reduce the risk of exposure to influenza, especially in infants younger than 6 months, who are too young to be immunized, it is essential that all contacts of high-risk children and all children younger than 5 years be immunized each year.

3. All high-risk children of any age, all healthy children 6 through 59 months of age, and all healthy 5- to 18-year-olds who are contacts of either high-risk persons or children younger than 5 years should be identified, and their parents should be informed that annual influenza immunization is due (Fig 1).
FIGURE 1
- Previously unimmunized children 6 months to younger than 9 years of age should receive 2 doses of influenza vaccine to maximize protection during the influenza season.

- Available data suggest that children younger than 9 years who did not receive the second dose of influenza vaccine in the initial year that influenza vaccine was given may not be adequately protected with only 1 dose the next influenza season. In this group, levels of protection can be suboptimal, especially if the antigenic specificity of the predominant strains has changed from the previous year. Thus, the American Academy of Pediatrics recommends that 2 doses be given to these children the following influenza season.* This recommendation applies only to the influenza season that follows the first year that a child younger than 9 years receives influenza vaccine.

4. Two of the 3 strains in the 2006–2007 influenza vaccine are different from last year’s vaccine. On the basis of global surveillance of influenza virus isolates, the influenza vaccine formulated for this season contains new components to match the strains expected to circulate this year.

5. Amantidine and rimantadine should not be prescribed during this influenza season. Widespread resistance to these antiviral medications now exists among influenza A viral strains. Therefore, the only antiviral therapies available for chemoprophylaxis or treatment of influenza in children this year are the neuraminidase inhibitors (ie, oseltamivir or zanamivir), which should be prescribed as recommended in the Red Book: 2006 Report of the Committee on Infectious Diseases.

6. Influenza vaccine should be offered throughout the influenza season, well into late winter and up to May 1, 2007. Because the influenza season peaks in January and February and often extends into March and beyond, administration of influenza vaccine later in the season can still offer protection to recipients during that specific influenza season. Therefore, if a child requires 2 doses of the influenza vaccine this year, the second dose can still be given later in the season. There may be more than 1 peak of activity during an influenza season, so later immunization may still help protect from a later peak caused by a different strain of the influenza virus that season (Fig 2).

7. Outreach and infrastructure to immunize more children should be developed. All health care professionals, influenza campaign organizers, and public health agencies should work together, especially if prioritization for administering influenza vaccine is indicated when vaccine supplies become delayed or limited.

**INFLUENZA VACCINES**

Tables 1 and 2 summarize information on the 2 types of influenza vaccine used to immunize both children and adults—trivalent inactivated influenza vaccine (TIV) and live-attenuated influenza vaccine (LAIV)—as well as the licensed age group of each available preparation. Both vaccines contain 3 virus strains (2 strains of influenza A [subtypes H1N1 and H3N2] and 1 strain of influenza B) that are selected annually on the basis of the viruses anticipated to be circulating during the upcoming influenza season. Children with serious allergies to chicken or egg proteins should not receive these vaccines, because both TIV and LAIV are developed with embryo-nated hen eggs. Inactivated influenza vaccine is preferred for close contacts of very severely immunosuppressed people.

TIV is an inactivated vaccine, administered intramuscularly, that contains killed viruses and, therefore, cannot produce signs or symptoms of influenza caused by active virus infection. The most common symptoms associated with TIV administration are soreness at the injection site and fever. Fever, usually occurring 6 to 24 hours after immunization, affects approximately 10% to 35% of children younger than 2 years. Mild systemic symptoms such as nausea, lethargy, headache, muscle aches, and chills also can occur with TIV injection.

TIV is administered intramuscularly into the anterolateral thigh of infants and young children and into the deltoid muscle of older children and adults (injection-site recommendations are outlined in the Red Book: 2006 Report of the Committee on Infectious Diseases). Recent concerns about thimerosal have prompted some parents to reconsider influenza immunization. However, the benefits of protecting children against the known risks of influenza far outweigh the theoretic risks associated with the small amounts of thimerosal in some currently available forms of influenza vaccine. In addition, certain types of TIV without thimerosal can be obtained, including single-dose Fluzone (sanofi pasteur, Swiltwater, PA).

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*This recommendation differs from that of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention. Because of discordant recommendations, the American Academy of Pediatrics Committee on Infectious Diseases reexamined the available data at its October 2006 meeting and reaffirmed its decision for 2 doses the second year on the basis of the following: (1) the serologic data suggest that more children would potentially be protected by giving 2 doses the following year, especially because the formulation of influenza vaccine routinely changes to match circulating strains of virus; (2) it would be easier for the practitioner to implement this strategy if the recommendation were to give 2 doses the second year whenever only 1 dose was given in the first year, rather than if a different recommendation were made annually on the basis of whether the formulation of the vaccine had changed from the previous year; (3) vaccine supply is adequate during the 2006–2007 influenza season to implement this recommendation, although delivery has been delayed, if it has not happened already, all orders will be filled very shortly; (4) a review of immunization records is necessary with each immunization visit, so deciding on the need for a second dose should not cause any increased hardship; and (5) taking the position that this cohort of children should not be included for 2 doses because it poses an increased burden for the pediatrician ignores the primary goal of this proposal—to reduce the burden of influenza for pediatric patients by improving their immunization status.
and Fluvirin (Novartis Vaccines, Emeryville, CA), but the latter is not licensed for children younger than 4 years.

LAIV is a live-attenuated vaccine that is administered intranasally and is licensed by the Food and Drug Administration for healthy individuals 5 through 49 years of age. LAIV has the potential to produce mild signs or symptoms related to influenza virus infection. The cold-adapted formulation that is licensed in the United States must be stored at −15°C or colder. LAIV may be stored in frost-free freezers without using a freezer box. When the vaccine is warmed to room temperature for intended use, it must be used within 30 minutes. It should not be refrozen after thawing because of decreased vaccine potency.

### TABLE 1

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Dose, mL/Presentation</th>
<th>Thimerosal Mercury Content, μg of Hg per 0.5-mL Dose</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated</td>
<td>TIV</td>
<td>Fluzone</td>
<td>0.25/prefilled syringe</td>
<td>0</td>
<td>6–35 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sanofi pasteur</td>
<td>0.5/prefilled syringe</td>
<td>0</td>
<td>≥36 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5/vial</td>
<td>0</td>
<td>≥36 mo</td>
</tr>
<tr>
<td></td>
<td>TIV</td>
<td>Fluvirin</td>
<td>0.5/multidose vial</td>
<td>25</td>
<td>≥6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Novartis (formerly Chiron)</td>
<td>&lt;1.0</td>
<td>≥4 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIV</td>
<td>Fluarix</td>
<td>0.5/prefilled syringe</td>
<td>24.5</td>
<td>≥4 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GlaxoSmithKline</td>
<td>&lt;1.25</td>
<td>≥18 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIV</td>
<td>Flulaval</td>
<td>10/multidose vial</td>
<td>25</td>
<td>≥18 y</td>
</tr>
</tbody>
</table>


### CURRENT RECOMMENDATIONS

Immunization with TIV is recommended for the following groups (Fig 1):

- Healthy children 6 through 59 months of age
- High-risk children 6 months and older and adolescents with underlying medical conditions, including:
  - Asthma or other chronic pulmonary diseases such as cystic fibrosis
  - Hemodynamically significant cardiac disease
  - Immunosuppressive disorders or therapy
  - HIV infection
  - Sickle cell anemia and other hemoglobinopathies
Diseases requiring long-term salicylate therapy, such as rheumatoid arthritis or Kawasaki disease

Chronic renal dysfunction

Chronic metabolic disease such as diabetes mellitus

Any condition that can compromise respiratory function or handling of secretions or can increase the risk of aspiration, such as cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders

Any female who will be pregnant during influenza season

To prevent additional cases of influenza and transmission from these patients to at-risk individuals, influenza immunization with TIV or LAIV is recommended for the following persons, unless contraindicated:

- Healthy household contacts and out-of-home caregivers of either high-risk children and adolescents or children younger than 5 years; immunization of close contacts of children younger than 6 months is especially important, because influenza vaccine is not licensed for use in these infants
- Healthy contacts and caregivers of other children or adults at high risk of complications from influenza infection
- Close contacts of immunosuppressed people
- Health care professionals or volunteers in hospitals or medical offices

Children or adolescents should not receive LAIV if they

- Are younger than 5 years
- Have a moderate-to-severe febrile illness
- Received other live-antigen vaccine(s) within the last 4 weeks
- Had a severe allergic reaction to a previous dose or vaccine component, including eggs
- Are receiving salicylates
- Have a known or suspected immunodeficiency
- Have a history of Guillain-Barré syndrome
- Have asthma or reactive airways disease
- Have other conditions traditionally considered to place them at high risk of severe influenza (chronic pulmonary or cardiac disorders, pregnancy, chronic metabolic disease, renal dysfunction, hemoglobinopathies, or immunosuppressive therapy)

PRECAUTIONS

Consideration of the potential risks and benefits of administering influenza vaccine to any child with known or suspected immunodeficiency is discussed in the Red Book: 2006 Report of the Committee on Infectious Diseases.

Precaution also should be taken when considering LAIV administration to persons with minor acute illness such as a mild upper respiratory tract infection with or without fever. Although the vaccine can most likely be given in this case, LAIV should be temporarily deferred if nasal congestion will impede the delivery of the vaccine to the nasopharyngeal mucosa until the congestion-inducing illness is resolved.

LAIV or TIV can be used to prevent influenza in those...
who are in close contact with most immunosuppressed individuals. People who are in contact with severely immunosuppressed individuals, such as those being cared for in a protective environment after hematopoietic stem cell transplantation, should not receive LAIV. For such individuals, TIV is recommended.

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Important Resources
Please refer to the Red Book: 2006 Report of the Committee on Infectious Diseases from the American Academy of Pediatrics and Recommendations and Reports: Morbidity and Mortality Weekly Report from the Centers for Disease Control and Prevention for additional details about influenza:


Antiviral Therapy and Prophylaxis for Influenza in Children

Committee on Infectious Diseases

ABSTRACT
Antiviral agents are available that are safe and effective for the treatment and prophylaxis of influenza virus infections in children. The neuraminidase inhibitors (oseltamivir [Tamiflu] and zanamivir [Relenza]) are preferred agents because of current widespread resistance to the adamantanes (amantadine [Symmetrel] and rimantadine [Flumadine]). Therapy should be provided to children with influenza infection who are at high risk of severe infection and to children with moderate-to-severe influenza infection who may benefit from a decrease in the duration of symptoms. Prophylaxis should be provided (1) to high-risk children who have not yet received immunization and during the 2 weeks after immunization, (2) to unimmunized family members and health care professionals with close contact with high-risk unimmunized children or infants who are younger than 6 months, and (3) for control of influenza outbreaks in unimmunized staff and children in an institutional setting. Testing of current H5N1 avian influenza virus isolates, the potential agents of pandemic influenza, suggests susceptibility to oseltamivir and zanamivir. Because no prospective data exist on the efficacy of these agents in humans for H5N1 strains, the dosage and duration of therapy in adults and children may differ from those documented to be effective for epidemic influenza strains.

INTRODUCTION
Antiviral agents for treatment and prophylaxis of influenza are safe and effective in children. Annual immunization against influenza is the preferred strategy for prevention of infection, but certain situations exist in which the use of antiviral agents is beneficial.

The morbidity and mortality of epidemic influenza in unimmunized children is substantial, particularly in those younger than 2 years.1–4 The purpose of this report is to offer guidance regarding antiviral treatment and prophylaxis to clinicians caring for children during yearly influenza epidemics and to provide resources for information on antiviral treatment in the event of an influenza pandemic, because no prospective human data currently exist on which to base recommendations for treatment of infections caused by potential H5N1 pandemic influenza virus strains.

ANTIVIRAL DRUGS FOR EPIDEMIC AND PANDEMIC INFLUENZA
Two classes of antiviral medications are currently available for treatment or prophylaxis of influenza infections: neuraminidase inhibitors (NAIs) (oseltamivir [Tamiflu; Roche Laboratories, Nutley, NJ] and zanamivir [Relenza; GlaxoSmithKline, Research Triangle Park, NC]) and the adamantanes (amantadine [Symme-
### TABLE 1  
Dosing Recommendations for Antiviral Agents for Treatment and Prophylaxis of Influenza

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Treatment Recommendations</th>
<th>Prophylaxis Recommendations</th>
</tr>
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</table>
| Oseltamivir (Tamiflu) | 75-mg capsule, 60 mg/5 mL suspension | For treatment, children ≥12 mo should receive 4 mg/kg per d divided into 2 doses for a 5-d treatment course:  
- ≤15 kg: 60 mg/d divided into 2 doses  
- >15–23 kg: 90 mg/d divided into 2 doses  
- >23–40 kg: 120 mg/d divided into 2 doses  
- >40 kg: 150 mg/d divided into 2 doses | Children ≤15 kg: 30 mg once daily;  
Children >15–23 kg: 45 mg once daily;  
Children >23–40 kg: 60 mg once daily;  
Children >40 kg: 75 mg once daily |
| Zanamivir (Relenza) | 5 mg per inhalation (Diskhaler) | 2 inhalations (10 mg total per dose), twice daily for 5 d | Children ≥7 y and Adults: 2 inhalations (10 mg total per dose), once daily for 10 d |
| Amantadine (Symmetrel) | 100-mg tablet, 50 mg/5 mL suspension | 5–8 mg/kg per d as a single daily dose or divided into 2 doses but not to exceed 150 mg/d; treat for 24–48 h after the disappearance of signs and symptoms. | 1–9 y: Same as treatment dose;  
9–12 y: Same as treatment dose;  
Adults: Same as treatment dose |
| Rimantadine (Flumadine) | 100-mg tablet, 50 mg/5 mL suspension | Not FDA approved for treatment in children, but published data exist on safety and efficacy. 6.6 mg/kg per d (maximum 150 mg/kg per d) divided into 2 doses. 200 mg/d, either as a single daily dose or divided into 2 doses^a,^b | 1–9 y: 200 mg/d, either as a single daily dose or divided into 2 doses^a,^b;  
≥10 y: 5 mg/kg per d once daily, not to exceed 150 mg^a,^b | 1–9 y: 200 mg/d, either as a single daily dose or divided into 2 doses^a,^b;  
≥10 y: 5 mg/kg per d once daily, not to exceed 150 mg^a,^b | 1–9 y: 200 mg/d, either as a single daily dose or divided into 2 doses^a,^b;  
≥10 y: 5 mg/kg per d once daily, not to exceed 150 mg^a,^b |

\(^a\) Amantadine and rimantadine should only be used for prophylaxis in winter seasons during which a majority of influenza A virus strains isolated are adamantane-susceptible; the adamantanes should not be used for primary therapy because of the rapid emergence of resistance. However, for those requiring adamantane therapy, a treatment course of approximately 7 days is suggested, or 24 to 48 hours after the disappearance of signs and symptoms.

\(^b\) For prophylaxis, antiviral drugs should be continued for the duration of known influenza A in the community because of the potential for repeated and unknown exposures or until immunity can be achieved after immunization.
trel; Endo Pharmaceuticals, Chads Ford, PA} and rimantadine [Flumadine; Forest Pharmaceuticals, St Louis, MO]). Guidelines for the use of these 4 antiviral agents are summarized in Table 1. Little is currently known about the efficacy of antiviral agents against H5N1 strains of influenza A virus that may ultimately cause an influenza pandemic. Current concerns about widespread resistance to the adamantanes limit the usefulness of this class of agents for both epidemic strains and H5N1 strains of influenza A virus.

The NAIs block the action of influenza neuraminidase, an enzyme present on the viral envelope that provides for the efficient release of progeny virion particles from the surface of an infected cell. The target of the adamantanes is the viral M2 matrix protein, an ion-channel protein that spans the viral envelope’s lipid bilayer and is required for viral uncoating. Detailed reviews of antiviral therapy have been published recently.6–12

With all antiviral medications, treatment earlier in the course of infection is likely to offer maximum benefit. Treatment starting as early as 12 hours after onset of symptoms has the greatest impact on disease resolution.13 Most studies have been performed in otherwise healthy children who had symptoms for less than 48 hours, with the reported improvement in outcomes being most profound in those children who were provided early therapy. Although study populations may not accurately reflect the diverse patient population seen by health care professionals, the longer symptoms extend beyond 48 hours before starting treatment, the less likely the child will benefit from antiviral therapy.

The antiviral agents discussed below that are approved for treatment and/or prophylaxis of influenza are active only against influenza viruses. Exposing children to antiviral therapy for noninfluenza infections results in unnecessary toxicity and cost and may deplete the supply of antiviral agents. Testing for influenza is encouraged if available and expected to influence clinical management, particularly at the onset of the influenza season. The sensitivity and specificity of rapid diagnostic tests for influenza have been reviewed recently.9

NAIs

Background

There are 2 NAIs approved by the US Food and Drug Administration (FDA): oseltamivir and zanamivir. Oseltamivir is available in tablet and liquid forms, but zanamivir is only available in an aerosol formulation.

Infection of the cell by influenza virus is initiated when viral hemagglutinin binds to sialic acid–containing glycoproteins on the cell surface. After the virus enters the cell and viral proteins and nucleic acid subsequently are produced, new viral particles assemble at the cell surface. The viral neuraminidase cleaves the virus from the host cell membrane attachment site, thus freeing the virus to infect other cells. The NAI antiviral agents inhibit productive infection by preventing release of infectious virus from host cell membranes and promote clumping of viral particles via binding to glycoproteins that are present in respiratory mucus.10,12

Oseltamivir Treatment

Oseltamivir has been investigated in a prospective, randomized, blinded, placebo-controlled study in children 1 to 12 years of age.14 A 5-day treatment course was associated with a median reduction in overall clinical illness of 36 hours and a reduction in fever in fewer than 25 hours in oseltamivir-treated children compared with placebo recipients. Furthermore, the incidence of acute otitis media (assessed by tympanometry and physician-prescribed antimicrobial therapy) was reduced by 44% compared with placebo recipients. A significant decrease in viral shedding was also noted in treated children, with few children still shedding virus on day 4 of therapy. The most common adverse drug effects noted were gastrointestinal tract disturbances, with vomiting in 14% of oseltamivir-treated children compared with 8% of children who were given placebo.

In studies of unimmunized children with asthma 6 to 12 years of age who received oseltamivir or placebo, no difference in the median time to freedom from illness was demonstrated, but a significant improvement in pulmonary function was noted on day 6 after treatment.15 For oseltamivir-treated children whose therapy was started within 24 hours of onset, a more dramatic difference in alleviation of all symptoms was noted, compared with those who were started on therapy after 24 to 48 hours of symptoms.

Although earlier therapy may lead to a more profound treatment effect, it is also possible that earlier treatment may impair the host immunologic response to influenza infection. An impaired immune response could leave the host susceptible on reexposure to the virus, as has been reported in 2 children with influenza B virus infections.16

Oseltamivir is not approved for therapy in children younger than 12 months because of concerns of central nervous system (CNS) toxicity seen in infant rats.17 Limited data on safety and efficacy of oseltamivir exist in this young age group, although no specific drug-attributable toxicities have been observed to date.18,19

Oseltamivir may be taken with or without food and is eliminated entirely by glomerular filtration and tubular secretion. The dose of oseltamivir should be decreased by 50% for children with decreased renal function associated with a creatinine clearance of between 10 and 30 mL/minute.

Unpublished safety data on oseltamivir were recently reviewed by the FDA on the basis of reports of neuropsychiatric events associated with patients treated for influ-
enza with oseltamivir (www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4254b.09.01_Tamiflu%20AE%20Review%202006%20Redacted.D060309.092.pdf). Although 92% of the most recent cases were reported from Japan, a country with approximately 4 times more courses of oseltamivir prescribed than in the United States, package labeling was changed in the United States in 2006 to alert physicians to the possibility of these rare and unusual clinical findings. Accurate data on the incidence of these events are not available, but they seem to be in the range of 1 in 10 000 to 100 000 treatment courses. On the basis of the FDA review, it is not known whether the spontaneous reports of neuropsychiatric behavior reflect a true adverse event caused by oseltamivir, perhaps with a greater incidence in populations with a certain genetic background; a result of CNS infection caused by influenza virus; or a combination of both drug and virus in the CNS. There are no reports of neuropsychiatric events in adults or children receiving oseltamivir prophylaxis for influenza infection.

Zanamivir Treatment
Zanamivir is administered by aerosol twice daily for 5 days. In a study of children 4 to 12 years of age, the mean duration of symptomatic illness was reduced by 1.25 days in children who received zanamivir, compared with those who received placebo. In 3 trials in subjects 12 years and older, zanamivir treatment decreased symptoms by 1 to 2.5 days in influenza-positive subjects. In a multicenter prospective study of subjects whose therapy was started within 30 hours of the onset of symptoms, resolution of major symptoms occurred 3 days earlier in the treatment group compared with that in controls.

Reported adverse effects in otherwise healthy children and adults were similar between those treated with zanamivir and those given placebo. However, concerns by the FDA regarding bronchospasm and decreased pulmonary function after inhalation of zanamivir in patients with underlying reactive airways disease, including asthma and chronic obstructive pulmonary disease, prompted warnings about use of zanamivir in this population. Potential risks and benefits should be carefully weighed before treatment of these children. Monitoring of respiratory function should be considered if treatment is given.

Zanamivir is minimally absorbed from the respiratory tract mucosa. No dosing changes are required for renal failure.

Prophylaxis With Oseltamivir and Zanamivir
Postexposure prophylaxis with oseltamivir has been reported in a multicenter study in North America and Europe for family contacts who were at least 1 year of age after identification of a documented index case within the family. In this setting, in which the index case was also treated with oseltamivir, the protective efficacy against proven influenza for individual contacts was 68%. In a similar multicenter study for household contacts 12 years and older, oseltamivir was 89% effective in the prevention of laboratory-confirmed symptomatic influenza infection when used within 48 hours of contact with an index case who had not been treated. Adverse events reported in treated subjects in this study, including gastrointestinal tract symptoms, were not different from those in controls.

Zanamivir was investigated as postexposure prophylaxis for family members 5 years and older, at a dosage of 10 mg, inhaled once daily for 10 days, with the index case also receiving treatment. After exposure to a virus-positive index case, the number of families with a clinically symptomatic member decreased 72%.

Antiviral Resistance
Development of resistance to NAIs while on therapy occurs less often than resistance to adamantanes. In a multicenter study in the United States, only 5% of children who received oseltamivir therapy developed in vitro resistance in influenza isolates cultured during therapy. In contrast, a study from Japan documented resistance of 18% in isolates cultured from 50 oseltamivir-treated children. Fortunately, oseltamivir-resistant isolates from children do not seem to be as capable of sustaining infection as wild-type strains as assessed in animal models of influenza infection. However, when generated entirely in vitro, some mutants are just as capable of infectivity as the parent strain, which indicates that the possibility still exists for the development and spread of oseltamivir-resistant strains among children. Zanamivir resistance was not reported in the published large-scale clinical trials.

Adamantanes
Background
Amantadine and rimantadine are approved for children 12 months and older. Amantadine, the first antiviral agent available against influenza, was approved by the FDA in 1966; rimantadine was approved in 1993. Antiviral activity is mediated by binding these agents to the M2 protein ion channels on the viral envelope, preventing acidic conditions within the virus that are required for uncoating and subsequent release of viral nucleic acid into the host cell. Only influenza A virus contains the M2 protein. A different envelope protein that does not bind to the adamantanes provides a similar function in influenza B virus; amantadine and rimantadine are not active against influenza B. The effectiveness of adamantanes has been limited by the emergence of widespread resistance in H3N2 strains isolated in the 2005–2006 influenza season. Recommendations for adamantane antiviral use in subsequent years will be based on the resistance patterns docu-
mented in strains circulating during those influenza sea-
sons.

**Amantadine Treatment**
Placebo-controlled, randomized clinical trials have doc-
umented that amantadine treatment decreases the du-
ration of fever and other influenza-attributable symp-
toms in influenza caused by adamantane-susceptible
strains by approximately 1 day in children 1 year and
older.36–40 However, many of the earlier placebo-con-
trolled studies that included children did not report age-
specific response or adverse-event rates. Adverse events
have been most accurately assessed and reported in
adults. The most commonly occurring (5%–10%) ad-
verse events are nausea, lightheadedness, and insomnia.
Those that occur infrequently (1%–5%) include anxiety,
nervousness, irritability, dry mouth, headache, fatigue,
and diarrhea.31 The incidence of CNS adverse effects
noted above is twofold higher in those taking amanta-
dine than in those taking rimantadine. Gastrointestinal
adverse effects are equivalent between the 2 agents.
These effects are dosage related and are usually mild,
resolving when the agent is discontinued. Serious ad-
verse effects have been reported in adults and are often
associated with either high plasma drug concentra-
tions in patients with renal insufficiency or in those with an
underlying psychiatric or seizure disorder.42

Although no prospective studies have been published
on the treatment of children with encephalitis as a com-
pliation of influenza, data on cerebrospinal fluid con-
centrations of amantadine suggest a high degree of ce-
реброspinal fluid penetration, with concentrations that
may provide antiviral activity.43

Amantadine is well absorbed orally and is excreted
almost entirely by the kidneys with variable metabolism
before elimination. The dose should be decreased 50%
in children with creatinine clearance between 30 and 50
mL/minute per 1.73 m². Additional reductions are re-
quired for more profound renal failure.

**Rimantadine Treatment**
Rimantadine was evaluated in prospective studies of
children using acetaminophen-treated controls between 1
and 12 years of age44 and 1 and 15 years of age.45 In a
study by Thompson et al.,44 no differences were recorded
in the reduction of symptoms between the 2 groups,
although the amount of virus shed was less during the
first 2 days of therapy for the treatment group. Of con-
cern, the virus shed by those who continued to have
positive culture results on the fourth day of treatment
was often resistant to rimantadine. Hall and colleagues45
noted a significant reduction in severity of disease, in-
cluding fever. However, a high rate of rimantadine re-
sistance occurred in treated children, with almost half of
the strains noted to be resistant when isolated from
children who were still shedding virus at the end of the
7-day treatment course. In addition, it is concerning that
rimantadine-treated children were more likely to be
shedding virus at the end of therapy than were controls.
No differences in adverse-event rates were noted be-
tween children treated with rimantadine and those
-treated with acetaminophen. In controlled studies in
adults, no drug-attributable adverse effects occurred in
more than 5% of the study subjects, with the most
commonly reported events being insomnia and dizz-
iness.46

Rimantadine is also well absorbed orally but, unlike
amantadine, undergoes extensive hepatic metabolism
with subsequent renal elimination. Dose adjustment
should be made for severe hepatic dysfunction or renal
failure.

**Prophylaxis With Amantadine and Rimantadine**
Early studies on the prevention of influenza with aman-
tadine were conducted in home or institutional settings
during the influenza season using prospective, double-
blind trial designs and documented a statistically signif-
icant benefit by reducing the attack rate of influenza
A.47–50 However, as with the early amantadine treatment
studies, age-specific data are lacking.

Studies on the use of rimantadine as prophylaxis for
children within families were conducted during influ-
enza seasons in which the predominant circulating
strains were H1N151 and H3N2.52 In both studies, pro-
phylaxis reduced the number of symptomatic influenza
cases in children relative to an attack rate of 15% to 20%
among placebo recipients. Prophylaxis in children also
reduced the number of cases of symptomatic influenza
in adult family members. Of note, cases of asymptomatic
influenza infection as documented by throat culture or
fourfold increase in influenza antibody titers did occur in
a small number of children who received rimantadine
prophylaxis.

**Antiviral Resistance**
Amantadine or rimantadine resistance develops in ap-
proximately one third of patients who receive antiviral
therapy.53 The development of resistance has implica-
tions for therapeutic failure for (1) the child, if resistance
develops early in therapy, (2) household or close con-
tacts, because resistance in the index case determines
which therapy is likely to be effective in those exposed to
the index case, and (3) communities, in which resistance
may be so widespread to a particular agent that empiric
therapy with that agent may no longer be recom-
manded.

Resistance to adamantanes occurs rapidly, often
within the first 3 days of therapy. Mutations lead to
structural changes at predictable, specific sites on the M2
protein. These changes are relatively stable, with little
reversion to wild-type susceptible virus after stopping
the adamantane. Appreciable differences in virulence or
transmissibility between resistant and susceptible viruses have not been noted. In a recent study, nasal swabs, nasal aspirates, or throat cultures were obtained from hospitalized children before, during, and after a 3- to 5-day course of amantadine, and 80% of isolates from treated children demonstrated amantadine resistance.\(^54\) Shedding of resistant strains was not associated with persistent or relapsing clinical disease, which is felt to reflect an adequate host immunologic response that develops as resistant strains are emerging. For the high-risk child with a poor immunologic response to infection, persistent disease or relapse is a concern.

Close contacts of an amantadine- or rimantadine-treated child who subsequently develop influenza infection are at high risk of infection caused by an adamantane-resistant influenza virus. If such patients require treatment or prophylaxis, an NAI should be used. During the 2005–2006 influenza season, data collected on widespread resistance to adamantanes in circulating influenza A strains in the United States led the Centers for Disease Control and Prevention to recommend against the use of these agents for either treatment or prophylaxis of influenza A infections.\(^55\)

Ribavirin
Ribavirin has in vitro activity against influenza virus but is not currently approved for treatment of influenza infection. Limited studies have been performed with aerosolized ribavirin in the treatment of influenza in children.\(^56\) For life-threatening influenza infection requiring parenteral therapy, intravenous ribavirin may be obtained as an investigational product through the FDA, as supplied by the manufacturer. No prospective, controlled data currently exist on the safety or efficacy of parenteral ribavirin for severe, invasive influenza infection, although limited data on pharmacokinetics of parenteral ribavirin exist for adults.\(^57\)

**INDICATIONS FOR THERAPY AND PROPHYLAXIS**

**Therapy**

- Influenza infection of any severity in high-risk children (see Appendix) regardless of immunization status
- Any otherwise healthy child with moderate-to-severe influenza infection who may benefit from the decrease in duration of clinical symptoms documented to occur with therapy

**Prophylaxis**

- High-risk children during the 2 weeks after influenza immunization, if influenza is active in the community
- High-risk children for whom influenza vaccine is contraindicated
- Family members or health care providers who are unimmunized and are likely to have ongoing, close exposure to (1) high-risk, unimmunized children or (2) infants who are younger than 6 months
- Control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with high-risk pediatric residents (eg, extended-care facilities)
- As a supplement to immunization among high-risk children
- Postexposure prophylaxis in a family setting
- High-risk children and their family members and close contacts, as well as health care workers, when circulating strains of influenza virus in the community are not matched with vaccine strains

**ANTIVIRAL THERAPY IN PANDEMIC INFLUENZA**

Antiviral therapy may play a major role in both treatment and prophylaxis during a pandemic.\(^58,59\) Pandemic influenza is likely to occur sometime within the next decade. Recent observations document the spread of an epidemic of H5N1 strain of avian influenza A virus in both wild and domestic bird species from southeast Asia to Indonesia, Europe, and Africa, with further spread felt likely to occur. As of October 16, 2006, 256 adult and pediatric cases of H5N1 influenza infection have been documented worldwide, associated with a mortality rate of 59%.\(^60\) These infections have occurred most often in those with close, direct contact with poultry. Efficient transmission of the virus between humans, an event that is required before a human pandemic can occur, has not been documented to date with any of the currently identified H5N1 strains.

Intense planning for the possibility of an influenza pandemic with a virulent strain of H5N1 or another influenza virus subtype is ongoing at international, national, state, and local levels. The American Academy of Pediatrics and other professional organizations and stakeholders have had important input into the Pandemic Influenza Strategic Plan of the US Department of Health and Human Services, which was released in late 2005.\(^61\) Interim priorities for antiviral therapy and vaccine are included as part of the plan and reflect a need to treat and protect those most at risk of severe and fatal influenza and to preserve critical societal infrastructure (eg, law enforcement, medical facilities, government). Efforts are currently underway to stockpile adequate supplies of antiviral drugs to address both health care and societal requirements. The Strategic National Stockpile currently includes oseltamivir and rimantadine. Although most strains of H5N1 are susceptible only to the NAIs, some are susceptible to the adamantanes. The dose
and duration of therapy for H5N1 infections may be different from those for currently circulating H3N2 or H1N1 infections. In the case of a pandemic, the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and state and local health departments will provide current recommendations for therapy and prophylaxis.

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APPENDIX: INFANTS AND CHILDREN AT HIGH RISK OF COMPLICATIONS FROM INFLUENZA INCLUDE THOSE WITH:

- Ages between 6 and 24 months (no antiviral agent is currently approved for infants younger than 12 months)
- Asthma or other chronic pulmonary diseases such as cystic fibrosis
- Hemodynamically significant cardiac disease
- Immunosuppressive disorders or therapy
- HIV infection
- Sickle cell anemia and other hemoglobinopathies
- Diseases requiring long-term aspirin therapy, such as rheumatoid arthritis or Kawasaki disease
- Chronic renal dysfunction
- Chronic metabolic disease such as diabetes mellitus
- Neuromuscular disorders, seizure disorders, or cognitive dysfunction that may compromise the handling of respiratory secretions
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Issues With the New Developmental Screening and Surveillance Policy Statement

To the Editor.—The American Academy of Pediatrics Council on Children With Disabilities deserves much commendation for its revised statement on early detection of developmental problems.1 The focus on surveillance enables providers to consider factors that are known to promote or deter children’s development such as family well-being, dimensions of psychosocial risk, and resilience. Addressing these factors may help prevent many problems from developing. The council wisely noted that occasional administration of validated screening tests is also essential for making careful decisions about the needs of children and families.

Nevertheless, the new policy failed to embrace—indeed, it scarcely mentioned—the need for validated screening with children older than 30 months. Given that developmental problems surface throughout the preschool, elementary, and adolescent years, surely the council did not mean to suggest that 30 months was a proscribed limit on the use of accurate screening tools. The woefully low detection rates of children with disabilities on the part of primary care providers (30%)2 speaks urgently to the need for careful measurement with quality instruments, not ad hoc checklists. Just as we would measure temperature with a thermometer rather than a hand to the forehead, we must also carefully measure children’s development, and measure it repeatedly, if we are to ensure their access to the innumerable benefits of early intervention. We urge the council to amend their statement so that it recommends quality screening at each annual well-child visit after 24 (or 30) months of age.

Of somewhat lesser importance, but concerning nonetheless, is the list of tools in their Table 1. Generalist providers are likely to be confused by the vast array of options, many of which are not suitable for primary care. The table would be greatly enhanced if the measures could be sorted as follows:

1. broadband screens that are appropriate for primary care, that is, screens that take less time than that usually allotted to a well-child visit (eg, Ages and Stages Questionnaire, Parents’ Evaluation of Developmental Status, Infant-Toddler Checklist);
2. broadband screens that exceed well-visit time frames but are still useful in primary care settings and use a gated screening process, in which nurse practitioners or developmental specialists are available to screen selected children more extensively (eg, Battelle Developmental Inventory Screening Test-II, Brigance Screens-II, Bayley Infant Neurodevelopmental Screener, etc);
3. narrow-band measures that serve only as second-stage screens because of their focus on a single domain (eg, Early Language Milestone Scale, Checklist for Autism in Toddlers, Modified Checklist for Autism in Toddlers, Capute scales); and
4. narrow-band measures that require specialty training to administer (eg, Screening Tool for Autism in 2-Year-Olds, Early Motor Profile).

There are also several errors in their table that are in need of correction:

1. The Brigance screens are incorrectly reported as criterion-referenced only. This is not the case. The screens produce quotients (age-equivalent) and cut-off scores that result from 2 extensive standardization and validation studies.3,4
2. Data on the sensitivity and specificity of the Denver-II are incorrectly reported.5 When children with questionable scores are nominated for referral, the Denver-II sensitivity was 83% (high), but specificity was 43% (poor). Given that few children with questionable results are referred, the more realistic figures are 56% sensitivity (poor) and 80% specificity (high).
amalgamating results, readers are left with the false impression that a parsimonious and acceptable balance between sensitivity and specificity can be found. Because most primary care providers only administer selected items, the accuracy of the Denver-II may be further compromised. Yet, information on this common application was not included in their table. Finally, the Denver-II was not normed in 2096 but rather in 1992.

3. The year of test standardization is inconsistently reported, which is critical because US population demographics are changing rapidly. Indeed, the National Council on Measurement in Education recommends restandardization every 10 years. Test purchasers need to know which measures are current and which are not.

It would be ideal if the council identified those instruments that clearly met standards for test construction, are appropriate for primary care (normed under such conditions, in the last decade), and have both sensitivity and specificity of ≥70%. Because few individuals have a background in psychometry, the data presented are unlikely to be readily interpreted by most readers. The American Academy of Pediatrics needs to offer guidance to its members about what constitutes a quality measure. We realize there may be a conflict of interest in our statement, given the screening measures we have researched, but psychometry is a process that takes hard work, great expense, and a willingness to reinvest revenues to prove that tests are accurate and current. We encourage other test authors to adhere to this process.

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REFERENCES

In Reply.—

In writing the new policy statement on developmental surveillance and screening,1 the American Academy of Pediatrics (AAP) Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee, and the Partnership for Policy Implementation joined together to forge a new policy that could address the recognized barriers to implementation of screening.2 As is clear from the title of the policy, we chose to highlight the need for early identification and create a system for surveillance and screening for the first 3 years of life. Although we emphasized implementation from birth to 30 months, we stated clearly in the policy that surveillance should continue throughout childhood and that school-readiness screening should be performed at 4 years of age.3,4 The third edition of the Bright Futures guidelines (in press) also includes the 9-, 18-, and 30-month developmental screening, as recommended in the algorithm for those visits.

We support the use of high-quality instruments in screening, as Drs Glascoe and Squires urge. However, they suggest a 2-stage system of “gated screening.” We have learned from pediatricians that such a process is difficult to implement because of issues of staff limitations, reimbursement, and time.2 Therefore, we instead chose to develop a model, centered on principles first put forth by Dr Paul Dworkin,3 that involves brief and repeated surveillance coupled with age-targeted formal instrument-based screening. We believe such a system is readily implementable in the medical office setting, is appropriate to current models of screening and clinical practice, and addresses the recognized barriers to developmental screening.

The policy statement is a guideline to clinicians and not a comprehensive review. The list of screening instruments, therefore, was intended also to guide the clinician in making a choice. The table consisted of instruments that did indeed meet standards for test construction and were appropriate for primary care. During review, our committee recognized limitations of all of the currently available instruments and therefore included some instruments that offered unique characteristics such as domain- and disorder-specific screening. We recommend that the child health care provider review the table and choose

* Dr Glascoe is the author of the Parents’ Evaluation of Developmental Status (PEDS), Developmental Milestones, Safety Word Inventory and Literacy Screener, and the Brigance Infant and Toddler Screen; and Dr Squires is the author of the Ages & Stages Questionnaire-2 (ASQ: Social-Emotional).
instruments that conform best to his or her population's needs. The pediatrician must consider multiple issues when choosing an instrument, and we tried to include such information in our table. We believe that limiting our readers to a small choice of instruments would be inappropriate. Additional information on screening instruments can be found in the literature.\(^4\,5\) In addition, a comprehensive review of developmental surveillance and screening instruments is currently in progress by Dr Dennis Drotar and colleagues through a grant provided by the Commonwealth Fund (www.cmwf.org/grants/grants.show.htm?doc_id=316732).

The terminology used in the policy statement was settled on by consensus. Drs Glascoe and Squires' first-stage broadband screen can conform to our model of surveillance. Rather than using the terms “broadband” and “narrow band” as they use in their model, we instead felt it most helpful to the health care provider to subdivide the instruments into the categories of “general” (synonymous with broadband), “domain specific” and “disorder specific” (narrow-band).

The best practices for developmental surveillance and screening are still being refined. Although the literature is dominated by general screening instruments, we do not know if using these tools is better than using instruments that target specific areas of development (such as motor or language) or specific disabilities (such as autism), so we included all of these in our table. At the current time, there is clear interest in the disability-specific approach in autism\(^6\) and hearing impairment.\(^7\) There are also no data that directly assess concordance between the caretaker-completed questionnaires and the hands-on screeners. Moreover, we do not know how factors such as socioeconomic status, age, or biomedical variables bias parent report. We hope that future projects will elucidate the best approach to take so that children with specific disabilities are best identified.

Drs Glascoe and Squires suggest that there are errors in our table. We appreciate the information provided to readers on the Brigance screens. The Denver-II data were based on a review of the extensive literature investigating this widely used instrument, and the information on its norming on 2096 children is correctly stated in our table.

In conclusion, the Policy Revision Committee for Developmental Surveillance and Screening, which represents both general pediatricians and subspecialists, strove to create a new policy that could effectively identify children with developmental disorders in early childhood. Through creation of a process that addresses the recognized barriers, we hope that this model offers pediatricians and other child health care providers a system that can be easily implemented to achieve this goal. We also hope that the algorithm will provide pediatricians with additional guidance on the subsequent developmental and medical evaluation, community-based intervention referral, and medical home chronic-condition management that such children with special health care needs deserve to ensure their achieving maximal health and well-being in their lives.

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on behalf of the AAP Policy Revision Committee on Developmental Surveillance and Screening

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Evidence-Based Medicine Practice by Hospitalists and Community Pediatricians

To the Editor—

The Pediatrics article “Variations in Management of Common Inpatient Pediatric Illnesses: Hospitalists and Community Pediatricians” by Conway et al\(^1\) is both interesting and provocative. The results demonstrated that the hospitalists practiced significantly more evidenced-based medicine than community pediatricians. The results remained the same, according to the authors, even after controlling such variables as postresidency years, fellowship training, time spent attending, and practice in academic or nonacademic centers. This is surprising, be-
cause these variables are major factors that would impact on the type of practice.

In their article, the authors stated: “Hospitalists both specialize in inpatient pediatrics and attend a greater number of inpatients per year, and this suggests that this expertise leads to greater adherence to evidence-based therapies.” This statement, however, was not supported by their findings. If this statement were true, then controlling such variables as years after residency, postgraduate training factor, time spent attending, and practice in an academic setting certainly would have erased the difference between the two in multivariate analysis. What, then, would make up this difference? There are several alternative and plausible explanations. One would be that hospitalists have a bigger incentive to practice evidence-based medicine. The incentive may be related to their increased responsibility in teaching students and residents as opposed to community pediatricians. An additional incentive may be a more closely monitored system in place to measure quality of care in the hospitals. The type of questions asked may be more related to strictly inpatient care than ambulatory care. It would be more informative if the authors included this type of information in their article. It is generally believed that the practice of evidence-based medicine is parallel to quality care. Therefore, the answer to the question of why hospitalists practice evidence-based medicine more often than community pediatricians is very important. The questionnaire used by these authors is quite creative, and I believe that it may yield quite informative data on the quality of care.

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In Reply.—

We thank Dr Inoue for the thoughtful comments on our article. We agree that the mechanisms driving hospitalists and pediatricians to follow evidence-based guidelines need to be explored further. Dr Inoue was concerned that our statement, “Hospitalists both specialize in inpatient pediatrics and attend a greater number of inpatients per year, and this study suggests that this expertise leads to greater adherence to evidence-based therapies,” was not supported by our findings. First, in terms of specialization, we controlled for postresidency training but did not control for expertise that may be gained by hospitalists through years spent practicing as a hospitalist, as opposed to years that a community pediatrician spends seeing mainly patients in the outpatient setting. Although not specific training per se, this experience may lead to greater adherence to evidence-based therapies and tests in the inpatient setting. In terms of the effect of volume on adherence to evidence-based medicine, we were able to control for number of days spent attending per year but did not have reliable data to control for the average number of patients on census per day between the 2 groups. It is plausible that hospitalists, on average, attend to more patients per day than community pediatricians, which could increase expertise and adherence to evidence-based medicine, but this hypothesis would need to be tested further. Dr Inoue makes an excellent point: hospitalists may have greater adherence to evidence-based medicine in the inpatient setting because of quality-measurement programs or incentives related to the teaching mission. In addition, we would add the possibility that some hospitals may have pay-for-performance initiatives to encourage hospitalists to follow evidence-based guidelines. We believe that questions relating to the mechanisms that increase adherence to evidence-based medicine need to be further explored in the future. Finally, the hypothesis that this adherence to evidence-based medicine improves outcomes for children and their families needs to be tested further, so we can identify the practices that best serve to improve the quality of care delivered to children.

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High-Dose Systemic Corticosteroids May Be Effective Early in the Course of Bronchiolitis

To the Editor.—

In their published guidelines, the American Academy of Pediatrics Subcommittee on Diagnosis and Management
of Bronchiolitis}

discounted studies that demonstrated benefit from systemic corticosteroids for bronchiolitis. In a randomized, double-blind, placebo-controlled trial of infants with bronchiolitis seen at the emergency department, Schuh et al demonstrated that fewer than half as many infants with bronchiolitis required hospital admission among those given 1 mg/kg of dexamethasone as compared with those given placebo, which is a significant difference (P = .039). In another controlled clinical trial, Csonka et al found that 2 mg/kg prednisolone in the emergency department and 1 mg/kg twice daily for 3 more days was associated with significantly shorter hospital stays among those who subsequently required hospitalization and a shorter duration of symptoms, averaging ~1 day less among the steroid-treated group as compared with randomized controls who received placebo. Although that study included both first- and second-time wheezers and included patients older than the more strict criteria in the study by Schuh et al, the response to prednisolone was similar among those having wheezing for the first time and those with a previous episode. A meta-analysis that included 6 controlled clinical trials of hospitalized patients with bronchiolitis concluded that there was a small but statistically significant benefit from prednisolone for bronchiolitis.

Asked to write an editorial to accompany the Csonka et al article, I speculated that the differences in outcome for hospitalized infants with bronchiolitis, in whom little or no benefit has been demonstrated, and those treated before hospitalization relate to the timing of treatment with relation to the pathology. Perhaps there is reversible inflammation initially, whereas progression results in the characteristic dense plugs composed of alveolar debris and fibrin within the bronchioles. A high dose of corticosteroid early in the course of bronchiolitis may be effective in preventing that progression and thereby preventing hospitalization, as demonstrated by Schuh et al, or at least modifying the course, as demonstrated with the lower doses of corticosteroids in the report by Csonka et al and a report by Goebel et al. The reported annual hospitalization rate for bronchiolitis has been ~3 per 100 infants in the United States, and the latest available data give no indication that these hospitalizations are decreasing. Treatment that has the potential to decrease the hospitalization rate by >50%, as in the Schuh et al study, warrants careful consideration in a guideline for treatment of bronchiolitis.

In Reply.—

The American Academy of Pediatrics (AAP) Subcommittee on Diagnosis and Management of Bronchiolitis thanks Dr Weinberger for his comments on the corticosteroid recommendation in the clinical practice guideline “Diagnosis and Management of Bronchiolitis.” He raises many points that were discussed by the subcommittee as we formed our recommendations. Schuh et al performed a well-designed study of the effect of 1 mg/kg oral dexamethasone in the emergency department using the Respiratory Distress Assessment Instrument (RDAI) and the related Respiratory Assessment Change Scale (RACS) to evaluate clinical response at 240 minutes. The mean RACS score showed a significant difference between those in the dexamethasone group and those in the placebo group. Although the mean RDAI score did show a trend in favor of dexamethasone, statistical significance was not achieved. There was a significant difference in hospitalization rate in favor of the treatment group. This study was included in the meta-analysis by both the Agency for Healthcare Research and Quality and the Cochrane Database of Systematic Reviews with a Jadad quality score of 5. Two other studies of comparable quality (Jadad quality score 4–5) in the Cochrane meta-analysis showed no difference in hospital admission rate.

In contrast, the Csonka et al study was excluded from these reviews because of methodologic issues. The age

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group included by Csonka et al was 6 to 35 months, with a mean age of 16.8 months, which is not the typical age for the majority of children with clinical bronchiolitis. The guideline only applies to children who are 2 to 24 months of age. In addition, 136 (59%) of the 230 subjects in the study had a previous history of wheezing.

The 2000 Garrison et al meta-analysis included 6 studies with 347 patients. The more recent Cochrane review, most recently updated in 2005, included these 6 studies plus 7 additional studies for a total of 1198 patients. As noted in the guideline, the Cochrane review concluded that “no benefits were found in either length of stay or clinical score in infants and young children treated with systemic glucocorticoids as compared with placebo.” The subcommittee agreed with this conclusion and, thus, recommended against the routine use of corticosteroids for bronchiolitis.

Subsequent to the submission of the guideline and not included in the subcommittee’s deliberations, the Pediatric Emergency Care Applied Research Network presented emergency department data at the 2006 AAP National Conference and Exhibition that showed no difference in rate of hospitalization of 1 mg/kg dexamethasone versus placebo. Full details of this large multicentered study will be published in the future. Also nearing completion is a similar study by the Pediatric Emergency Research Canada group.

As with all clinical practice guidelines produced by the AAP, the bronchiolitis guideline will be updated periodically as new literature becomes available.

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doi:10.1542/peds.2007-0030
ERRATA


doi:10.1542/peds.2007-0319


Several errors occurred in the article by Vohra et al, titled “Adverse Events Associated With Pediatric Spinal Manipulation: A Systematic Review” published in the January 2007 issue of Pediatrics Electronic Pages (doi:10.1542/peds.2006-1392). In Table 1, the entry in the “Shafrir and Kaufman” row, “Time to Adverse Event” column, should read: “Immediately after first SM.” Also, in the “Shafrir and Kaufman” row, “Type/Schedule of Spinal Manipulation” column, the phrase “at least 3 SMs over 2 d” should read: “2 SMs over 2 d.” In Table 2, an entry was omitted from the “Adverse Event” column of the “Nickerson et al” section. The missing entry is as follows: “Delayed treatment for diabetes mellitus; NS; NS; NS.” The errors have been corrected online.

doi:10.1542/peds.2007-0321


doi:10.1542/peds.2007-0483
Several inaccuracies occurred in a table in the AAP technical report “Spectrum of Noninfectious Health Effects From Molds” published in the December 2006 issue of Pediatrics Electronic Pages (doi:10.1542/peds.2006-2829). Table 4 should be replaced with the following table:

<table>
<thead>
<tr>
<th>Stachybotrys Metabolites</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atranones</td>
<td>Immunotoxic, inflammatory</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Immunosuppressive</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Collagenolytic proteinase</td>
</tr>
<tr>
<td>Stachyrase A</td>
<td>Hemolytic</td>
</tr>
<tr>
<td>Hemolysin</td>
<td></td>
</tr>
<tr>
<td>Stachyhemolysin</td>
<td></td>
</tr>
<tr>
<td>Macro cyclic trichothecenes</td>
<td></td>
</tr>
<tr>
<td>Isosatratoxins</td>
<td>Protein synthesis inhibitors, cytotoxic</td>
</tr>
<tr>
<td>Roridins</td>
<td></td>
</tr>
<tr>
<td>Satratoxins</td>
<td></td>
</tr>
<tr>
<td>Verrucarin</td>
<td></td>
</tr>
<tr>
<td>Microbial VOCs</td>
<td>Iritant</td>
</tr>
<tr>
<td>1-butanol</td>
<td></td>
</tr>
<tr>
<td>3-methyl-1-butanol</td>
<td></td>
</tr>
<tr>
<td>3-methyl-2-butanol thujopsene</td>
<td></td>
</tr>
<tr>
<td>Phenylspirodrimanes</td>
<td>Immunosuppressive</td>
</tr>
<tr>
<td>Spironolactones</td>
<td></td>
</tr>
<tr>
<td>Spiro lactams</td>
<td></td>
</tr>
<tr>
<td>Simple trichothecenes</td>
<td>Not well defined</td>
</tr>
<tr>
<td>Trichodermol</td>
<td></td>
</tr>
<tr>
<td>Trichodermin</td>
<td></td>
</tr>
<tr>
<td>Trichovernoid trichothecenesa</td>
<td>Not well defined</td>
</tr>
</tbody>
</table>

This table illustrates the many Stachybotrys mycotoxins and metabolites that may contribute to toxicity and is not meant to be comprehensive.

*a Lie along the biosynthetic path between the simple and the macrocyclic trichothecenes.

doi:10.1542/peds.2007-0482