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Gun violence and public health

The blood had not yet dried in the lecture rooms of Virginia Tech, Blacksburg, Virginia, before polarised camps claimed that the slaughter of 32 students and teachers vindicated their particular stance on gun control. So shrill was the debate about whether the tragedy would have been better prevented by reducing firearms through stronger gun laws or by increasing availability through liberalising right-to-carry legislation, that the more important issue of gun violence as a public-health menace has been neglected. Until the debate widens to address violence as a preventable social problem, rather than solely a legal concern, mass shootings will continue. To pretend that the Blacksburg tragedy is unique ignores the legacy of school shootings in Dunblane, Columbine, and elsewhere, and deprives people of an opportunity to reduce future risks.

Violence is a broad problem that involves communities, not just criminals, and populations around the world, not just the USA. In 2003, 1·6 million people were killed by violence worldwide, more than by road traffic crashes or malaria. One-third died as a result of homicide. The incidence is rising, fuelled by inequalities, victimisation, and lack of social trust, so that gunshot wounds are a major cause of death for young men.

Because the USA has the highest homicide and gun-homicide rates of any industrialised democracy, the country is a natural focus for attempts to learn more about violence. But despite many Federally funded programmes, objective research on interventions to reduce violence is lacking. Nor has the Campbell Collaboration, established to synthesise evidence for the social sciences, provided guidance. In 2004, the US National Research Council critically reviewed gun violence and concluded that there was little quality science to inform decision making. The reason is that most studies are based on associations or on before-and-after series.

A 2004 survey from Harvard estimated that 38% of households and 26% of individuals had at least one of the 283 million private firearms in the USA. Even teenagers report ready access to guns. Several studies in the USA and elsewhere cite protection as the main reason for having a gun, despite the fact that guns are far more likely to be used offensively, including suicide, than for self-defence. The association of firearms and their use in homicide between populations (four shooting deaths per 100 000 in the USA vs 0·15 per 100 000 in Cameroon where private guns are banned) is complex and obviously involves cultural factors as well.

Yet, interventions within populations that remove guns do seem to reduce gun crime in a reproducible manner. In 2003, more than half the guns retrieved from crimes were traced to 1% of dealers. When such a dealer in Milwaukee stopped selling inexpensive handguns, local gun crime was reduced by 96% and the transfer of new weapons to criminals decreased by 44%. In Indianapolis, Pittsburgh, and Kansas City, policing to remove illegal firearms from the street reduced gun crime as well. Multiple interventions combining social networks with stronger enforcement can also be successful, such as the 63% drop in homicides after Operation Ceasefire in Boston. Tougher gun laws in Brazil in 2003, allied with a buy-back programme of 450 000 guns, reduced the gun-homicide rate by 8% and hospitalisation for gunshots by 4·6%.

How can such findings inform sensible policy decisions? The National Research Council concludes that individual-level data are needed. Characteristics of victims can be enhanced with WHO’s International Classification of External Causes of Injuries, which by introducing standard reporting criteria, enables comparisons between studies. But there are few details about perpetrators, since criminal background checks for sales by gun dealers are destroyed within 24 h and private second-hand sales, which constitute 40% of gun transfers in the USA, are not recorded. To understand assailants’ risk factors requires records of gun ownership or ballistic fingerprinting, to which the powerful US National Rifle Association is opposed.

The events in Blacksburg on April 16 demand a more mature evaluation of gun violence, based on the right to health instead of the right to bear arms, and which places public welfare above self-interest. The National Research Council’s call for accurate, individual-level data from rigorous studies is essential, in order to provide robust information on which sound interventions can be based. But until such data are available, the best current evidence clearly supports an immediate reduction in the availability of firearms as a public-health priority. ■ The Lancet
Imagine a world where no one is blinded by trachoma or onchocerciasis, no woman is ostracised because of her maiming Buruli ulcer, no man lives with the pain, shame, and unemployment caused by his genital and limb disfigurement due to lymphatic filariasis, and no child is orphaned by African trypanosomiasis. That world could exist now—all these diseases are preventable and treatable—but for our collective failure to tackle these so-called neglected tropical diseases.

The first WHO Global Partners’ Meeting on Neglected Tropical Diseases held on April 19–20 in Geneva marks a turning point for these diseases. Led by Margaret Chan, Director-General of WHO, political leaders and health ministers from affected countries, academics, and private and public sector partners expressed a commitment to combat these diseases, to reduce poverty, to promote equity of access to treatment, and therefore to drive sustained socioeconomic development.

Achieving the high-level political advocacy to ensure that control of neglected tropical diseases gets onto the agendas of the G8 in 2008 and the African Union will be paramount. Partnerships with the pharmaceutical industry remain crucial. With Merck KGaA’s announcement at the meeting of its donation of praziquantel, all key drugs except diethylcarbamazine are now partly or totally donated. But getting the free drugs to those who need them relies on community drug distributors, teachers in schools, or health systems that are often failing or nonexistent. Strengthening health systems, which is the proposed new World Bank strategy instead of funding vertical programmes, is fundamental to disease control.

The man, woman, or child with a neglected tropical disease is also sometimes HIV positive, has malaria, or tuberculosis, and is poor. Integration of disease control strategies and intersectoral approaches are needed. So, for example, delivery of deworming drugs and bednets for school-age children might best be achieved by collaboration between the health and education sectors, beginning at ministerial level. Coordinated approaches to deliver what those plagued with disease need are what should drive public-health strategy and sustainable development. ■ The Lancet

**Ensuring autopsy lives on**

Autopsy is a highly sensitive issue in the UK, following the organ-retention affair at Alder Hey Children’s Hospital, Liverpool, UK, in the late 1990s, in which organs and tissues from infants who died at the hospital were kept for study without consent. The public concern and regulation that followed this troubling case are likely to have contributed to the subsequent drop in hospital autopsy rates in the UK. But as Julian Burton and James Underwood highlight in their Review in today’s Lancet, autopsy rates were in decline before Alder Hey and not only in the UK. Rates of autopsy in adults have been falling in most developed countries since the 1960s.

Refusal by the family for religious or cultural reasons is often cited as the main reason for this trend. However, studies suggest that it is clinicians’ unwillingness to seek consent, rather than relatives’ refusal, that has contributed most to the drop in hospital autopsy rates. Although legislation making the consent process more detailed and time-consuming might make clinicians reluctant to approach families, the perceived value of autopsies is also an issue. Some clinicians feel that advances in premortem diagnostics have reduced the need for autopsy. But clinical autopsies not only help to establish the true cause of death, they also provide an insight into how patients’ deaths can be prevented in future, aid research and undergraduate medical education, and can help relatives with the grieving process by providing an explanation of why the death occurred.

Clinicians might find it difficult to approach recently bereaved families to discuss autopsy, especially if public mistrust surrounding the process is high. Training in the consent process and the religious and cultural issues that surround the procedure could help. In Switzerland, training in communication with relatives contributed to an increase in autopsy rates in the late 1990s.

Evidence shows that relatives are most likely to grant consent when clinicians strongly recommend autopsy. Addressing the barriers to clinicians seeking relatives’ consent will therefore ensure the valuable practice of autopsy lives on. ■ The Lancet
Do doctors have a future?

In 2005, the Royal College of Physicians published results of a year-long inquiry into the state of medical professionalism. That investigation, chaired by former Health Minister Baroness Cumberlege, devised a new definition and description of professionalism (panel). The College’s working party also examined six implications of this revitalised conception of professional values—for leadership, teams, education, appraisal, careers, and research. It went on to make 19 recommendations, affecting the General Medical Council, the Royal Colleges and Academy of Medical Royal Colleges, medical schools, the British Medical Association, Department of Health, research funding bodies—and individual doctors themselves.

Despite this detailed critique of UK medicine, medical professionalism, and the conditions in which it operates, the College was upbeat. Research into the views of its fellows and trainees showed that professionalism was greatly valued as the embodiment of what it means to be a doctor in a health service that is undergoing rapid and continuous reform. Professional values meant something important to doctors. The College’s report ended with the aspiration that “Our abiding wish is to put medical professionalism back onto the political map of health in the UK”.

The Royal College of Physicians has continued to develop these conclusions in its work on setting and monitoring standards of clinical care. The College also joined forces with the King’s Fund, which had recently published its own report on medical professionalism. Together they have run nine roadshows in England and Wales during 2006 and 2007. The aim was to stimulate debate within and beyond the profession at a time when many doctors perceived the notion of professionalism to be under threat. These events comprised introductory scene-setting, consideration of a series of questions about the future of doctors and professionalism, electronic voting, small-group discussions, and a question-and-answer panel debate not only about professionalism but also about the uncertain future of Britain’s health system.

Several common themes emerged. On professional values, many participants thought that being a doctor was similar to other roles within the NHS. To be sure, judgment, complexity, and uncertainty are unifying features of modern clinical practice. But trust, an ethical code, and a commitment to care are common to all health professions. A robust debate is needed about the part that each professional group should play in an evolving health service. This debate is not flourishing as it should be at a time of unprecedented change.

Can professionalism be taught? A doctor’s education embeds professional values at every stage. But whether values can be taught explicitly or whether they are learnt through exposure and experience is still open to question. One variable in the teaching of professionalism is the maturity of the student. It is expecting a great deal of a 20-year-old to adopt a full range of professional behaviours. Moreover, as the health service has changed, so the kinds of values expected of doctors have changed too. New technologies, the importance of team-based working, a public expectation to be more the equal partner of a doctor—all of these shifts mean that mid-career doctors, who are often role models for their younger colleagues, will need to rethink, sharpen, and update their professionalism.

An even more difficult challenge is the assessment of a doctor’s professionalism. Although there was substantial agreement that appraisal was welcome and much needed, there was great uncertainty about how this assessment should be done. Appraisal of professional values would not prevent another Harold Shipman from emerging. Indeed, the Chief Medical Officer of England’s proposals

Panel: Royal College of Physicians’ definition and description of medical professionalism

Definition
Medical professionalism signifies a set of values, behaviours, and relationships that underpins the trust the public has in doctors.

Description
Medicine is a vocation in which a doctor’s knowledge, clinical skills, and judgment are put in the service of protecting and restoring human wellbeing. This purpose is realised through a partnership between patient and doctor, one based on mutual respect, individual responsibility, and appropriate accountability.

In their day-to-day practice, doctors are committed to:
• integrity
• compassion
• altruism
• continuous improvement
• excellence
• working in partnership with members of the wider health-care team.

These values, which underpin the science and practice of medicine, form the basis for a moral contract between the medical profession and society. Each party has a duty to work to strengthen the system of health care on which our collective human dignity depends.
Comment

on regulation and revalidation received a mixed response. Although some kind of recertification was clearly essential, his plans were regarded by some participants as an over-reaction, a resort to bureaucracy that would erode rather than strengthen professionalism.

In *Doctors in Society*, the working party reported that “leadership in medicine today is seriously failing. The profession is underselling itself”. This view was repeated by many who attended the roadshows. Medical leadership was too fragmented. Too often we heard that no one is leading doctors. The public is confused and even doctors are confused about who speaks for medicine. Yet there was a desperate need for leadership on a range of clinical and professional issues central to the health of the nation. Doctors are frequently silent on the most important matters of the day.

The final theme that emerged concerned the National Health Service (NHS) itself and the responsibilities of the profession to influence public policy and to deliver health-service reform. Here, there was also great uncertainty. Managing the health service responsibly is key to the fair, effective, and efficient allocation of resources. The College’s report concluded that “Doctors currently have a neglected role in health-service management and leadership”. The King’s Fund had emphasised the part the profession should play in public debate and health-service improvement: “The medical profession should aim high. It should seek to define a modern professionalism that focuses on the interests and experiences of patients and requires doctors to take part in improving health services.” The consultation was less confident than either report. Doctors and managers have different priorities. Doctors may not have the time, skill, or desire to be effective managers. And adopting a management role—adhering to a target culture, for example—may actually damage professionalism.

The consultation phase of the Royal College of Physicians’ inquiry came to a close with a final meeting in London on April 25, 2007. What conclusions can be drawn? First, doctors are less optimistic about their future than non-doctors. Doctors want to debate their prospects openly and energetically. Professional values are not redundant. They reflect the purpose and identity of doctors, and they translate directly to the quality and continuous improvement of patient care.

But second, many doctors feel dangerously disengaged and alienated. Roadshow participants discussed the fiasco of the implementation of Modernising Medical Careers, the paralysis of Connecting for Health, the rhetoric of patient choice—they felt these initiatives, launched with large and loud claims, have demoralised health workers. Add to these, payment by results, independent-sector treatment centres, Healthcare Commission ratings, contestability, and financial failure, and one has drawn the contours of a health system passing through a phase of extraordinary instability. The evidence we have gathered from the roadshows indicates that the re-engagement of the health professions in policy and strategy is critical for the restoration of order in the NHS.

And here lies the third lesson. This joint initiative showed the power of working in a different way—not as discrete professional groups, but as cross-disciplinary teams, including managers, students, patients, and the public. This spirit must be amplified across the health service.

The process this latest alliance has sustained has created a hope and expectation that more will follow. More engagement, more consultation, more leadership, more thinking, and more advocacy from the professions to secure the public interest. “Will anything change?”, asked several of those who took part. Part of the answer lies with the profession itself and the willingness of doctors and managers, together with other professions and patients, to work effectively on shaping and running their services at local level. Partly, it is also about leadership at the top of the profession and how government behaves.

The government is now seeking to involve the profession more in its work. Doctors are mobilising to act on important issues of the moment. Although it is too early to tell whether measurable systemic change has taken place, medical professionalism is now back on the political map of UK health. It is up to the professions to make something of that success, for the benefit of patient care and the long-term future of the NHS.

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Sum and substance in the Jikei Heart Study

In today’s Lancet, Seibu Mochizuki and colleagues report the results of the Jikei Heart Study.\(^1\) The addition of the angiotensin-II type-1 receptor antagonist (ARB), valsartan, to conventional therapy in patients with hypertension, coronary heart disease, or heart failure reduced the primary composite endpoint by 39\% (95\% CI 21–53\%). We know how difficult it is to do a randomised trial in Japan. The Jikei investigators are therefore to be congratulated for this trial in more than 3000 patients. Nevertheless, one should not accept at face value the main conclusions of the Jikei report. The investigators suggest that addition of valsartan to conventional therapy prevented more cardiovascular complications than added non-ARB therapy and that, in line with previous publications of one of the co-authors,\(^2\) the benefit of the ARB could not entirely be explained by differences in blood pressure.

The major weakness of the Jikei Heart Study stems from the compromises the investigators had to accept to make their trial feasible. The sample size and incidence of “hard” events were lower than in many other trials.\(^3\)\(^,\)\(^5\) In terms of standardised daily doses, the added non-ARB therapy (the comparator) did not catch up with the addition of valsartan until after the second year of follow-up. Furthermore, the Jikei Heart Study had a prospective randomised open-blinded-label endpoint (PROBE)\(^6\) design. Although an independent and blinded endpoint committee adjudicated endpoints, PROBE does not protect against possible bias of the investigators in reporting events or admitting patients to the hospital. New admissions for angina pectoris (relative risk reduction 65\%, 95\% CI 42–80\%) and heart failure (47\%, 6–69\%) were the main drivers of the benefit in the primary composite endpoint in the Jikei study. We find it difficult to understand how in an open trial, in which investigators were fully aware of the treatment being administered, admission could be part of the primary outcome measure. The 77 cerebrovascular events also included nine cases of transient ischaemic attacks, a “weak” event not usually considered in outcome trials. However, limiting the analyses to the 68 cases of confirmed strokes, according to our estimates, would not remove the significance of the cerebrovascular endpoint (p for comparison of rates, 0.031).

Stroke is the complication of hypertension most directly linked to blood pressure.\(^7\) By our calculations, during follow-up in the Jikei Heart Study, the baseline-adjusted blood pressure was lower (0.6 mm Hg systolic, 1.0 mm Hg diastolic) with valsartan than with non-ARB therapy. The Jikei investigators stated that overall this difference was not statistically significant. We used a large-sample Z test to compare the blood pressure levels at each time point of follow-up, as presented in table 3 of the Jikei report. During the first year, blood pressure was significantly lower on valsartan than on comparator. At 6 months, the differences averaged 2.1 mm Hg systolic (p=0.0005) and 2.1 mm Hg diastolic (p<0.0001), and at 12 months 1.5 mm Hg (p=0.0034) and 1.3 mm Hg (p=0.0003), respectively. The trial stopped early. Of the 8627 patient-years, at least 2965 (34.4\%) accrued during the first year after randomisation.

The Systolic Hypertension in Europe trial\(^8\) and theValsartan Antihypertensive Long-term Use Evaluation study\(^9\) showed that immediate versus delayed blood pressure lowering translates into early benefit. Narrowing the blood pressure gradient between the groups randomised in those two trials did not erase the initial benefit. As in the Jikei Heart Study, the survival curves started diverging early after randomisation, and continued doing so when the blood pressure difference was minimised\(^8\) or even abolished.\(^9\) Furthermore, in

Figure: Plasma renin activity before and after single dose (day 1) and 7-day (day 8) treatment with different angiotensin-II type-1 receptor blockers in normal volunteers

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keeping with large-scale prospective observational studies, meta-regression showed that small gradients in the achieved systolic blood pressure explained most of the differences in cardiovascular outcomes, as observed in randomised trials. This association was particularly strong for the prevention of stroke and weakest for heart failure. It required from 150 000 to 180 000 randomised patients followed up for 3–5 years to show a 10–15% benefit beyond blood pressure lowering with calcium-channel blockers or angiotensin-converting enzyme (ACE) inhibitors over other classes of antihypertensive drugs in the prevention of stroke or myocardial infarction, respectively. By contrast with ACE inhibitors, ARBs do not produce a reduction in the relative risk of coronary heart disease that is independent of blood pressure.

The average daily dose of valsartan was 76 mg in the Jikei study, which is within the range (40–80 mg, maximum 160 mg) recommended by the Japanese Society of Hypertension. In 24 healthy volunteers, Mailard and colleagues compared blockade of the angiotensin-II type-1 receptor after acute (4 h) and chronic (8 days) administration of valsartan (daily doses of 80, 160, and 320 mg), irbesartan (150 mg), candesartan (8 mg), and losartan (50 mg) in an in-vitro radioreceptor-binding assay and by the reactive rise in plasma renin activity. At 4 h, valsartan induced a dose-dependent blockade of the receptors. The 160 mg and 320 mg doses blocked the receptors by about 65%, which was similar to the effect of 150 mg irbesartan, but less than that of 80 mg valsartan (about 55%) and 50 mg losartan (about 50%). With plasma renin activity as a marker of receptor blockade, on day 8, 80 mg valsartan was equivalent to 50 mg losartan and 8 mg candesartan (figure). One can only speculate whether these pharmacological characteristics of ARBs in white individuals apply to Japanese people, or what the Jikei Heart Study would have reported had a higher dose of valsartan been used.

The Jikei trial ran at tertiary care referral centres. Its results cannot therefore be easily extrapolated to general practice. The key question then is whether after the publication of the Jikei Heart Study the increase in knowledge will be large enough to benefit patients with hypertension, coronary heart disease, or heart failure, in particular Japanese patients. The answer is no, if marketers would spread the message that valsartan, or for that matter other ARBs, might confer benefits beyond blood pressure lowering. Indeed, comprehensive reviews of the literature do not support this point of view. On the other hand, the answer might be yes, if doctors would learn from the Jikei results that aggressive antihypertensive treatment is safe and prevents cardiovascular complications. Here, aggressive means optimisation of treatment at acceptable tolerance and the combination of several classes of antihypertensive drugs, each to be prescribed at the lowest dose to attain targets.

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JAS has consulted for and received funding for studies, seminars, and travel from manufacturers of drugs that lower blood pressure. TR declares that he has no conflict of interest.


Childhood pneumonia: we must move forward

Childhood pneumonia is the most important global cause of death in children,1 and, in addition to preventive strategies of improved nutrition and use of vaccines, appropriate treatment is the key control strategy. Since 1985, WHO has recommended presumptive treatment of pneumonia, with an algorithmic approach.2 The initial recommendations suggested that children who met the clinical criteria of rapid breathing (presumed pneumonia) should receive antibiotic treatment at home with co-trimoxazole for 5 days. If chest indrawing was present, severe pneumonia was presumed and referral for further treatment was recommended. These recommendations were initially based on limited data and expert opinion,3,4 and were validated in research from 1988 through the early 1990s.5 Furthermore, a series of studies since 2000 has shown that oral amoxicillin and 3 days of treatment were equivalent in outcomes to the previous recommendations. In addition, a recent study showed that if wheezing children, who often meet the respiratory rate and indrawing clinical criteria for presumed pneumonia, respond to bronchodilator therapy, they do not benefit from antibiotic treatment.6 Because an increasing proportion of young children have HIV infection, with increased rates of pneumonia, revised guidelines for presumptive treatment of young children in regions with a high HIV prevalence have been developed.7

In today's Lancet, Lisa McNally and colleagues8 show that a high proportion of South African children with severe pneumonia fail to improve on therapy recently recommended in WHO guidelines. Most likely to fail were children under 1 year of age and born to HIV-positive mothers, and those with more than one organism detected at the time of admission. Although the generalisability of these data might be limited, the authors suggest that current WHO guidelines for presumptive treatment of children with severe pneumonia in HIV-endemic areas should be modified. They note that without better data on causation, designing appropriate presumptive treatment regimens for these regions is difficult.

The progress in revising and validating pneumonia treatment guidelines seems slow, given the importance of pneumonia and lower respiratory tract disease in children in low-income settings.1 The new WHO guidelines for regions with a high prevalence of HIV await assessment in routine practice in several regions. This slow pace is reflective of childhood pneumonia inexplicably remaining the forgotten killer for more than 20 years,9,10 despite causing the deaths of more children than AIDS, tuberculosis, malaria, and measles combined.11 We urge the development of new research programmes to gather necessary evidence to improve guidelines for the treatment of presumptive pneumonia in children in regions with low and high prevalences of HIV. The path of carefully selecting research questions, answering them in efficacy trials in a research setting, and then measuring effectiveness during routine implementation will be the most efficient approach to improve outcomes in children with pneumonia, and to respond to changing disease patterns.12 Better causal data are needed to inform prevention efforts and tailor presumptive treatment. Childhood pneumonia pathogens were extensively studied by the BOSTID group in the 1980s,13 but the recent advances in diagnostic technology, including nucleic acid and antigen detection and use of host response factors, have not been widely applied in low-resource settings to determine the full spectrum of agents. In addition to research diagnostics, practical clinical diagnostic devices at the point of care for the detection of tuberculosis, Pneumocystis jiroveci (formerly carinii), and antimicrobial-resistant bacteria would improve therapeutic decisions in the clinical setting and are likely to improve outcomes.14

In addition to the need for research to guide antimicrobial therapy, there is a need for work on predictive

The printed journal includes an image merely for illustration

Child with AIDS and pneumonia, Thailand
guidelines to identify children who will have poorer outcomes and need modified care. It has long been clear that hypoxaemia is an important predictor of poor outcomes; in well-resourced regions, hypoxaemia is managed with oximeters for detection and oxygen therapy. The hesitancy in making investments for providing oximeters and oxygen concentrators could be due to the need for robust evidence that provision of these technologies would improve outcomes in the typical low-resource setting.

Achieving the Millennium Development Goal for child survival will require a new coordinated effort of research and implementation to prevent and control childhood pneumonia. This need is now urgent and the effort must be aimed at disease reduction in areas with low or high prevalences of HIV infection.

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The burden of dengue infection

Using a prospective population-based cohort of 2119 school-age children in a rural area of Thailand, Katie Anderson and colleagues1 provide, in today’s *Lancet*, important insights into the burden—both economic and human—imposed by dengue infections. Quantification of these burdens is crucial to the formulation by governments, donors, and industry of decisions for the prevention and management of dengue, especially for the potential introduction of dengue vaccines or other technologies.

Anderson and co-workers studied the children for 5 years, allowing them to identify a ten-fold variation in dengue incidence and hospitalisation rates from year to year that an earlier study,2 which ran for only 1 year, would not have detected. A further strength of Anderson and colleagues’ study is their intensive surveillance of both mild and severe disease. Usually, notification of suspected dengue cases to public-health authorities depends on passive surveillance of hospitalised cases. Although legally mandated in most countries where dengue is endemic, notification is rarely enforced.3 Because most ambulatory cases of dengue and some hospitalised cases are generally not officially notified, under-reporting is usually the most important challenge to obtaining reliable national estimates of dengue diseases. On the basis of studies like Anderson’s, expansion factors can be derived to adjust for this under-reporting.

Of the 328 symptomatic confirmed dengue infections in Anderson and colleagues’ study, 52 (16%) were classified as dengue haemorrhagic fever on the basis...
of WHO criteria. Hence, for each case of dengue haemorrhagic fever, there were about five cases of dengue fever. Additionally, for each of the 96 hospitalised cases (44 cases of dengue fever and 52 of dengue haemorrhagic fever), there were three ambulatory cases of dengue. Therefore the number of dengue cases (both dengue fever and dengue haemorrhagic fever) was about six times the number of hospitalised cases of dengue haemorrhagic fever or, more informatively, four times the number of hospitalised cases of dengue. If these expansion factors are representative of the experience of symptomatic dengue infection in a homogeneous population such as that of Thailand, estimates of the burden of illness for the entire nation can be calculated from hospitalised cases reported to national authorities.

Globally, illness expression in dengue can vary enormously. Factors that affect disease severity include ethnicity, age, nutritional status, the exact sequence of two different dengue infections, the genotype of infecting virus, and, of course, the competence of the clinical and laboratory surveillance systems. To document and study virus, and, of course, the competence of the clinical and laboratory surveillance systems. To document and study

**Piperazine designer drugs of abuse**

In today’s Lancet, David Wood and colleagues report on the first case of poisoning with 1-benzylpiperazine (BZP) in the UK. This case report is a valuable contribution to the development of a better understanding of the toxicity of this new drug of abuse. To date, only a few cases of poisonings and deaths with BZP have been reported. However, in these reports, no detailed clinical data were given, the cases were polydrug intoxications, or only limited analytical toxicological analysis was available. The case reported by Wood...
Comment

and colleagues describes for the first time the clinical symptoms of an acute mono-intoxication with BZP, which was confirmed by toxicological analysis.

BZP is the most prevalent compound of a new class of designer drugs of abuse called piperazines (figure). Besides BZP and 1-(3,4-methylenedioxybenzyl)piperazine (MDBP), there are the phenylpiperazine derivatives: 1-(3-trifluoromethylphenyl)piperazine (TFMPP), 1-(3-chlorophenyl) piperazine (mCPP), and 1-(4-methoxyphenyl)piperazine (MeOPP).5

The amfetaminergic effects of BZP have been known since the 1970s. A mixture of BZP and TFMPP mimics the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy).3,5–8 The phenylpiperazines are well-characterised serotonergic compounds, which is also the reason for the use of 1-(3-chlorophenyl)piperazine (mCPP) as a probe drug in psychiatric research.5–7 Commonly, piperazines are sold as party pills in the form of tablets, capsules, or powders on the black drug-market and in so-called headshops or over the internet. They are also found in tablets sold as ecstasy or amfetamine. Generally, piperazine blends are consumed. Besides the most prevalent mixture of BZP with TFMPP, there are also blends of up to four different piperazines (named X4). Furthermore, mixtures of piperazines with other drugs of abuse, such as ecstasy or cocaine, have been reported.5,7 Since the end of the 1990s, piperazines are often proffered as a legal and safe alternative to amfetamine-derived drugs. The discussion on their legal status is ongoing in many countries. However, some countries (eg, the USA, Australia, Japan, and some European countries) already control BZP under drug control or equivalent legislation.6,29 Thus the claimed advantage of legality is not given anymore in these countries. In March, 2007, in the UK, the Medicines and Healthcare products Regulatory Agency declared the selling of BZP products illegal.30 Predictably, the legal measures started a kind of cat-and-mouse play. Instead of BZP, other, not yet scheduled, piperazines, mainly mCPP, increasingly appeared on the market.

The widespread use of piperazines with only a low record of attributable toxicity is stated by activists as proof of safety for legalisation of these drugs. However, from a toxicological point of view, such a stance cannot be affirmed. In view of the similar pharmacological modes of action of piperazines and amfetamines, similar toxicity has to be assumed. This assumption is supported by the reported cases of piperazine poisonings31–3 and by the occurrence of serotonin syndromes in a clinical study.11

Special attention should be paid here to polydrug use. Synergistic effects of piperazine blends have been described.3 Furthermore, particularly the phenylpiperazines are extensively metabolised, mainly by the polymorphically expressed cytochrome P450 2D6 (CYP2D6) which might result in an increased risk of toxic side-effects for CYP2D6 poor-metabolisers.5 In addition, these compounds are liable for drug–drug interactions with inhibitors or other substrates of this enzyme (eg, MDMA, cocaine), which might similarly increase the risk of toxicity, especially because piperazines seem to have a narrow safety margin.6,8,11

The low record of reported poisonings with piperazines has also to be put into perspective. Many clinicians are not aware of newer classes of drugs of abuse. Piperazines and amfetamines are similarly marketed, consumed by the same population, and show similar pharmacological symptoms. Therefore a piperazine poisoning can easily be wrongly diagnosed as an amfetamine poisoning. Furthermore, piperazines are not detected by routinely used immunochemical screening procedures for drugs of abuse, but require an appropriate toxicological analysis (eg, by gas-chromatography mass-spectrometry).12,31

Hence Wood and colleagues’ case report is an excellent example to raise clinicians’ awareness of newer drugs of abuse and substantiates the importance of a sound toxicological analysis for a correct clinical diagnosis. As a result, more cases of abuse of new designer drugs will be detected, which in turn will yield data essential for a toxicological risk assessment. Besides piperazines, there are also further new classes of designer drugs of abuse, such as phenethylamines (2C-series), α-pyrrolidino-phenones, and new phenacyclidine derivatives.15

Figure: Piperazine designer drugs of abuse
Thromboembolism prevention in ischaemic stroke

Screening venography to detect asymptomatic deep-vein thrombosis of the legs, usually done at discharge from hospital or about 10 days after surgery, is the preferred way to assess the efficacy of prophylaxis for venous thromboembolism in high-risk patients. An advantage of routine venography is that it is a sensitive test which yields high frequencies of deep-vein thrombosis and has statistical power to compare methods of prophylaxis in modest numbers of patients (eg, hundreds rather than thousands). A disadvantage is that most of the thrombi detected are small, generally confined to deep veins of the calf, and of little clinical importance. Therefore asymptomatic deep-vein thrombosis detected by screening venography serves as a surrogate for clinically important venous thromboembolism and, ultimately, fatal pulmonary embolism.

Evidence supports deep-vein thrombosis detected venographically as a valid surrogate for symptomatic venous thromboembolism. For example, controlled trials have shown that an extra 4–6 weeks’ duration of treatment with low-molecular-weight heparin after major orthopaedic surgery results in much the same relative risk reduction for venographically detected deep-vein thrombosis (9.6% vs 19.6%, odds ratio 0.48, 95% CI 0.36–0.63) and symptomatic deep-vein thrombosis or pulmonary embolism (1.3% vs 3.3%, 0.24–0.61).1 However, deep-vein thrombosis detected venographically has limitations as a surrogate because of an inconsistency between the frequency of symptomatic venous thromboembolism and venographically-detected deep-vein thrombosis. For example, there is a higher frequency of deep-vein thrombosis detected venographically (about 1.5-fold) but a lower frequency of symptomatic venous thromboembolism (about 0.5-fold) after knee replacement than after hip replacement.2,3 There is also a higher frequency of venographically-detected deep-vein thrombosis (relative risk for all deep-vein thrombosis 1.5, 95% CI 1.3–1.8) but a similar frequency of symptomatic venous thromboembolism (relative risk for clinical pulmonary embolism 1.1, 0.6–2.1) with warfarin than with low-molecular-weight heparin after major orthopaedic surgery.4 Therefore deep-vein thrombosis detected venographically seems to be a valid surrogate when antithrombotic regimens that have a similar mechanism of action (eg, different doses of the same drug, or two similar drugs) are compared in the same populations, but might not be a valid surrogate when these two conditions are not met.

Even when deep-vein thrombosis detected venographically is a valid surrogate for comparisons of...
regimens of venous thromboembolism prophylaxis, the clinical importance of reductions in asymptomatic deep-vein thrombosis and increases in symptomatic bleeding is often difficult to balance. Most asymptomatic deep-vein thromboses do not progress to cause symptoms, and the proportion that does progress is expected to differ between populations (eg, higher rates of progression after hip than after knee surgery; probably higher rates of progression after stroke than after surgery with rapid mobilisation). By contrast, most confirmed episodes of bleeding that are reported in clinical trials are associated with symptoms and are clinically important.

How then should the findings of the recent PREVAIL trial that compared enoxaparin (40 mg once daily) with unfractionated heparin (5000 U twice daily), both subcutaneously, in patients with acute ischaemic stroke be interpreted?5 David Sherman and colleagues reported that enoxaparin reduced the frequency of all venous thromboembolism at 14 days (relative risk 0.57, 95% CI 0.44–0.76). However, of the 189 episodes of venous thromboembolism that occurred, 95% were asymptomatic deep-vein thromboses detected by routine venography (roughly half involved the proximal deep vein and half were confined to the distal deep veins). There was a non-significant reduction in the number of symptomatic episodes of venous thromboembolism with enoxaparin (0.3% vs 1.0%, 0.29, 0.06–1.38) that was consistent with the relative risk reduction reported for asymptomatic deep-vein thrombosis. Also, there was one fatal pulmonary embolism in the enoxaparin group and two in the unfractionated heparin group. Therefore PREVAIL provides clear evidence that enoxaparin is more effective than unfractionated heparin for prevention of venous thromboembolism in patients with acute ischaemic stroke.

What about safety, and in particular bleeding, with the two antithrombotic regimens? Clinically important bleeding (commonly referred to as major bleeding), which was symptomatic by definition, occurred in 1.3% of the enoxaparin group and in 0.7% of the unfractionated heparin group (relative risk 1.82, 0.68–4.91). These major bleeding episodes included symptomatic intracranial haemorrhages in four patients in the enoxaparin group and in six patients in the unfractionated heparin group (0.66, 0.19–2.34), and major extracranial haemorrhage occurred in seven and none, respectively (p=0.015). Two of the extracranial haemorrhages were fatal. The number of patients who had asymptomatic intracranial haemorrhage in each of the groups was not reported. Evidence suggests that asymptomatic intracerebral haemorrhage is not necessarily benign, and the frequency of this finding in the two treatment groups would help to clarify whether enoxaparin truly was not associated with an increased risk of intracranial bleeding.6

In the 1762 patients with acute ischaemic stroke in PREVAIL, enoxaparin resulted in five fewer episodes of symptomatic venous thromboembolism and one less episode of fatal pulmonary embolism, but was associated with five more episodes of major bleeding and one more episode of fatal bleeding than unfractionated heparin. Consequently, although the enoxaparin regimen is more effective at prevention of venous thromboembolism, whether this benefit outweighs a higher risk of bleeding is uncertain. The risk-to-benefit ratio of these two antithrombotic regimens should become clearer when neurological outcomes in the two groups are reported. Hopefully, that report will include the frequencies of all intracranial haemorrhages, including those that were considered to have been asymptomatic.

Another important issue relating to the use of routine venography to assess the efficacy of venous thromboembolism prophylaxis in clinical trials is that this assessment, by leading to the detection and treatment of asymptomatic deep-vein thrombosis, changes the subsequent frequency of symptomatic venous thromboembolism.7 If routine venography with long-term follow-up had not been done in PREVAIL, the relative and absolute risk reduction in symptomatic venous thromboembolism with enoxaparin could have been greater.

In view of the uncertain clinical importance of asymptomatic deep-vein thrombosis, and because screening venography and treatment of asymptomatic thrombi precludes a valid assessment of symptomatic outcomes with longer follow-up, we suggest that phase III randomised trials should avoid the use of asymptomatic deep-vein thrombosis as an outcome to assess the efficacy of venous thromboembolism prophylaxis. Trials that use clinically important outcomes to assess both efficacy and safety would yield more definitive results that are easier to interpret and more relevant to clinical practice.
Value-based pricing of drugs in the UK

The Pharmaceutical Price Regulatory Scheme (PPRS), launched over 50 years ago, was designed to secure safe and effective drugs for the UK National Health Service (NHS) at reasonable prices, and to promote a strong and profitable pharmaceutical industry able to develop new and improved drugs.1 On Feb 20, 2007, the Office of Fair Trading (OFT), the UK’s independent competition and consumer protection authority, recommended to the UK Government that the PPRS should be radically reformed to deliver better value for money from the NHS drug budget and to focus business investment on drugs that have the greatest benefits for patients.2 The OFT argues that the PPRS does not offer a sufficient incentive to innovation or drug development in areas of unmet medical need. In addition, the OFT estimates that the proposed reform would release about £500 million, from a total spend of £8 billion on branded prescription drugs, to give patients access to treatments to which they might otherwise be denied. Health services in many countries base their prices on those in the UK, so implementing this reform might well have wider international consequences.

The proposed reform, not to be introduced before 2010, is in two parts. First, the OFT suggests a review of drugs at the time of licensing, in terms of cost-effectiveness measured in quality-adjusted life-years (QALYs). If new drugs provide poor value for money, the price would be further negotiated. Second, the OFT proposes re-negotiation of prices within a drug class when the first member of that class goes off patent, because of the large differences in cost between generic and branded drugs (eg, ten-fold for statins). These reviews, the additional cost of which is estimated at around £6 million a year, will be done by existing bodies, including the National Institute for Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC).

Are the OFT right to make efficiency (ie, maximum health gain from the budget available) the main policy objective? The Association of the British Pharmaceutical Industry has expressed concern about possible adverse effects on stability and investment into research and development in the UK,3 but should the hard-pressed NHS drugs budget bear this cost? Indeed, there are other ways to maintain a strong and profitable UK pharmaceutical research and development base, including maintenance of a strong science base within universities and procedures to support drug development.4 We must hope that PPRS reform can be delivered through a positive engagement with industry.

This reform should give the NHS increased flexibility in responding to new drugs. At present, the manufacturer of a new drug presents the clinical evidence and (fixed) price to the NHS (via NICE or SMC). If this package does not achieve acceptable cost-effectiveness, the only responses are to recommend it should not be made available, or to try to define a subgroup of patients in whom it is cost effective. If price is also negotiable, there is the prospect that more drugs may be made available to patients. These negotiations should not be designed to delay decisionmaking, and need to allow for further review in the light of new evidence. One concern is that manufacturers might price to the upper limits of cost, so that the QALYs the NHS currently obtains fairly cheaply might become more expensive. In addition, drugs that

would currently not be funded on cost-effectiveness grounds might squeeze through as a result of price negotiation, such that the NHS could be faced with even more (although acceptably) expensive QALYs. The net result could be an upward pressure on the average cost per QALY for funded drugs, with the result that the NHS gets less QALYs from a given budget (figure). There are many related issues to be resolved, such as the definition of acceptable cost-effectiveness and how drugs for rare diseases would be handled. However, the knowledge that other countries have successfully introduced value-based pricing and reimbursement schemes (ie, Sweden, Australia, Canada) is reassuring.

Reform of the PPRS is opportune, and the principle of adopting an approach that is based on service and value has much to commend it. The UK Government now needs to give the OFT’s detailed observations and recommendations, within this intelligent, well-argued, comprehensive, and timely study, the careful consideration they deserve.

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DJW has had fellowships and grants from the pharmaceutical industry within his department for research on drugs. AW has received honoraria and speakers fees from Astra Zeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, and Schering-Plough, and his department has received funding for commissioned work from Merck Sharp & Dohme and Roche. DJW and AW are members of the Scottish Medicines Consortium (SMC), but this Comment represents their personal views and not those of SMC.


Cardiology: call for papers

To coincide with this year’s annual European Society of Cardiology meeting in Vienna on Sept 1–5, The Lancet is planning to publish a special issue.

We therefore issue a call for high-quality research papers on any aspect of cardiology. We are specifically interested in the results of randomised trials and other clinical studies that will have a profound effect on clinical practice. If your study’s results have been accepted for presentation at the meeting, please let us know, so that we can plan publication, possibly online, to comply with any embargo policies. Our fast-track system allows us to consider late-breakers up to 28 days before the meeting. Please contact a fast-track editor if you would like us to consider such a submission.

Papers should be submitted online by May 18, 2007, at the latest, and the covering letter should state that the submission is in response to this call for papers.

Stuart Spencer
The Lancet, London WC1N 7BY, UK

To submit a paper go to http://ees.elsevier.com/thelancet
Child malnutrition rises in India despite economic boom

The growth of India’s economy during the past decade has had little effect on the nutritional status of its youngest citizens. Even in affluent states, the percentage of underweight children younger than 3 years has risen over the past 10 years. Patralekha Chatterjee reports.

Chandigarh, the joint capital of Haryana and Punjab—two of India’s richest states—is an elegant city, with the highest yearly per head income in the country. The signs of affluence are everywhere: glitzy malls, luxury cars, and a high-spending middle class. But on the outskirts of this town, the underbelly of India’s booming economy is clearly visible.

In the Azadpur slum, crouched on the floor of her one-room shack, Krishna Devi, twenty-something and 8 months pregnant with her second child, looks listlessly out the door. Her husband, Hriday Ram, a migrant, works as a gardener in middle-class homes. Theirs is a hand-to-mouth existence. But the future holds more promise than in their native village in the under-resourced, over populated state of Uttar Pradesh.

Krishna is anaemic. Kiran, her 2 year-old son, is severely malnourished. Although anaemia can be tackled with iron and folic acid tablets, Krishna is unaware of their importance. A tin of protein supplements and packs of iron and folic acid tablets lie on a shelf in the corner of the room, unconsumed. “I did not like the taste”, she says.

Krishna has had no antenatal check ups to date. A private doctor prescribed expensive protein supplements but did not explain the need for an iron-rich diet during pregnancy. Every morning, Krishna gives her son a cup of milk diluted with water along with a few biscuits. Like most people in the Azadpur slum, Krishna’s contact with the public-health system is negligible.

In February this year, UNICEF officials created a stir by telling a gathering of national and international journalists in Delhi that an Indian child is more likely to be malnourished than a child in Ethiopia, the Horn of Africa nation known for its periodic droughts, famines, and long civil conflict and border war with Eritrea.

The comment stemmed from India’s 2005-06 National Family Health Survey (NFHS), which reveals that almost half of Indian children younger than 3 years are underweight. The results show that the malnutrition crisis is not confined to migrants huddled in urban shanties like Krishna and her family. Anaemia and undernutrition in small children and pregnant women in their prime is growing, even in India’s prosperous states like Haryana.

Life in Dundahera village in the Gurgaon district of Haryana, offers a glimpse of perhaps why economic boom is not translating into better maternal and child health in India. In recent years, Gurgaon has emerged as one of India’s hottest outsourcing hubs. Shopping centres, multinational companies, and industrial complexes dot the cityscape. Eager to tap the emerging commercial opportunities, Dundahera’s farmers are selling their land to builders. New houses have been built to accommodate the growing number of migrant families streaming into the area to fuel the economic boom. Many families who have sold their land have suddenly become rich. But within the family and this highly patriarchal society, the status of women has scarcely improved.

“Alcoholism is on the rise in Dundahera. The new rich spend their extra cash on beautifying their house, on clothes, and gadgets. The health of the woman is not a top priority for most families. Even if the family owns cattle, they will prefer to sell most of the milk. There is no one really to ensure that an expecting mother eats well. More money in hand does not mean healthy mothers and children”, says Sharda, a village-level anganwadi (child development and nutrition) worker.

The latest NFHS data are preliminary findings. Detailed analyses are awaited, but nevertheless, the current findings have sparked justifiable concern: 41.9% of children under 3 years in Haryana...
were clinically underweight (too thin for their age) in 2005–06 compared with 34.4% in 1998–99. During the same period, the number of children younger than 3 years who are too thin for their height rose from 5.3% to 16.7%. Disturbingly, the new data also reveal that 69.7% of pregnant women in the 15–49 year age group in Haryana are anaemic compared with 55.7% 7 years ago.

The discrimination against girls and women in affluent Haryana might explain some of the increase in anaemia. Girls continue to be worse fed than boys in most families, especially in rural areas.

The latest NFHS data also support other recent sample surveys in the state. A community-based study in ten villages in Haryana in 2004–05 found that 25 out of every 100 newborn babies in rural Haryana are low birthweight (less than 2500 g at the time of birth). The prevalence of low birthweight babies in rural Haryana has remained nearly constant for the past two decades, despite the state’s rapid economic progress.

“The problem of low birthweight is due to inadequate food intake and maternal anaemia. There is little awareness among mothers about what food to eat, how much to eat, and an inability to co-relate the food intake with the outcomes. If this is showing up as low birthweight and child malnutrition, failure to identify maternal anaemia is to blame”, says Arun Aggarwal, one of the researchers on the study based at The Postgraduate Institute of Medical Education and Research in Chandigarh.

“Pregnant women take tetanus toxoid injections. So, there is a contact with the health-care system but this is not translating into awareness about anaemia. Health workers in the villages rarely conduct haemoglobin tests on pregnant women.”

“Other problems on the ground include irregular supplies of the reagent required to conduct haemoglobin tests. Tetanus toxoid has been flagged, anaemia has not. The community health worker is supposed to identify anaemic women on laboratory and other clinical parameters and provide double dose of iron folic tablets but such tablets also are often in short supply. There is an urgent need to make the monitoring and evaluation system for maternal anaemia more rigorous”, Aggarwal told The Lancet. By the time, the anaemia is diagnosed in a pregnant woman, it is often too late.

However, there are signs of change. The Government of Haryana and UNICEF have signed a Memorandum of Understanding to work together to improve social indicators for women and children in the state. Recently, the Haryana Government has set up a state-level steering committee on nutrition. Attempts are finally being made to address the root causes affecting child nutrition. And following the advice of community doctors, health and nutrition workers have begun focusing on the health of the adolescent girl.

“If we want to fight under-nutrition among small children, we have to target mothers before they become pregnant. Today, we are targeting young girls—those who are in the 11 to 18 year age group, who are likely to become young mothers in a few years, through ‘balika mandals’ (support groups of young girls). We counsel them about health and hygiene, about deworming, prepare them for motherhood, sensitise them about the need to take iron tablets. This goes hand-in-hand with our continuing work with expecting mothers”, says Chanchal Dhalwal, who is in-charge of Gurgaon district’s Integrated Child Development Services—a nation-wide nutrition and health programme that serves millions of women and children.

The Haryana Government has also decentralised the supplementary nutrition scheme to improve efficiency. Now, self-help groups of women are given cash to procure raw materials locally and make local preparations. Other attempts to improve maternal health and nutrition include “best mother contests”. Best mothers are those with the best scores in a health education quiz.

“The contests, which began 3 years ago, are intended to get mothers hooked to the health-care system. The initiative is now being taken to other districts in Haryana. It is a slow process but women are becoming more nutritionally literate in [the] Gurgaon district and severe malnutrition among children under 6 [years] is going down”, adds Dhalwal.

Patralekha Chatterjee
Canadian soldiers and doctors face torture allegations

In the mid-1990s, Canadian troops stationed in Somalia were found guilty of torturing and murdering detainees. Now Canadian soldiers and doctors are under investigation again, this time for human rights abuses following recent operations in Afghanistan. Paul Webster reports.

Canadian soldiers and military physicians face torture allegations stemming from recent combat operations in Afghanistan. Amnesty International and the British Columbia Civil Liberties Association (BCCLA) say Canadians fighting in Afghanistan might be complicit in torture practices similar to those that disgraced Canadian military operations in Somalia more than a decade ago.

The two groups filed an official complaint in February this year and called for a public judicial review of an agreement, signed by Canadian military officers in 2005, minimising Canadian responsibility for the humane treatment of war prisoners. This complaint came shortly after University of Ottawa law professor, Amir Attaran, alleged that Canadian interrogators—possibly aided by military doctors—might themselves have directly abused several Afghan detainees.

Four official investigations are now examining the role of Canadian military interrogators seeking military intelligence from detainees, along with the practice of rendering prisoners to Afghan officials implicated in systematic torture. In interviews with The Globe and Mail newspaper, several detainees transferred by Canadian military police complained of torture—including the use of electric shocks, and sustained whippings—at the hands of Afghanistan’s National Directorate of Security.

When political pressure over the treatment of detainees began mounting in March, Canadian defence minister Gordon O’Connor, a former brigadier general with 30 years experience in the military, made a surprise visit to Afghanistan in order to belatedly sign an agreement with the Afghanistan Independent Human Rights Commission, which will in future attempt to monitor the treatment of detainees transferred from Canadian facilities to Afghan prisons.

The Canadian Government has also now admitted that it is unable to locate several detainees already transferred to Afghan jails, including three who are suspected of having been beaten by Canadian interrogators before being transferred.

Although the disappearance of these detainees could simply be a matter of sloppy administration, says Amnesty International spokesman John Tackaberry, “we fear, however, that the worst may have happened to them”.

In a court filing, supporting a call for a judicial review of Canadian detainee policies in Afghanistan, Amnesty International and the BCCLA say the detainee transfer agreement between the Canadian and Afghan militaries, signed in December, 2005, but kept confidential for more than a year afterwards, was designed to give Canadian interrogators maximum flexibility while gathering military intelligence from detainees. In calling for a judicial review of the agreement to determine whether it is acceptable under Canadian law, Amnesty and the BCCLA argue that Canadian detainees are subject to protection under the Canadian Charter of Rights and Freedoms.

Ottawa lawyer Paul Champ, who drafted the call for a judicial review, says Canadian detainee policies seem to have been modelled in part on controversial US rendition policies designed to expedite the movement of US prisoners of war to countries where torture is used in interrogations.

Canadian officials have admitted to participating in US rendition efforts in the past and have paid substantial compensation to an Ottawa man who was tortured in Syria after US officials flew him there with help from Canadian security police. A legal inquiry is now examining several other such cases.

Champ notes that Canada’s agreement with Afghanistan allows Canadian detainees to be passed to third countries “who may torture or execute the detainees”. He notes that the UK agreement with Afghanistan concerning detainees does not allow this, and that other NATO countries operating in Afghanistan, including the Netherlands and the UK, have always included provisions to ensure the Afghanistan Independent Human Rights Commission monitors detainees once they are transferred to Afghan jails.

Along with the charge that Canada’s official agreement with Afghanistan fails to protect detainees from torture once they are transferred to Afghan
prisons, Canadian Forces interrogators have also been suspected of torturing one or more detainees during interrogations in Canadian military facilities.

These suspicions stem from an investigation by Amir Attaran, a professor of law at the University of Ottawa and an Editorial Consultant at The Lancet, who used Canada’s freedom of information law to force the Canadian military to release records relating to detainees captured in Afghanistan.

In late January, Attaran asked Canada’s Military Police Complaints Commission (MPCC) to specifically investigate the interrogation of three men captured in early April, 2006. “My working hypothesis”, says Attaran, “is that at least one detainee was beaten while in the custody of a Canadian Forces interrogator”. In his request for an investigation, Attaran also hypothesised that “there was also systematic roughness among [Canadian Forces] which resulted in two other men described as ‘fit’ actually having unexplained injuries (contusions and abrasions) on their upper bodies”.

Attaran suggests that Canadian Military Police (MP) at Kandahar airfield in Afghanistan were “aware that they possessed three injured detainees about whom questions might be asked” and “acted with unusual speed to get the men permanently off the base and into Afghan custody. To that end the MPs failed to investigate the cause of the three detainees’ injuries. MPs shortcutted the standard procedure of bringing the detainees for medical attention or treatment, as this would have resulted in the injuries being noted in a sick report or other medical records.”

Attaran says he wants the MPCC to look closely at the role of medical staff on Canadian military bases. Military physicians are required to document the physical condition of detainees as they pass through Canadian hands in Afghanistan.

Although Attaran says it “doesn’t seem that the doctors were asleep at the wheel” in the case of the three detainees who might have been injured by Canadian interrogators, he is prevented from reaching firm conclusions because of heavy censorship of the records he has reviewed. Attaran notes that under UN medical ethics principles it is unethical for health personnel, “to certify, or to participate in the certification of, the fitness of prisoners or detainees for any form of treatment or punishment that may adversely affect their physical or mental health”. Under the term of the UN principles, Attaran argues, Canadian medical staff in Afghanistan should not agree to certify detainees to be fit for transfer to Afghan jails in light of the risk that they will be tortured. Instead of transferring detainees, Attaran believes that Canada and other NATO countries fighting in Afghanistan should maintain separate detention facilities.

Attaran says he was prompted to begin seeking information about the fate of Canadian detainees after Canadian military officials refused to allow him to review the agreement they signed with their Afghan counterparts. When the agreement was ultimately released to a member of parliament, Attaran says he was shocked by its laxness in protecting detainees’ human rights. “I had assumed that Canada would have an exemplary approach to this issue given what happened in Somalia in the 1990s”, Attaran says. “It looks, however, like they learned very little in Somalia.” Attaran’s complaint has been accepted for investigation by the MPCC, along with the broader policy-related complaint filed by Amnesty and the BCCCLA.

“The medical condition of the prisoners is an issue”, says MPCC chief of staff Stanley Blythe, “if we turn up evidence of injuries we will have to look at the role of the military police, including whether they ensured proper medical care was provided.” If the MPCC encounters “a lack of cooperation” Blythe says, “we can call for a public hearing”.

Blythe says the MPCC requested documents from the Canadian Forces as a first step in its investigations after receiving the complaints in February. “For reasons they know better than us they are still compiling the documents”, Blythe told The Lancet. “We’ve had signs of cooperation, but the actual process has been disappointingly slow.”
Vaccines occupy a peculiar place in medicine and society. That they prevent disease is incontrovertible; ample evidence for their effects is obvious in the industrialised countries and increasingly so in the developing world. Only clean water has a greater impact on infectious diseases. Molecular biology now permits the development of more vaccines, perhaps even some against non-infectious diseases. Yet vaccination has been controversial from its inception in the primitive practice of variolation against smallpox to its latest avatar in the form of purified pseudoparticles composed of single papillomavirus proteins that prevent cervical cancer. Objections to vaccination have evolved from early theological concerns that it countered God’s will to the belief in certain circles today that for a healthy immune system disease is preferable to vaccines. This paradox is explained by two factors: first, that vaccines are usually given to healthy people, and reactions to vaccines may make some of those healthy people ill; and second, that vaccination is often made compulsory by governments because of the state’s interest in protecting children and in maintaining the herd immunity provided by vaccines. On one side, society insists that refusal to be vaccinated is an act that threatens the community, whereas on the other side, libertarians insist that vaccination should be done only with consent. Thus, we live in a time when vaccines have never been more effective and when vaccine science has never been more promising, but when opposition to vaccines is, nonetheless, flourishing.”

Allen begins with detailed historical description of the early discoveries that led to the eventual eradication of smallpox, follows with a middle section recounting the development of vaccines that were produced in the past 150 years, and concludes with a description of the controversies regarding alleged causation of encephalopathy by whole-cell pertussis vaccine, and of autism by thiomersal-containing vaccines. He then states: “Thus, we live in a time when vaccines have never been more effective and when vaccine science has never been more promising, but when opposition to vaccines is, nonetheless, flourishing.”

Allen is clearly most interested in the controversies that surround vaccination. He gives insight into the dilemma that although vaccines give more benefit than harm, there will always be the risk of reactions, which come in three varieties: real, false, and uncertain. The real ones, such as paralysis after oral polio vaccine, are discovered after licensure and result in revised recommendations or withdrawal; the false ones, such as the claimed consequence of multiple sclerosis after hepatitis B vaccine, are disproved by studies and disappear into urban legend; but the ones that are uncertain, because of their rarity or the difficulty in designing studies, remain to agitate sincerely concerned individuals and conspiracy enthusiasts.

The problem is that each reaction to vaccines—real, false, or uncertain—needs resources to fund studies, and the results of studies do not convince everyone. Allen describes in detail the controversy over thiomersal, or ethyl mercury, which had been used for many years as a way to prevent contamination of multidose vaccine vials. After the realisation that the total quantity of mercury administered to some infants exceeded margin safety guidelines issued by one of three US government agencies, manufacturers were pushed to eliminate thiomersal from paediatric vaccines. They had already begun to do so before the controversy, but the panic generated in paediatric organisations accelerated the removal, and now no paediatric vaccine in the USA contains more than a trace of thiomersal, with the exception of hepatitis B vaccine, are disproved by studies and disappear into urban legend; but the ones that are uncertain, because of their rarity or the difficulty in designing studies, remain to agitate sincerely concerned individuals and conspiracy enthusiasts.

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Advisory Committee on Immunization Practices, the data on thiomersal in vaccines and autism were presented by an academic investigator. Although none of the epidemiological or ecological data yet available supports an association between the two, and indeed removal of thiomersal has not changed the incidence of autism, representatives of lay organisations at the meeting refused to accept the investigator’s conclusions, relying instead on extrapolation of harm from in-vitro toxicology studies. Additional controlled clinical data will be reported in the next year or two, but it is doubtful that all participants in the controversy will be satisfied by them. Allen does a good job of describing the antagonists in this controversy, with their strongly held views that sometimes run counter to the evidence.

Vaccination will never be without controversy and without risk, as Allen emphasises. An example of this was the fate of the rotavirus vaccine licensed in 1998 that rarely caused intussusception in infants, but prevented diarrhoea, dehydration, and hospital admission. Neither the USA nor any other country would accept its use, and the vaccine was withdrawn despite its benefits. It took 6 years and vaccine trials that involved 150 000 children before replacement vaccines came on the market that are not associated with a higher risk of intussusception. During those 6 years at least 2 million children died of rotavirus disease worldwide.

A contrasting example is the US government’s smallpox vaccine programme, which was enacted under unrelenting pressure by Vice-President Dick Cheney, only to be halted when unexpected cases of myocarditis were seen in vaccinees. Had there been a real terrorist attack with smallpox virus, the programme would have seemed prudent and prescient, but in the absence of such events those who were vaccinated had assumed an unnecessary risk.

It is this tension between risk of disease and risk of vaccination that animates vaccine developers and vaccine objectors. Allen offers no solution to this conflict, and indeed there may be none, as rational calculation of risk is likely to remain scarce among the critics of vaccination. Nevertheless, the vaccine enterprise is alive and well, largely because technology is improving and new manufacturers from other continents are joining those in North America and Europe.

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### In brief

**Book**  *Never say die?*

“I don’t want to achieve immortality through my work”, said Woody Allen, “I want to achieve it through not dying”. He’s not alone. Bryan Appleyard’s latest book details a growing brigade of “immortalists” convinced that old age and death are mere technicalities that medical science will one day overcome. Appleyard seems alternately bemused and beguiled by this group of people who are either freaks or unique, depending on your view. The notion of immortality is as old as humanity, and the book embraces several strands of thinking from mythology, philosophy, and religion. Modern-day believers bide their time in different ways: some opt to be cryogenically frozen; others restrict their calorie intake to fewer than 1500 a day, while popping a pharmacy of vitamin pills.

Appleyard makes clear that he is talking about medical immortality rather than some kind of Greek-god indestructibility. Advanced medicine and better sanitation have seen lifespans lengthen since the 19th century, but what would be the breakthrough that “solves death”? Nanotechnology, suggests Appleyard, could repair physical damage quickly and easily; geneticists could alter the genes that control our lifespan; or stem-cell science could rejuvenate our brains, heart, and muscles. The book skims over the science pretty quickly, lingering instead on the implications of such technology for society. Those who oppose the quest for immortality do so for many reasons, one being its staggering impracticality. Only the rich are likely to be able to afford such technology. And if people had children without dying themselves, society would need stringent fertility control, but who would enforce it? Our social fabric too would in all likelihood be ripped apart as relationships break down under the strain of being wedded to the same person for centuries.

More profound would be the potential for utter boredom. As Appleyard points out, there is already much we could do but don’t bother to. Moreover, if we were immune to disease but still vulnerable to being killed by an accident, we might become more risk-averse. Languish in eternal ennui or be thrilled at the idea of having all the time in the world; however you feel about the idea of living forever, if the immortalists are right you might not have to wait long to find out.

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Profile

Susan Sawyer: advancing our knowledge of adolescent health

One day in the early 1990s, when Susan Sawyer was training as a paediatrician at the Royal Children’s Hospital, Melbourne, Australia, three or four teenage patients with cystic fibrosis came to her with some awkward questions about sex. They were all girls, aged 15–16 years, and “had obviously sat around and asked themselves these questions”, Sawyer recalls. Knowing that most men with the disease are infertile, they wanted to find out about their own fertility and what that meant in terms of contraception. Sawyer didn’t know the answers but promised to get back to the girls once she’d checked with senior colleagues, except it soon became clear that neither they, nor anyone else, had any good answers. “The girls were really unimpressed”, she remembers. “They said to me, can’t you find out, can’t you use us?”

Sawyer realised that although medical advances had improved the survival rates of children with cystic fibrosis during the 1980s and 1990s, the field had failed to keep up with a developmentally appropriate response to the needs of these patients. “These young people had never had discussions about their reproductive futures, and we had not invested in developmentally relevant research; we didn’t know what their reproductive futures were”, she says. “They had also not been encouraged to invest in social relationships, let alone in their education.” For Sawyer, that realisation became a turning point. She broadened her horizons toward a specialty that hardly even existed at the time in Australia—adolescent medicine. “As it turned out, those girls were extremely influential in my future career.”

Earlier in her training, Sawyer hadn’t been so sure what direction she wanted her career to take. “I grew up in country Victoria and my mum was a country GP. All I knew then was that I didn’t want to work in the country”; she says. After finishing her medical training at the University of Melbourne, Sawyer interned at the Royal Melbourne Hospital and did postgraduate training in paediatrics at the Royal Children’s Hospital, where respiratory medicine became an interest. In 1991, as part of her academic training in respiratory medicine, she began looking at issues facing teens with cystic fibrosis. Coincidentally at that time, the Centre for Adolescent Health was founded in Melbourne, and the inaugural Director of the Centre, Glenn Bowes, became a co-supervisor of her doctoral studies. “At that time, I was interested in how it is that we best equip young people with chronic diseases with the skill set that will allow them to have a good quality of life, not just to survive”, she says. That interest took her to the Harvard School of Public Health, Boston, MA, USA, and the Children’s Hospital, Boston, where she did postdoctoral training in respiratory medicine and adolescent medicine.

In 1995, she returned to the University of Melbourne and the Centre for Adolescent Health at the Royal Children’s Hospital. Since then, she’s risen through the ranks and became Director of the Centre in 2004.

For Sawyer, adolescent medicine can be seen as a “point of convergence” for many different areas of medicine. “Adolescent medicine can be thought of as a ‘generality’ as much as the specialty area of practice it also is. I think the challenge for all health professionals who work with young people is to have the skill set to manage complex health-care needs in adolescents just as well as we do in younger children and older adults. The principles of working with young people can and should be taught”, she says. Sawyer explains how “The health issues facing young people are complex, and we are only starting to appreciate that many of the problems arising in adolescence have long-term implications for health. Adolescence is a far more critical time than people have realised. It deserves to be much more rigorously appreciated from a scientific perspective.”

That’s exactly what the Centre for Adolescent Health aims to do. It brings together people from a range of disciplines in clinical medicine, biology, social sciences, and epidemiology to advance adolescent health knowledge, practice, and policy. Considered Australia’s centre of excellence in adolescent health, it is led by Sawyer and George Patton, a psychiatrist, who is Director of the Centre’s research agenda and the VicHealth Professor of Adolescent Health Research. Staff work across research, education, and clinical initiatives, and within health settings, schools, and the community. “We bring together people who embody very different skill sets”, she says. “There is something about the creative tensions generated at the point of overlap of expertise that generates innovative ideas”. It’s an approach that underpins work in projects as diverse as mental health, drug use, bullying in schools, violence and crime, chronic illness, and genetics.

In the Director’s seat, Sawyer sees the need for increased recognition of, and funding for, the challenges facing adolescents in Australia and worldwide. “Compared with children and adults, the health profiles of adolescents have not improved with time, and the potential risks facing our youth—whether in terms of rising obesity, mental disorders, HIV/AIDS, or dangerous patterns of drug use—are greater than ever before”, she warns. “Investment in training health professionals is one thing; investing in more complex system responses that go beyond the domain of clinical medicine is the greater challenge.”

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As Adam Fleisher was finishing his residency in neurology at Johns Hopkins University in 2002, he was looking for training in neuroscience research. “I asked around, and in particular, Jack Griffin, who was chairman at Hopkins, said to me, ‘if you want to learn good research in neurosciences and memory disorders, you go to San Diego and you work with Leon Thal’”, recalled Fleisher, who spent 2 years as a fellow at the University of California, San Diego, and whom Thal later tapped to be medical director of the Alzheimer’s Disease Cooperative Study (ADCS).

Thal had run the ADCS—a consortium of about 80 centres in the USA and Canada—since its inception in 1991. At the time, he was just finishing up a trial of tacrine, one of the first cholinesterase inhibitors used in Alzheimer’s disease. The drug was approved by the US Food and Drug Administration in 1993, although its side-effects meant that it has been replaced by other drugs in its class. The ADCS “was established in recognition that there was a need to provide a stable and ongoing mechanism for translating opportunities in Alzheimer’s research into the best candidates in treatment and prevention”, Richard Hodes, director of the US National Institute on Aging, which funds the ADCS, told The Lancet.

In its first 13 years, the ADCS organised 18 major trials of strategies to prevent and treat the disease. That meant establishing a new network for trial recruitment, Hodes said. “This is where Leon’s talents were remarkable and unusual”, he said. “He was a person in whom we all recognised a great intellect and an enormous commitment to treatment. He certainly had expertise in both the clinical and basic science of neurodegenerative diseases. What distinguished him was the combination of his scientific expertise and his leadership abilities.”

A pivotal trial that came out of the ADCS showed that oestrogen was not useful in Alzheimer’s disease (JAMA 2000; 283: 1007–15). Another was the trial of donepezil (Aricept) and vitamin E for mild cognitive impairment (NEJM 2005; 352: 2379–88). “We showed we could delay progression to Alzheimer’s disease by about 18 months using Aricept, but after 3 years, there seemed to be no benefit”, Fleisher said. “I’m sure that no one felt it was more unfortunate than Leon did that we never reached the goal of a highly effective intervention”, Hodes said. The Aricept trial was, however, important according to Hodes: “It was modest, but regarded as a first step, or a proof of principle. Now there’s increased optimism, and we’re building on that now.”

The ADCS also did a trial showing a lack of benefit of prednisone in Alzheimer’s disease, and one establishing that vitamin E or selegiline could slow the progression of disease in patients with moderately severe impairment. The ADCS “has developed many instruments for the evaluation and management of clinical trials”, Fleisher said. “It has revolutionised the way people run clinical trials, particularly with measurements of activities of daily living, new testing methods, and standardisation of cognitive testing.”

Thal earned his bachelor’s from Tufts University, Medford, MA, USA, in 1965, and then his medical degree from the State University of New York in Brooklyn, NY, USA, in 1969. He trained as a neurology resident at Albert Einstein College of Medicine, Bronx, NY, and stayed as a faculty member there before moving to the University of California, San Diego in 1985. Thal published about 300 papers; in addition to leading the ADCS, he worked with basic neuroscientists such as Rusty Gage. He served on the US National Advisory Council on Aging, the board of directors of the Alzheimer’s Association, and in 2004 was appointed to the California Institute for Regenerative Medicine. That year, he also shared the Potamkin Prize with Roger Nitsch. A year ago, Thal helped launch the Alzheimer’s Disease Neuroimaging Initiative. “He was unlike anyone else I had ever worked with”, Fleisher said. “He was one of the most well respected and well established researchers in the field, and yet at the same time he was so modest and humble that working with him felt more like a friendship than a work relationship. Everyone he worked with felt like that. He was a straight shooter, a pragmatist, and a realist.” Thal is survived by his wife, Donna, and two sisters, Joyce Hollman and Terri Thal.

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High-dose pralidoxime for organophosphorus poisoning

Kirti S Pawar and colleagues (Dec 16, p 2136) report that a high-dose regimen of pralidoxime reduces morbidity and mortality in moderately severe cases of acute organophosphorus pesticide poisoning. We have some concerns.

First, owing to repeated drought in rural India and dowries for daughters’ marriages, farmers are in heavy debt and many are committing suicide by consuming readily available organophosphorus compounds. The total cost of successful treatment of one patient with high-dose pralidoxime is US$400—ie, 3 years’ salary for a poor farmer. Thus this regimen is not at all practicable to rural India.

Second, that severely intoxicated villagers in Pawar and colleagues’ study were excluded and admitted to government hospitals with no intensive-care facilities instead is demoralising and unethical.

Third, we were surprised to note that Pawar and colleagues did not find any cardiovascular abnormalities, including shock, irrespective of severity.1,2

Finally, good nursing care, close monitoring of pneumonia and its rapid treatment, and prolonged ventilator use might be a more worthy management strategy than expensive pralidoxime therapy. M K Inamdar, in the same district as Pawar and colleagues, treated 68 patients with organophosphorus poisoning without pralidoxime; 28 required a ventilator for 6 days and three died (personal communication).

In conclusion, there is a need to devise a practicable management strategy for organophosphorus poisoning in rural India, perhaps including development of newer antidotes with oximes such as obidoxime.3 Additionally, restriction of access to highly toxic pesticides and use of safer alternatives should result in fewer deaths.3

We declare that we have no conflict of interest.

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Kirti Pawar and colleagues compare two pralidoxime regimens in 200 patients with moderately severe organophosphorus poisoning in an open-label randomised trial.3 The patients receiving the higher dose had less morbidity, pneumonia, and need of atropine or ventilatory support, and a shorter duration of intubation than those on the regular dose. Although the effectiveness of oximes is yet to be established,4,5 a control group was not included in the design. It is unclear how moderately severe illness was defined (two-thirds of the patients required ventilatory support) and which relative of the poisoned patient consented to participation. That those not satisfying inclusion criteria were shifted to a nearby government hospital poses a strong ethical concern. The very low atropine requirement in the study group is confusing and suggests that the study group had milder or dissimilar illness.6 A 1.8 mg unit dose given every 15 min should exceed the quoted median dose within the first 2 h when the dose of atropine would be the same in the two groups. It is surprising that without any external funding, all patients were able to afford pralidoxime for the entire period of administration and that there were no dropouts for this reason. That Pawar and colleagues were able to determine the amount of pesticide ingested is also interesting because it proves challenging in clinical practice. We declare that we have no conflict of interest.

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The Article on oxime therapy in acute organophosphate poisoning by Kirti Pawar and colleagues1 supports our hypothesis that the time of administration of the antidote might be a crucial factor in determining response to therapy.2 However, several concerns need to be addressed.

Surprisingly, no patients with mild intoxication nor many patients presenting between 2.5 h and 24 h of ingestion were recorded. The resuscitation intubation rate was relatively high (66%). Given comparable initial treatment and disparate “resuscitation” group intubation rates, time to intubation (not provided) could have potentially confounded treatment efficacy. Although study group relative risk seemed extremely favourable, the

References

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probability of a favourable treatment result for a randomly selected member of one group over a member of the other, calculated as 0·53 and 0·68 (for “deaths” and “intubation during admission”, respectively), suggests otherwise. The mortality treatment effect also seems fragile: a minimum change in the number of deaths (two and seven vs one and eight) renders the mortality effect non-significant.

The results of this trial have limited applicability to late presentation (in our centre only 15% reach hospital within 6 h), when oxime therapy can be potentially harmful owing to acetylcholinesterase ageing. Median initial 24-h atropine requirements (6 mg treatment group, 30 mg control group) compared with reported requirements in oxime-treated organophosphorus poisoning and mean atropine use during resuscitation (23·4 mg), suggest mild intoxication in the Pawar study, as do the small recorded poison volumes (median 15 mL, lowest 5 mL).

Thus physicians should continue to use judgment regarding oxime use in severe organophosphorus poisoning and in late presentation where the evidence for benefit is not shown.

We declare that we have no conflict of interest.

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Kirti Pawar and colleagues report that high-dose pralidoxime infusion in patients with organophosphorus pesticide poisoning is associated with a positive clinical outcome. This surprising conclusion contradicts previously published evidence.

First, the case fatality rates in the study group and the control group (1% vs 8%) are much lower than in a systematic review of two clinical trials (182 people): 22% versus 14% and 29% versus 5%, respectively. Also, the median atropine dose needed to dry the tracheobronchial tree in the study and control groups (6 mg and 30 mg, respectively) within 24 h of admission was much smaller than that in a previous trial. Of note, although Pawar and colleagues enrolled only mildly poisoned patients, they intubated a much larger proportion of them (study group, 64%; control group, 88%) than the authors of a previous study (23%). The report does not explain these contradictions.

Second, the study patients were asked to buy pralidoxime at a cost of about US$400 for the first 48 h, an amount “far beyond the capacity of most patients in rural Asia” in Pawar and colleagues’ words. We believe that study patients should not pay for trial medications and are surprised that the local ethics committee ignored this fact.

Finally, because there was no binding, as the trial advanced and the data accrued, Pawar and colleagues were aware that the study group was doing significantly better than the control group (one death vs eight deaths). Did Pawar and colleagues share this fact with the participants who were enrolled late in the study? Was it ethical to continue the trial despite this observation?

We declare that we have no conflict of interest.

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Kirti Pawar and colleagues show that a high-dose regimen of pralidoxime reduces the need for intubation, the duration of mechanical ventilation, and the amount of atropine required to offset the muscarinic consequences of organophosphorus poisoning. Some issues warrant additional information before a therapeutic approach that is neither cheap nor innocuous is translated into everyday practice.

Since the main clinically relevant outcome of the study is the need for intubation, it is crucial to detail indications of such a decision, particularly in an open-label trial such as this. The general intubation criteria provided in the Methods section should have been adapted to the specific condition of organophosphorus poisoning. Intubation in such patients is usually indicated by acute respiratory failure induced by organophosphorus poisoning itself (depression in respiratory centres, bronchorrhoea, or bronchospasm). Intubation is also done to protect the airways. The beneficial effects of oximes are expected to reduce organophosphorus-related respiratory failure. Accordingly, the respective
Authors’ reply

The authors of three letters concur with our conclusions that the cost of pralidoxime is prohibitive and that all efforts should be made to reduce the cost of treatment with the high dose of pralidoxime. In the context of exaggerated amounts of atropine, is difficult to distinguish from organophosphorus-induced coma. This “iatrogenic” encephalopathy can contribute to the prolongation of mechanical ventilation. Of interest, the control group in Pawar and colleagues’ study had both increased amounts of atropine and prolonged duration of mechanical ventilation.

I declare that I have no conflict of interest.

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Peter and colleagues, Goel and colleagues, and Rajnish Joshi and S P Kalantri suggest that the dose of atropine used in our study was too low. This impression might result from our use of endpoints for atropinisation—ie, control of secretions from the tracheobronchial tree, return of pupils to their normal size, and heart rate 80–100 bpm, rather than tachycardia or dilated pupils. In a study by Eddleston and colleagues, the mean dose of atropine required was 23.4 mg (range 1–75 mg), which is similar to that received by our control group.

On the other hand, F Abroug asks whether the development of “atropine encephalopathy” in the control group could have resulted in prolonged duration of mechanical ventilation. CNS stimulation by atropine occurs only with excessive atropinisation, and is uncommon with the relatively low dose used in our study. None of our patients developed atropine-induced CNS toxic effects.

Lastly, Joshi and Kalantri ask whether it was ethical to continue the trial if we found better outcomes in the study group while the study was in progress. The Comment on our paper highlighted that availability of good research facilities and advice could have enhanced our study. Unfortunately, no interim analysis was planned, and hence no rules for early stopping of the study were defined.

We declare that we have no conflict of interest.

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Plagiarism is not fair play

I beg to differ with the view of Karim Vessel and Farrokh Habibzadeh (Feb 24, p 641) that non-English-speaking researchers’ plagiarism of scientific text should be dealt with leniently. Reviewers should not be tolerant of suspected plagiarism from such authors even if they have little limited access to editorial assistance.

Unfortunately, we in the Arab world have few data about the prevalence of plagiarism, honorary authorships, or other violations of research integrity. This lack of knowledge is probably because of the poor functioning of ethics committees, the scarcity of medical information, the small number of regional journals on MEDLINE, or the rarity of authors commenting on medical writing.

Although Arab researchers might be aware of a problem, it is always swept under the carpet. However, the definition of plagiarism needs reiteration because its meaning could differ between cultures, countries, or “within the cultural context of the writing or development of ideas”, even within the same country.

I agree with the authors that a non-English-speaking author “might insert phrases and even sentences from a previously published article simply because he or she is disinclined to sacrifice quality and accuracy for want of linguistic expertise”. That could happen because international journals are still biased against authors or diseases of poor countries. The reasons that there is little interest in the problems of developing countries and the role of medical journals in addressing the global inequity were discussed in an article last year. I hope that the AuthorAID project will bridge “the publishing gap between rich and poor”.

I declare that I have no conflict of interest.

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Gene-signature-based prognostic tools in breast cancer: not yet

Your Editorial (Feb 17, p 531) is justifiably cautious about the use of aromatase inhibitors in breast cancer. However, at the same time it is vaguely supportive of, and offers undue hope about, the availability of 70-gene tests, prematurely assuming that the availability of this and other such tests will help in making better treatment decisions.

The 70-gene test is a prognostic tool based on retrospective data. It does not have any predictive qualities that can help patients in deciding which treatment might be best suited for them. The prognostic abilities of this tool are similar to those of many other tools, none of which has yet completed prospective validation. Whether the prognostic information provided by these high-tech tests is useful in making better treatment decisions in the clinic is the central question for the two prospective trials testing the 70-gene test and the recurrence-score tool.

It is not appropriate to offer hope on the basis of poor-quality evidence, and it might also prove counterproductive by encouraging patients to seek these tests instead of enrolling themselves in trials. It is most appropriate for the leaders and opinion-formers in medicine to facilitate the scientific process of generating good-quality evidence; I expect the same from The Lancet.

I declare that I have no conflict of interest.

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The women’s conspiracy

Sadly, The Lancet is still part of the plot (March 3, p 715). Of course sex-specific health policies to reduce inequalities are needed. However, all the data point to the issue being men’s health. Mortality is greater in men of all ages and this difference has remained almost constant over the past 20 years. Throughout the world, child mortality is higher in boys than in girls, with only a few exceptions; teenage boys have 65% higher mortality than girls; and mortality is 2–8 times higher for men than for women aged 20–24 years. Life expectancy is 5 years longer for women than men. Among EU member states, France, Finland, and Spain are where the greatest disparities lie.

Inequalities relating to socio-economic status are less important
Anti-HIV microbicides: don’t forget basic immunology

Jan Balzarini and Lut Van Damme (March 3, p 787) provide an excellent Review of candidate microbicide agents to prevent or minimise HIV infection in the vaginal canal. In panel 1 of their article, they list the properties of an ideal anti-HIV microbicide. However, the list does not include what might be the most important caveat: the agent should not attract inflammatory cells to the vaginal canal. Basic immunology details that the human body responds to the presence of non-self molecules by mobilising inflammatory cells, including antigen-presenting cells and T cells. Both of these cell types are subject to HIV infection. Accordingly, should large numbers of inflammatory cells be present after administration of candidate microbicides, and should the latter microbicides fail to neutralise or kill 100% of infectious HIV particles, the stage would be set for higher HIV infection rates. Evidence to support this hypothesis is provided in reports of a terminated phase III clinical trial of the microbicide cellulose sulfate, in which more new HIV infections were noted in women who were using the microbicide than in women who used a placebo gel.

This is not the first time in HIV/AIDS research that basic immunological concepts have failed to get the attention they deserve. After the isolation of HIV-1 in 1983–84, the scientific community pursued an intensive, but ultimately fruitless, programme to develop a vaccine. In using HIV-1 proteins extracted from virus grown in tissue culture or produced through genetic engineering, researchers failed to take account of the high rate of mutation of HIV and how HIV strains evolve over time in vivo.

These early failures in HIV vaccine development could have been anticipated, as could the possibility of failure of a candidate microbicide. Accordingly, the first property to be assessed with any candidate microbicide is how strong an immune response it elicits when chronically applied in the vaginal canal.

Suckling and sugar for pain reduction in babies

Frank Shann (March 3, p 721) suggests that breastfeeding plus sucrose might be better than breastfeeding or sucrose alone in reducing procedural pain in babies.

However, this finding comes from only one trial in which breastfeeding was stopped before the procedure. Even if this finding was confirmed by other studies, it might not necessarily be clinically significant.

In this regard, we would like to summarise our findings on non-pharmacological analgesia in newborn babies. We studied 197 healthy term infants (birthweight 2500–4500 g) at the time of blood sampling by heel prick for metabolic screening. They were randomly assigned to one of four groups: (1) breastfeeding 2 min before and during the procedure; (2) 2·0 mL 20% glucose 2 min before and during the procedure; (3) sensory stimulation by holding, speaking, and fondling; or (4) wrapping. Pain was evaluated with the premature infant pain profile (PIPP score).

As in Carbajal’s study, we found no difference between breastfeeding and glucose (table). In both studies, mean PIPP scores were very similar and quite low. It might well be that sucrose plus breastfeeding will further lower the pain score. However, in the average nursery, this can represent an additional burden in an already busy routine. One might wonder whether lowering an already low score is worth the effort.

We declare that we have no conflict of interest.

Table: Effect of different types of non-pharmacological analgesia on pain scores in newborn babies

<table>
<thead>
<tr>
<th>Number of infants</th>
<th>Mean (SD) PIPP score</th>
<th>Relative risk ratio p (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastfeeding</td>
<td>48</td>
<td>4·2 (2·9)</td>
</tr>
<tr>
<td>20% glucose</td>
<td>50</td>
<td>4·3 (3·4)</td>
</tr>
<tr>
<td>Sensory stimulation</td>
<td>51</td>
<td>7·7 (3·9)</td>
</tr>
<tr>
<td>Wrapping</td>
<td>48</td>
<td>7·5 (4·2)</td>
</tr>
</tbody>
</table>

*Breastfeeding was arbitrarily regarded as the reference group.

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I declare that I have no conflict of interest.

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Table: Breakdown of how individual components contribute to the composite primary endpoint of death, recurrent ischaemia, or coronary-artery occlusion

<table>
<thead>
<tr>
<th>Clotidogrel (n=1752)</th>
<th>Placebo (n=1739)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Recurrent ischaemia</td>
<td>Coronary-artery occlusion*</td>
</tr>
<tr>
<td>45 (2.6%)</td>
<td>38 (2.2%)</td>
<td>192 (11.7%)</td>
</tr>
<tr>
<td>44 (2.5%)</td>
<td>63 (3.8%)</td>
<td>301 (18.4%)</td>
</tr>
<tr>
<td>192 (11.7%)</td>
<td>301 (18.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>262 (15.0%)</td>
<td>377 (21.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*TIMI grade 0 or 1 on angiography.

Endpoints in studies on myocardial infarction

Mortality has historically been the primary endpoint in studies on myocardial infarction. However, composite endpoints combining death, reinfarction or recurrent ischaemia, and stroke have been progressively introduced over the past decades to assess the risk-benefit ratio of various drugs. More recently, death has been combined with recurrent ischaemia, angiographic results, congestive heart failure, or shock in primary endpoints.

The wisdom of this evolution is questionable because mortality and non-fatal events are regarded as having similar effects, whereas individual and collective effects are clearly very different. Studying patients with ST-elevation myocardial infarction (STEMI), Sabatine and colleagues reported a 2.6% mortality rate, a 2.5% reinfarction rate, and a 11.7% rate of coronary-artery occlusion as judged by angiographic data in patients treated with clopidogrel versus those given placebo (table). This last criterion strongly influenced the composite endpoint and thus the final results. 70% of patients fulfilled this criterion, contributing to the endpoint to the same extent as mortality; however, mortality associated with reinfarction or coronary-artery occlusion was less than 10%.

We believe that endpoints used in studies on STEMI should be reassessed. A crucial point is that, as mortality rate reaches a low level in STEMI, many patients are needed to show an effect on mortality. To show decreased mortality associated with a strategy such as the one used by Sabatine and colleagues, 46 000 patients would have been required. However, abandoning mortality as a major endpoint or altering this criterion would not be acceptable. On the other hand, it is not realistic to promote studies using mortality as the exclusive endpoint. The exact effect of each criterion should be taken into consideration. It is also crucial that these criteria are not modified study after study while inclusion criteria remain identical. This practice interferes with the ability to compare study results.

How could we limit the bias introduced by these “modern” endpoints? Even if morbidity is closely associated with mortality, morbidity criteria should be specifically studied without being considered on the same level as mortality. Criteria other than mortality could be assessed, for example, according to their effect on mortality, morbidity, or cost. Alternatively, morbidity could be studied as a composite primary endpoint to assess the risk-benefit ratio, and mortality as secondary endpoint.

Reflection and discussions are required to reach a large consensus on endpoints in studies on STEMI. We declare that we have no conflict of interest.

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Department of Error

Pan P. Osman R. From fact to fiction. Lancet 2007; 369: 450—in this Comment (Feb 10), the sixth sentence should have read: “Perhaps you are motivated by the tale of pioneering psychiatrists in Sebastian Faulks’ historical drama Human Traces.”
Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study

Seibu Mochizuki, Bjorn Dahlöf, Mitsuyuki Shimizu, Katsunori Ikewaki, Makoto Yoshikawa, Ikuo Taniguchi, Makoto Ohta, Taku Yamada, Kazuhiko Ogawa, Kyoshi Kanae, Makoto Kawai, Shingo Seki, Fumiko Okazaki, Masayuki Taniguchi, Satoru Yoshida, Naoko Tajima, for the Jikei Heart Study group*

Summary

Background Drugs that inhibit the renin–angiotensin–aldosterone system benefit patients at risk for or with existing cardiovascular disease. However, evidence for this effect in Asian populations is scarce. We aimed to investigate whether addition of an angiotensin receptor blocker, valsartan, to conventional cardiovascular treatment was effective in Japanese patients with cardiovascular disease.

Methods We initiated a multicentre, prospective, randomised controlled trial of 3081 Japanese patients, aged 20–79 years, (mean 65 [SD 10] years) who were undergoing conventional treatment for hypertension, coronary heart disease, heart failure, or a combination of these disorders. In addition to conventional treatment, patients were assigned either to valsartan (40–160 mg per day) or to other treatment without angiotensin receptor blockers. Our primary endpoint was a composite of cardiovascular morbidity and mortality. Analysis was by intention to treat. The study was registered at clintrials.gov with the identifier NCT00133328.

Findings After a median follow-up of 3·1 years (range 1–3·9) the primary endpoint was recorded in fewer individuals given valsartan than in controls (92 vs 149; absolute risk 21·3 vs 34·5 per 1000 patient years; hazard ratio 0·61, 95% CI 0·47–0·79, p=0·0002). This difference was mainly attributable to fewer incidences of stroke and transient ischaemic attack (29 vs 48; 0·60, 0·38–0·95, p=0·028), angina pectoris (19 vs 53; 0·35, 0·20–0·58, p<0·0001), and heart failure (19 vs 36; 0·53, 0·31–0·94, p=0·029) in those given valsartan than in the control group. Mortality or tolerability did not differ between groups.

Interpretation The addition of valsartan to conventional treatment prevented more cardiovascular events than supplementary conventional treatment. These benefits cannot be entirely explained by a difference in blood pressure control.

Introduction Cardiovascular disorders are the leading cause of mortality worldwide,1 and are expected to continue to increase with general ageing of the world’s population and rapid socioeconomic changes in the developing world. Hence, optimum pharmacotherapy for cardiovascular disease is urgently needed, in addition to lifestyle changes, to provide symptomatic relief and long-term protection. Hypertension is the most common cause of coronary heart disease and heart failure in Japan, and cerebrovascular disease is more prevalent in the Japanese population than in western societies.2 Angiotensin II has a well defined role in the pathogenesis of hypertensive left ventricular hypertrophy, stroke, coronary heart disease, and heart failure.3–5 Over the past decade, several clinical trials have shown the benefits of treatments that specifically block the renin–angiotensin–aldosterone system. Angiotensin receptor blockers were originally targeted at hypertension, but also benefit patients with a range of diseases6–12 and reduce the incidence of new onset type II diabetes.13,16

Direct implementation of available evidence into clinical practice in Japan might not be warranted by the available data, since responses to drug intervention and its clinical consequences might differ between ethnic groups. Clinical trials of angiotensin receptor blockers on end-organ damage in Japanese patients show cardiovascular benefits, but because of shortcomings such as small sample sizes and observational data, these results are not conclusive and cannot be directly translated into clinical outcomes.17–21 Thus, further large-scale Japanese clinical trials are needed.

We aimed to implement a large-scale clinical trial to investigate the effect of control of blood pressure (to a target of less than 130/80 mm Hg) with an added angiotensin receptor blocker, valsartan, compared with conventional treatment in a large Japanese population that was representative of the cardiovascular continuum of disease.22 Our hypothesis was that treatment with valsartan would yield additional protective benefits, compared with conventional treatment, beyond those attributable to control of blood pressure.


See Comment page 1407

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Methods

Participants

Our study design, organisation, clinical measurements, endpoint definitions, power calculations, and recruitment rates have been published previously. Briefly, between January, 2002, and December, 2004, we recruited patients to an investigator-initiated, independent, investigator-led, multicentre, controlled trial. Participating centres included the four hospitals of the Jikei University in Tokyo, which has some of the largest inpatient and outpatient facilities in Japan, and 17 associated hospitals led by physicians from Jikei University. We used a prospective randomised open blinded endpoint (PROBE) design.

We recruited patients with hypertension, coronary heart disease, heart failure, or a combination of these cardiovascular disorders. The study population was selected and stratified to be representative of the range of cardiovascular disease in a Japanese population. Participants could be 20–79 years of age, and of either sex. Patients with hypertension must have been diagnosed at least 3 months before enrolment, and have been under treatment with antihypertensive drugs. Patients with coronary heart disease were enrolled if they had either a history of the disease or had been newly diagnosed on the basis of typical symptoms, with coronary angiography showing at least one coronary stenosis of more than 75%. Patients with heart failure (New York Heart Association [NYHA] class II–IV), diagnosed on the basis of a historically low ejection fraction (echocardiography) or diastolic dysfunction, were enrolled if they had received standard treatment (diuretics, angiotensin-converting enzyme [ACE] inhibitors, β blockers, or a combination of these) for at least 4 weeks before enrolment.

Exclusion criteria included acute coronary syndrome or myocardial infarction within 6 months, any cerebrovascular event within 3 months, serum creatinine higher than 265 μmol/L, potassium higher than 5 mmol/L, treatment with an angiotensin receptor blocker 4 weeks or less before randomisation, or judgment by the physician that participation was unwise on the basis of patient characteristics and drug safety.

We used good clinical practice guidelines in accordance with the Declaration of Helsinki. Institutional review boards at every participating hospital approved the protocol and subsequent amendments. At the first hospital visit, 4 weeks before randomisation, we carefully explained the trial objectives and study design, and the risks and benefits of participation to all patients and obtained written informed consent. Patient privacy was strictly protected. The study was registered at register.clintrials.gov with the identification number NCT00133328.

Study design

Eligible patients with more than one cardiovascular disorder were stratified into groups according to the following sequence of severity: heart failure, coronary heart disease, and hypertension. We then used a computer-generated list of random numbers to assign patients to receive either valsartan or conventional treatment. We used the minimisation method to adjust for baseline characteristics. Investigators entered all patient data on a secure website. Electronic case report forms were then transferred to the data centre in Kobe. A data management team updated the database every month. All data were kept independently of the funding source.

The primary endpoint was a composite of cardiovascular mortality and morbidity. Components of the endpoint included the following: hospital admissions for stroke or transient ischaemic attack (neurological deficit persisting for less than 24 hours); myocardial infarction (chest pain, ECG-changes, and biomarkers for myocardial necrosis); admission for congestive heart failure (clinical symptoms including dyspnoea, shortness of breath, and peripheral oedema, together with left ventricular dysfunction by echocardiography, according to the guidelines of the American College of Cardiology and American Heart Association [AHA/ACC]); admission because of angina pectoris (diagnosed as ECG changes along with chest discomfort or pain, with documented coronary heart disease according to AHA/ACC guidelines); dissecting aneurysm of the aorta (diagnosed by imaging technique); doubling of serum creatinine; or transition to dialysis. The first of these events to arise in any specific patient was noted as the primary event.

Any component of composite primary endpoint for which a patient could be counted once in each category was treated as a secondary endpoint. Death from any cause was also designated a secondary endpoint. A cardiovascular event was regarded as causal of death on the basis of the judgment of a participating physician, irrespective of the time between the event and death.

Procedures

At enrolment we recorded patients’ demographics and baseline characteristics, including sex, age, height, bodyweight, symptoms and signs, and risk factors for cardiovascular disease (smoking, hyperlipidaemia, and diabetes mellitus). We assessed cardiac function, cardiac remodelling, and renal function at baseline and at 6-month intervals. The general clinical laboratory tests were urinalysis (proteinuria); blood chemistry (creatinine, sodium, potassium, total cholesterol, triglyceride, low density lipoprotein cholesterol and high density lipoprotein cholesterol, plasma glucose, and haemoglobin A1c) measured in the fasting state after an overnight 12 h fast; electrocardiography (ECG); echocardiography (left ventricular diastolic dimension, ventricular systolic dimension, ejection fraction, fractional shortening, intraventricular septum, and posterior wall thickness); and chest radiogram. We assessed the quality of life of patients with congestive heart failure with the modified Minnesota living with heart failure and NYHA cardiac functional class scales. Patients could be seen every 2–4 weeks, at least every 6 months for up to 3·5 years. At every visit, a skilled
A physician took standard blood pressure measurements, with the patient at rest (5–10 min) in the sitting position, with a validated mercury sphygmomanometer. The mean of three measurements was calculated and recorded. The timing of blood pressure measurement was not constant in relation to patients’ intake of medication.

We aimed to control blood pressure in both treatment groups to less than 130/80 mm Hg. Figure 1 shows the phases of treatment in our study protocol. Hypertensive patients in the valsartan group were initially given 80 mg of valsartan orally, once daily in the morning, flexibly adjusted to a dose of 40–160 mg per day, as needed to control blood pressure. Patients with heart failure or coronary heart disease in the valsartan group were started on 40 mg once daily and uptitrated as tolerated. Controls were given either an increased dose of their existing treatment or an additional conventional treatment to achieve the blood pressure goal.

Diagnoses of endpoints were verified automatically by the computer system and by a data monitoring committee consisting of four expert cardiologists from Jikei University. An independent endpoint committee of three members who were not affiliated with the University, all of whom were unaware of treatment allocation, also adjudicated the diagnoses. The endpoint committee reviewed all available documentation, including patient records. Endpoints were confirmed only after agreement from all members of this committee.

Statistical analysis
Few epidemiological data about cardiovascular risk profiles in Japan were available. Information about the prognosis of patients treated by specialist doctors at specialised hospitals was especially scarce. Although the cardiovascular event rate in the Japanese population is low, the hospitals participating in our study undertake tertiary care of cardiovascular disease and therefore treat more severely ill patients than those seen in other hospitals. We estimated that the 3-year event rate for cardiac mortality and morbidity for patients with complicated cardiovascular disease would be about 12%. The findings of a retrospective investigation of a few patients under treatment at our participating sites were almost identical to this estimate.

Since our study was event-driven, we calculated that to include 300 primary events, we would need a sample size of at least 3000 patients, followed up for an average of 3 years. We assumed that the valsartan group would achieve a 20% reduction of risk compared with the conventional treatment group, giving our study 80% statistical power and an α error of less than 5% if 10% of patients discontinued treatment or were lost to follow-up.

Analyses were based on intention to treat. The statistical analysis group at Osaka City University, which was independent of the study implementation group and the funding source, did data analyses. We checked that patient characteristics were uniformly distributed between groups, and used Cox’s proportional hazard regression analysis to compare the rate of event development. For primary analysis of intergroup differences in endpoints we used inference testing (95% CIs) with significance defined at an α level of less than 5%. Hazard ratios were calculated and adjusted for sex, age, hypercholesterolaemia, diabetes mellitus, smoking, and concomitant antihypertensive treatment with Cox’s proportional hazard model. To assess significance, we compared categorical data between groups with the χ² test or Fisher’s exact test and compared quantitative data between groups with the t test or analysis of variance. We compared the total number and rate of adverse events for each group.

Our data safety and monitoring board reviewed effectiveness and safety at regular intervals throughout the study. This board did three interim analyses, with the O’Brien–Fleming method, beginning 6 months after the

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**Figure 1:** Schematic of study protocol with treatment phases

Doses of valsartan were given once daily. ARB=angiotensin receptor blocker. “Both groups given conventional non-ARB treatment.

**Figure 2:** Trial profile
last person had been enrolled. In December, 2005, the data safety and monitoring board recommended that the study should be stopped for ethical reasons, because additional valsartan treatment was associated with a reduction in the primary endpoint (p<0.001, adjusted for three interim analyses). This recommendation was endorsed by the executive and steering committees. In January, 2006, all patients were recalled for final visits. Since the event rate was lower and the risk reduction larger than expected, the premature end of the study coincided with the planned duration of follow-up.

Role of the funding source
The sponsor had no role in study design, data collection, data analysis, data interpretation or writing of the report. The executive committee had full access to all the data at the end of the study, and had final responsibility for the decision to submit for publication.

Results
Figure 2 shows the trial profile and table 1 the baseline characteristics for all the 3081 patients who were assigned to treatment. The two treatment groups were well matched for baseline characteristics: all patients were Japanese, with a mean age of 65 years, a mean body-mass index (BMI) of 24 kg/m², and a blood pressure of 139/81 mm Hg. About a third were female. Patients were censored at death or at last known visit, with a median follow-up of 3.1 years (SD 0.8, range 1–3.9). In total the study gathered information for 8627 patient years (4326 in the valsartan group and 4321 in the control group). Figure 2 shows that 14 patients (0.5%) withdrew consent after random allocation and 15 patients (0.5%) were lost to follow-up. We obtained complete endpoint information at the end of the study for 3052 patients.

Table 1 shows that, at baseline, blood pressure in both groups combined was at a mean of 139/81 mm Hg (SD 11/11). Throughout the study it fell to 131/77 mm Hg (12/8) in the valsartan group, and 132/78 (11/8) mm Hg in controls. The changes in blood pressure were 8.2/4.7 mm Hg in the valsartan treatment group and 7.2/3.7 mm Hg in controls. At the end of the trial only 122 (4%) of patients in both groups had blood pressure greater than 140/90 mm Hg. 1118 (75%) of patients given valsartan and 1033 (70%) in the control group achieved the target blood pressure of less than 130/80 mm Hg. The Levene test for equality of variances showed no differences between the groups. Blood pressure and heart rate did not differ between the valsartan regimen and the control regimen throughout the trial (table 3, p=0.196 for

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Valsartan treatment group (n=1541)</th>
<th>Non-ARB treatment group (n=1540)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>521 (34%)</td>
<td>517 (34%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (10)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>259 (17%)</td>
<td>262 (17%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>139.2 (11.4)</td>
<td>138.8 (10.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>81.4 (10.5)</td>
<td>81.4 (10.8)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>71 (11)</td>
<td>72 (11)</td>
</tr>
<tr>
<td>Body-mass index (kg/cm²)</td>
<td>24 (3)</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Electrocardiograph (S V1 wave and R V5/V6 wave, mm)</td>
<td>29 (11)</td>
<td>28 (11)</td>
</tr>
</tbody>
</table>

HbA₁c (%) 5.6% (1.0%) 5.6% (1.0%)
Total cholesterol (mmol/L) 5.4 (0.9) 5.4 (0.9)
LDL cholesterol (mmol/L) 3.2 (0.8) 3.1 (0.8)
HDL cholesterol (mmol/L) 1.4 (0.4) 1.4 (0.4)
Triacylglycerol (mmol/L) 1.7 (0.9) 1.7 (1.0)
Fasting plasma glucose (mmol/L) 6.5 (1.9) 6.6 (2.2)
Serum creatinine (µmol/L) 71 (13) 71 (13)
Sodium (mmol/L) 142 (2.6) 142 (2.8)
Potassium (mmol/L) 4.2 (0.4) 4.2 (0.9)

Medical history
Hypertension 1358 (88%) 1341 (87%)
Coronary heart disease 514 (33%) 522 (34%)
Heart failure 176 (11%) 174 (11%)
Hyperlipidaemia 812 (53%) 813 (53%)
Diabetes mellitus 315 (20%) 314 (20%)

All patients Valsartan group Non-ARB treatment group Patients with hypertension Patients with coronary heart disease Patients with heart failure
Calcium-channel blocker 2052 (67%) 1041 (68%) 1011 (66%) 1933 (72%) 626 (60%) 108 (31%)
ACE inhibitor 1073 (35%) 548 (36%) 525 (34%) 979 (36%) 340 (33%) 173 (49%)
β blocker 988 (32%) 486 (32%) 502 (33%) 897 (33%) 342 (33%) 145 (41%)
α blocker 167 (5%) 74 (5%) 93 (6%) 164 (6%) 32 (3%) 13 (4%)
Thiazide 68 (2%) 29 (2%) 39 (3%) 63 (2%) 10 (1%) 13 (4%)
Antialdosterone agent 116 (4%) 57 (3%) 64 (4%) 81 (3%) 31 (3%) 81 (23%)
Other diuretics 243 (8%) 117 (8%) 126 (8%) 170 (6%) 78 (8%) 162 (46%)
Statin 951 (31%) 461 (30%) 490 (32%) 807 (30%) 515 (50%) 58 (17%)
Fibrate 79 (3%) 42 (3%) 37 (2%) 70 (3%) 27 (3%) 5 (1%)

Table 2: Medication at baseline

AR=angiotensin receptor blocker. LDL=low-density lipoprotein. HDL=high-density lipoprotein. Hb=haemoglobin.
Data are mean (SD) or number (%).

Table 2: Medication at baseline
systolic blood pressure and p=0.176 for diastolic blood pressure at end of study).

Table 2 shows patients on medication at baseline: about two-thirds were receiving a calcium antagonist, a third an ACE-inhibitor, another third a β blocker, a tenth a diuretic, and almost a third a statin. A webtable sets out all doses of antihypertensive medications in more detail. The average additional dose of valsartan was 75 (SD 14) mg per day. Other additional treatments in both groups were mainly calcium-channel blockers, ACE-inhibitors, and β blockers (table 3). The average number of antihypertensive drugs taken during the study was slightly higher in the valsartan group than in controls. However, when doses for all drugs were adjusted to a standard dose, according to Japanese clinical practice, the dose-adjusted numbers of drugs for all treatment groups were identical at the end of the study (table 3). Table 4 shows selected biochemical results.

Figure 3 shows that the primary endpoint was recorded in fewer patients given valsartan (92, 6·0%) than in those given additional non-ARB treatment (149, 9·7%); the hazard ratio was 0·61 (0·47–0·79) for the composite endpoint (stroke or transient ischaemic attack, myocardial infarction, angina pectoris requiring hospitalisation, or heart failure requiring hospitalisation) compared with controls. The incidence of new or recurrent myocardial infarction or hospitalisation for exacerbation of heart failure was significantly lower in the valsartan group (0·35 (0·20–0·58)) compared with controls (0·53 (0·31–0·94)); p=0.023 vs 0.90 (0·47–1·74) in the non-ARB treatment group. The incidence of all-cause mortality was significantly lower in the valsartan group compared with controls (0·53 (0·34–0·81) vs 0·93 (0·43–2·06); p=0.04 vs 0.19 (0·04–0·88)).

Table 3: Patient characteristics and medications throughout the study in the two treatment groups

Baseline | Month 6 | Month 12 | Month 24 | End of study
--- | --- | --- | --- | ---
Valsartan | Control | Valsartan | Control | Valsartan | Control | Valsartan | Control | Valsartan | Control
(n=1541) | (n=1540) | (n=1129) | (n=1127) | (n=1479) | (n=1488) | (n=1148) | (n=1120) | (n=1433) | (n=454)

Blood pressure
Mean SBP (mm Hg) 139·2 (11) 138·8 (11) 131·5 (15) 133·6 (13) 130·4 (14) 131·9 (14) 131·9 (14) 132·2 (13) 132·0 (14) 132·0 (14)
Mean DBP (mm Hg) 81·4 (11) 81·4 (11) 76·1 (9) 78·2 (10) 76·2 (9) 77·5 (10) 77·1 (9) 77·3 (9) 76·7 (8) 76·6 (9)
Pulse rate (bpm) 71·4 (11) 71·7 (10) 72·0 (10) 72·4 (10) 70·9 (10) 70·9 (10) 69·8 (11) 70·0 (10) 70·3 (10) 71·0 (9)

Medications
Valsartan 0 0 0·93 0 0·93 0 0·93 0 0·95 0
ACE inhibitor 0·42 0·48 0·38 0·50 0·38 0·60 0·33 0·56 0·29 0·58
CCB 0·81 0·76 0·79 0·89 0·70 0·87 0·67 0·87 0·67 0·95
β blocker 0·23 0·18 0·22 0·19 0·23 0·21 0·20 0·21 0·20 0·22
All diuretics 0·07 0·07 0·11 0·14 0·07 0·07 0·07 0·07 0·06 0·17
All antihypertensive drugs 1·79 1·79 2·69 2·11 2·55 2·39 2·55 2·39 2·41 2·44

SBP=systolic blood pressure. DBP=diastolic blood pressure. ACE=angiotensin-converting enzyme. CCB=calcium-channel blocker. bpm=beats per minute. *Doses of individual drugs adjusted as fractions of the standard dose of those drugs in Japan. For example, the standard dose of valsartan is 80 mg; if 90% of patients took an average dose that was 110% of this standard dose, the dose-adjusted figure would be 99% (0·9×1·1). For valsartan, the dose-adjusted figure was 95% at the end of the study, representing an average dose of 76 mg.

Figure 3: Effect of treatment on all endpoints
Hazard ratios are adjusted for sex, age, hypercholesterolaemia, diabetes, smoking, and concomitant antihypertensive treatment. Diamonds and squares indicate the hazard ratio estimate for each type of event; horizontal lines show 95% CIs.
## Table 4: Biochemical variables

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>p</th>
<th>Mean value at follow-up</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemoglobin (%)</strong></td>
<td>5.6 (1.0)</td>
<td>5.7 (0.9)</td>
<td>0.1 (0.5)</td>
<td>5.6 (1.0)</td>
<td>5.7 (0.9)</td>
<td>0.1 (0.5)</td>
<td>0.01 (0.08-0.06)</td>
<td>0.8059</td>
<td>0.01 (-0.08-0.05)</td>
<td>0.6761</td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/L)</strong></td>
<td>5.4 (0.9)</td>
<td>5.2 (0.7)</td>
<td>-0.1 (0.6)</td>
<td>5.4 (0.9)</td>
<td>5.2 (0.7)</td>
<td>-0.1 (0.6)</td>
<td>0.02 (0.04-0.09)</td>
<td>0.4705</td>
<td>0.03 (-0.03-0.08)</td>
<td>0.3208</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/L)</strong></td>
<td>3.2 (0.8)</td>
<td>3.1 (0.7)</td>
<td>-0.1 (0.6)</td>
<td>3.1 (0.8)</td>
<td>3.1 (0.7)</td>
<td>-0.1 (0.6)</td>
<td>0.02 (0.04-0.07)</td>
<td>0.5510</td>
<td>0.03 (-0.02-0.08)</td>
<td>0.295</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/L)</strong></td>
<td>1.4 (0.4)</td>
<td>1.4 (0.3)</td>
<td>-0.02 (0.2)</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.3)</td>
<td>-0.02 (0.2)</td>
<td>0.01 (-0.04-0.01)</td>
<td>0.3696</td>
<td>0.01 (-0.04-0.01)</td>
<td>0.319</td>
</tr>
<tr>
<td><strong>Triglyceride (mmol/L)</strong></td>
<td>1.7 (0.9)</td>
<td>1.7 (0.8)</td>
<td>-0.05 (0.3)</td>
<td>1.7 (1.0)</td>
<td>1.6 (0.8)</td>
<td>-0.03 (0.7)</td>
<td>0.04 (-0.02-0.11)</td>
<td>0.2036</td>
<td>0.02 (-0.04-0.08)</td>
<td>0.4747</td>
</tr>
<tr>
<td><strong>Fasting plasma glucose (mmol/L)</strong></td>
<td>7.0 (2.1)</td>
<td>7.0 (1.9)</td>
<td>0.05 (1.6)</td>
<td>7.0 (2.2)</td>
<td>7.1 (2.0)</td>
<td>0.1 (1.7)</td>
<td>-0.08 (-0.24-0.07)</td>
<td>0.2968</td>
<td>-0.09 (-0.24-0.05)</td>
<td>0.1839</td>
</tr>
<tr>
<td><strong>Serum creatinine (μmol/L)</strong></td>
<td>71 (18)</td>
<td>71 (18)</td>
<td>1.8 (8.9)</td>
<td>71 (18)</td>
<td>71 (18)</td>
<td>1.8 (8.9)</td>
<td>0.35 (-1.1-1.8)</td>
<td>0.6261</td>
<td>0.46 (-1.1-2.0)</td>
<td>0.5560</td>
</tr>
<tr>
<td><strong>Potassium (mmol/L)</strong></td>
<td>4.2 (0.4)</td>
<td>4.3 (0.3)</td>
<td>0.07 (0.9)</td>
<td>4.2 (0.9)</td>
<td>4.3 (0.3)</td>
<td>0.02 (0.9)</td>
<td>-0.01 (-0.02-0.003)</td>
<td>0.1169</td>
<td>0.004 (-0.002-0.01)</td>
<td>0.2207</td>
</tr>
<tr>
<td><strong>Sodium (mmol/L)</strong></td>
<td>142 (2.5)</td>
<td>142 (2.0)</td>
<td>0.5 (2.2)</td>
<td>142 (2.8)</td>
<td>142 (1.9)</td>
<td>0.4 (2.4)</td>
<td>0.05 (-0.03-0.13)</td>
<td>0.2268</td>
<td>0.07 (0.01-0.13)</td>
<td>0.0228</td>
</tr>
<tr>
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<td>7.0 (2.1)</td>
<td>7.0 (1.9)</td>
<td>0.05 (1.6)</td>
<td>7.0 (2.2)</td>
<td>7.1 (2.0)</td>
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<td>-0.03 (0.7)</td>
<td>0.04 (-0.02-0.11)</td>
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<td>142 (1.9)</td>
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<td>142 (1.9)</td>
<td>0.4 (2.4)</td>
<td>0.05 (-0.03-0.13)</td>
<td>0.2268</td>
<td>0.07 (0.01-0.13)</td>
<td>0.0228</td>
</tr>
</tbody>
</table>

Values are mean (SD). Hb=haemoglobin. eGFR=estimated glomerular filtration rate (normal range of 90–130 mL/min per 1·73 m²).

**Figure 4: Kaplan-Meier curves of cumulative frequency of the primary endpoint**

The event rate curves in figure 4 show that, excluding any of the components of the primary endpoint, the overall significance of the primary endpoint was maintained in all cases. For the endpoint of stroke or transient ischaemic attack, nearly all events were strokes: 25 strokes and four transient ischaemic attacks in the valsartan group, and 43 strokes and five transient ischaemic attacks in the conventional-treatment group.

Table 5 shows that only 2·5% of patients reported any adverse event during the study, with no significant difference between treatment groups. The only difference between the groups was a higher incidence of dizziness in the valsartan group, with nine cases compared with three in the control group.

**Discussion**

Addition of the angiotensin receptor blocker valsartan to standard cardiovascular treatment, compared with an increased dose or number of standard drugs, in Japanese patients with cardiovascular disease, reduced the incidence of the primary composite endpoint, of heart, brain, and kidney complications. The main effect of addition of valsartan was to reduce stroke, angina pectoris, dissecting aortic aneurysm, and heart failure. These benefits were noted despite a short median follow-up of 3·1 years, and were seen across various subgroups (data not shown).

Unfortunately, Asian patients have often been under-represented in cardiovascular trials, including trials of angiotensin receptor blockers. For example, Asians made up 2·8%, 3·5%, and less than 2% of the populations in the Val-HeFT trial,16 the VALUE trial,17 and the LIFE trial,11 respectively. None of these trials included a Japanese centre. One previous study on the effects of the angiotensin receptor blocker candesartan compared with standard treatment in a hypertensive Japanese population10 had shortcomings such as deficiencies in randomisation and quality control, and large numbers lost to follow-up.

Patients in both treatment groups showed a similar degree of blood pressure control, achieving good control of the same magnitude. Since this was an active-controlled study, we could not ascertain to what degree regression-to-the-mean or placebo effects might have contributed to the result.
The mean dose of valsartan in this study (75 mg) might seem low, but studies in Japanese people have shown that 80 mg of valsartan produced similar antihypertensive effects to those of nifedipine (20 mg) and amlodipine (5 mg). Moreover, because the mean BMI in our study was low (24, compared with the VALUE trial, for which mean BMI was 28), the doses we used would seem sufficient. Doses of all antihypertensive drugs, including valsartan, were based on the guidelines of the Japanese Hypertension Society.

The Kaplan-Meier curves for the primary endpoint diverged early and separated throughout the trial (figure 4), indicating that the response to treatment was early and sustained. The overall reduction in the primary composite endpoint was not driven by any one component, indicating a broad range of benefit—ie, a reduction of the total burden of cardiovascular disease. The effects on myocardial infarction and renal endpoints were neutral. However, event rates for secondary endpoints were low, and these results should not be overinterpreted.

Some further comments are warranted. The reduction in angina with valsartan treatment (65%) was not matched by a similar reduction in myocardial infarction, although some underlying pathophysiological processes would be similar. However, other large-scale trials such as LIFE and VALUE have also failed to show significant differential effects of myocardial infarction with angiotensin receptor blockers compared with other treatments, despite other cardiac benefits. We could speculate that the renin–angiotensin–aldosterone system has a larger role in the development of angina than in myocardial infarction, in which other factors more related to rupture of atheromas and thrombosis are major determinants. A possible caveat should be noted: the PROBE design used in our study is highly unlikely to account for differences between groups of the magnitude we recorded.

The reduction in the risk of stroke with added valsartan treatment was consistent with that reported with losartan in the LIFE study. However, we recorded a much lower absolute risk than that reported by LIFE, which is probably related to the lower mean blood pressure in our study population. The stroke endpoint combines both stroke and transient ischaemic attack, but the rates of transient ischaemic attacks were very low in our study. Debate about the degree to which reduction of stroke in the LIFE trial should be attributed to losartan and how much to a lack of stroke benefits in the group given the comparator (atenolol) is unresolved. In our study, atenolol was used in only 5% of patients in each group. In both studies, benefits for stroke reduction were noted at a similar degree of blood pressure control in treatment and control groups.

These findings contrast with the VALUE trial, in which valsartan treatment did not reduce the frequency of strokes compared with amlodipine. In the VALUE trial, blood pressure differed much more between the groups, consistent with the notion that stroke risk is mainly, but not entirely, related to blood pressure, especially in high-risk patients. Any benefits associated with valsartan treatment in the VALUE trial could possibly have been masked by the early differences in blood pressure. The low blood pressures in our study, and the fact that they were masked by the early differences in blood pressure. The low blood pressures in our study, and the fact that they were highly relevant to the Japanese population, in which stroke incidence is 30% lower than in white populations.

Aortic dissection or lower limb arterial obstruction was reduced in the valsartan group, although the number of events was very low. Since blood pressure was similar between the two treatment groups, the reduced aortic dissection could indicate that valsartan had a beneficial

### Table 5: Adverse events occurring in more than one case

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Valsartan</th>
<th>Control group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer or metastasis</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rashes</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Zoster</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Liver function</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fracture</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Infraconjunctival haemorrhage</td>
<td>0</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Haemoptysis</td>
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<td>2</td>
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<tr>
<td>Dry cough</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>42</td>
<td>36</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>2.7%</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

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effect on the aortic wall. Second, neither transition to dialysis nor doubling of creatinine concentrations were associated with cardiovascular benefits from valsartan. These events are standard endpoints in trials to assess the renal protection of angiotensin receptor blockers in diabetic patients with nephropathy.12,13 However, since numbers of participants with impaired renal function in our study were low, our findings lack sufficient power to draw any conclusions.

A third limitation of our study was that doses of ACE inhibitors given to some patients before the start of our study were low by western standards, although consistent with clinical practice recommendations in Japan. Thus, we have no proof that the renin–angiotensin–aldosterone system had been adequately inhibited before the trial, and we cannot exclude the possibility that the results would have differed in patients who had already been given high doses of ACE inhibitors, or that increasing the ACE inhibitor dose would have provided benefits in these patients. Last, our study was not adequately powered to detect changes in cardiovascular or all-cause mortality and our median follow-up of 3–1 years was short.

Contributors
SM and BD designed the study, wrote the protocol, supervised the implementation of the research, coordinated data collection, wrote the analysis plan, supervised the analyses, interpreted the results, and wrote the report. All members of the steering committee approved the protocol and analysis plan, supervised the study and had input to the report. All authors have seen and approved the final version.

Study organisation

Executive committee
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Steering committee
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Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study

Lisa M McNally, Prakash M Jeena, Kavitha Gajee, Stanley A Thula, A Willem Sturm, Sharon Cassol, Andrew M Tomkins, Hoosen M Coovadia, David Goldblatt

Summary

Background HIV-related pneumonia is the main cause of paediatric hospital admissions in southern Africa. We aimed to measure predictors of treatment failure and the cause of non-responsive pneumonia in children admitted to hospital with severe pneumonia in Durban, South Africa.

Methods We investigated 358 children aged 1–59 months who presented with WHO-defined severe or very severe pneumonia. Children were recruited irrespective of HIV status and started on a standard antimicrobial regimen of benzylpenicillin and gentamicin. All infants also received high-dose trimethoprim-sulfamethoxazole. The primary outcome measure was treatment failure at 48 h.

Findings 242 (68%) children were HIV exposed, 41 (12%) HIV infected, and 75 (21%) HIV uninfected. Failure to respond by 48 h was predicted by age under 1 year (adjusted odds ratio 6·38, 95% CI 2·72–14·91, p<0·0001), very severe disease (2·47, 1·17–5·24, p=0·0181), HIV status (HIV infected 10·3, 3·26–32·51; HIV exposed, uninfected 6·02, 1·55–23·38; p=0·0003), and polymicrobial disease (one organism 2·06, 1·05–4·05; two organisms 10·75, 4·38–26·36; p<0·0001) on logistic regression analysis. All children with three organisms failed treatment. 72/110 treatment failures had at least two organisms isolated. Three of nine HIV-exposed, uninfected infants, 29/74 HIV-infected, but no HIV-uninfected infants who failed study therapy had Pneumocystis jirovecii pneumonia.

Interpretation For children younger than 1 year, the WHO guidelines are inadequate and need to be revised since both HIV-infected and HIV-exposed, uninfected infants had more treatment failures than did HIV-uninfected infants. Polymicrobial disease is an important reason for treatment failure, and we need to identify rapid low-cost diagnostic methods to assist clinicians.

Introduction Acute respiratory infections are the leading cause of childhood mortality worldwide.1 Initial WHO management guidelines were based on studies undertaken in the pre-HIV era.2,3 However, between 11% and 45% of children admitted to hospital with severe pneumonia in southern African countries are co-infected with HIV-1,4,5 and HIV-related pneumonias are the leading cause of these admissions.6

WHO guidelines for the management of acute respiratory infections in children younger than 5 years were initially published before the HIV-1 pandemic.7 Children are classified according to the severity of their respiratory symptoms, and empirical management is recommended for all groups. All children younger than 2 months are given benzylpenicillin and gentamicin. For children 2 months or older, benzylpenicillin alone is recommended for severe pneumonia (ie, cough with tachypnoea and chest indrawing) and chloramphenicol alone for very severe disease (ie, the presence of danger signs, including inability to drink, central cyanosis, abnormal sleepiness, or severe malnutrition).

The term disease is used because of the similarity between symptoms in very severe pneumonia and other illnesses, such as malaria and sepsis. A study from Papua New Guinea12 has shown that benzylpenicillin and gentamicin can be used as an alternative to chloramphenicol for very severe disease. We therefore adapted the existing pre-HIV WHO guidelines3 so that all children received high-dose benzylpenicillin and gentamicin irrespective of age, and all infants received high-dose trimethoprim-sulfamethoxazole because of the increased risk of Pneumocystis jirovecii pneumonia.3,5

In 2003, (after recruitment closed), a WHO consultative meeting concluded that children admitted with severe pneumonia in HIV-endemic areas should be given benzylpenicillin or ampicillin, plus gentamicin. High-dose trimethoprim-sulfamethoxazole was also recommended for infants younger than 1 year because of the high prevalence and severity of P jirovecii pneumonia.14 The guidelines suggested changing to second-line treatment if there was no clinical response by 48 h. There are no reported studies on the response to these treatment guidelines.

Previous studies in Africa of the cause of pneumonia in HIV-infected children have either used indirect means of establishing the respiratory infection such as blood
cultures,9,10,15 studied selective populations such as intensive-care patients,6,7 or used post-mortem findings.8,9 Identification of the cause of lower respiratory tract infections in children is technically difficult. Blood cultures yield an organism only in 10–20% of cases, and previous studies have shown discrepancies between organisms isolated from blood and lung.10,21 Sputum gram stain and culture is less useful in children than in adults because of the high bacterial nasopharyngeal colonisation rates.22 Previously, lung aspiration was the gold-standard technique.7,21 However, HIV-infected children have high rates of interstitial lung disease, which is unsuitable for lung aspiration.23–24 Bronchoalveolar lavage (BAL) is the technique of choice for such patients. Several studies have shown that the diagnostic accuracy of non-bronchoscopic BAL (NB-BAL) is similar to that of bronchoscopic-BAL.25–27

We therefore undertook a prospective descriptive study of children admitted to hospital with WHO-defined severe pneumonia with or without signs of very severe disease using NB-BAL. We aimed to measure the response rates to standard antimicrobial therapy in an HIV-endemic area, the cause in children who failed to respond, and the relation of response rates and treatment failure with HIV status.

Methods

Study site

Durban is the largest city in the Province of KwaZulu-Natal, South Africa, with a population of 3·09 million.26 At the time of our study (2002), the provincial antenatal HIV-1 seroprevalence rate was 36·5%,29 and antiretrovirals were not available in the public-health care sector. King Edward VIII Hospital provided primary, secondary, and

![Study profile](image-url)

Figure 1: Study profile
Panel: Definition of study endpoints

Primary outcome (treatment failure by 48 h)*
No sustained improvement or an increase in:
- heart rate
- respiratory rate
- temperature
Increased oxygen requirements
Inability to drink at 48 h
Appearance of new danger signs
Carer withdrew consent
Child left without medical advice
Change of antimicrobials for positive blood culture or new comorbid condition
Death

Secondary outcome (treatment failure at any time during hospital admission)
Increase in respiratory rate or oxygen requirement
Inability to begin weaning oxygen by 5 days
Appearance of new danger signs
Carer withdrew consent
Change of intravenous antimicrobials for positive blood culture or a new comorbid condition
Previously defined as failure at 48 h
Death

* Adapted from reference 31.

tertiary paediatric care at the start of the study, but in June, 2002, the paediatric intensive care unit moved to a new hospital. *Haemophilus influenzae* type b vaccination was introduced in South Africa in July, 1999.31

Patients and procedures

Children aged 1–59 months who were admitted to hospital with WHO-defined severe pneumonia (with or without very severe disease) between January, 2001, and December, 2002, were eligible for study enrolment. Severe pneumonia is classified as cough with tachypnoea and chest indrawing. The presence of danger signs, including inability to drink, central cyanosis, abnormal sleepiness, or severe malnutrition, defines the child as having very severe disease. Enrolment was between Saturday 0800 h and Wednesday 1800 h, 24 h per day to restrict the number of NB-BAL or lung aspirates done over weekends, to ensure adequate observation after the procedure. Study nurses were available 24 h a day. Exclusion criteria are outlined in the study algorithm (figure 1). Children known to be HIV-1 infected were not excluded from the study.

Approval for the study was obtained from the ethics committees of the Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa and the Institute of Child Health, University College, London, UK. There was a two-stage consent process. Initial consent was obtained for study entry with further written consent obtained if the child required additional investigations.

A detailed history was taken and physical examination done, and investigations included a full blood count, blood culture, chest radiograph, nasopharyngeal aspirate for viral culture, urine for antiretroviral activity, induced sputum for *P jirovecii* pneumonia and tuberculosis, three gastric washings for tuberculosis, and an HIV test. Any pleural effusion was tapped and sent for microscopy and culture, including tuberculosis.

Whole blood for HIV testing was obtained in tubes containing EDTA and labelled with study number and date of birth but not the patient’s name. Study HIV results were only made available after study recruitment had ended and all other data had been entered into a database. As part of the informed consent process, guardians were pre-test counselled and encouraged to have a parallel provincial HIV test for the child since study HIV test results would not be known to the study team or the child’s clinicians. If consent for the provincial HIV test was refused, guardians were further counselled during the child’s admission if HIV was clinically suspected. Post-test counselling was given with provincial HIV test results. Children who were suspected to be infected with HIV-1 but whose guardians refused testing were treated as HIV-infected during their admission, discharged on trimethoprim-sulfamethoxazole prophylaxis, and followed up in paediatric outpatients. Provincial HIV testing was not a pre-requisite for study entry because the stigma associated with HIV diagnosis at the time of this study would have substantially biased our recruitment and results.

A positive HIV ELISA antibody test (Vironostika IMPVD, Biomérieux, Boxtel, Netherlands) was followed by measurement of HIV viral load (NuclIsens HIV-1 assay [Biomérieux, Boxtel, Netherlands]). Children who were HIV ELISA positive but RNA negative, or had viral loads less than 10000 copies per mL had a confirmatory HIV-1 DNA PCR (Molecular Diagnostic Services, Westville, South Africa). All HIV DNA and RNA tests were concordant. Infants younger than 1 year were classified into three groups—HIV-infected children who were ELISA positive and RNA positive, HIV-exposed, uninfected infants who were ELISA positive and RNA and DNA negative, and HIV-uninfected children who were ELISA negative. Children 1 year or older were classified into two groups (those infected and those uninfected) according to the results of HIV testing.

Children received the study antibiotics for a minimum of 48 h and changed to oral treatment when no longer hypoxic (oxygen saturations less than 92% on room air). No child waited more than 1 h from study enrolment to first antimicrobial dose. Adjunct intravenous dexamethsone (0–6 mg/kg per day given every 6 h) was provided for children with proven *P jirovecii* pneumonia.

Oxygen saturations were maintained above 92% by nasal cannulae oxygen to a maximum of 3 L per min with
the addition of rebreathing mask if needed. Heart rate, respiratory rate, and oxygen saturations (Tuff Sat, Data Ohmeda, Louisville, KY, USA) were recorded every 4 h. The study doctor (LM) assessed all children within 12 h of admission and twice daily until discharge. When LM was absent, three other paediatricians covered the work (PJ, ST, and NN). We standardised the assessment of respiratory rate, lower chest wall indrawing, and danger signs with prestudy training followed by training sessions every 3 months throughout the study.

The primary endpoint was treatment failure at 48 h. Secondary endpoints were cumulative treatment failure at any time during hospital admission and death (in-hospital mortality; see panel), with definitions adapted from a previous WHO study. Children who had a clinically significant organism isolated from admission blood culture that was resistant in vitro to the study antimicrobials were changed to appropriate antimicrobials and defined as non-responders.

Children who failed treatment were transferred to the paediatric intensive care unit for further investigations. The investigations were only done if a ventilator was available (as per study protocol); otherwise the antibiotics were changed empirically. Children had a repeat blood culture, nasopharyngeal swabs, and a chest radiograph. If there was dense peripleural consolidation, a lung aspirate under ultrasound guidance was done. If lung aspiration was contraindicated, NB-BAL was undertaken as previously described elsewhere. A chest radiograph was done after the procedure.

**Laboratory methods**

A set of Bactec (Becton and Dickinson, New Jersey, USA) bottles were used for every blood culture. Bottles were incubated in the Bactec 9240 shaking incubator for a maximum of 7 days. Gram-stain microscopy and culture were done on pleural fluid, BAL fluid, and lung aspirates. Specimens were inoculated onto 7% horse-blood agar, chcolated-blood agar, colistin-nalidixic acid amphotericin blood agar, and McConkey number 1 plates. Horse-blood agar and McConkey number 1 plates were incubated aerobically and cholchated-blood agar and colistin-nalidixic acid amphotericin blood agar in a humidified atmosphere containing 5% carbon dioxide, all at 37ºC. Induced sputa, gastric washings, NB-BAL, and lung aspirate specimens were digested and decontaminated with the N-acetyl-L-cysteine-sodium hydroxide method. Pleural fluids were decontaminated only if bacteria other than *M tuberculosis* were present. Auramine stained slides were examined for acid-fast bacilli. All specimens were inoculated onto a Middlebrook 7H11 agar, a Lowenstein-Jensen slant, and a Middlebrook 7H9 broth. The Middlebrook agar was incubated in a sealed carbon dioxide permeable plastic bag at 37ºC for 3 weeks. The other media were incubated for 8 weeks and all media were read every week. Only children with culture-proven *M tuberculosis* were defined as having tuberculosis.

A bag or catch urine specimen was obtained from children before study antimicrobials were started. If the child was clinically too ill to wait for the urine sample, this specimen was not obtained. A Whatman number 1 filter paper disk, with a diameter of 6 mm, was impregnated with urine. The disk was placed on the surface of a Mueller-Hinton agar plate seeded with a fully susceptible *Bacillus subtilis*. The plate was incubated overnight at 37ºC, and any zone was interpreted as presence of antimicrobial substances.

Direct immunofluorescence for detection of *P jirovecii* was undertaken according to the manufacturer’s instructions (Detect IF PC, Axis-Shield, UK). A positive test was defined as the presence of five or more cysts.

Respiratory viral infections were diagnosed by direct immunofluorescence with murine monoclonal antibody conjugates (Light Diagnostics, Chemicon International, USA) for respiratory syncytial virus, influenza A or B virus, parainfluenza virus types 1–3, cytomegalovirus, and adenovirus. Respiratory samples were also inoculated into shell vial and tube cultures for 21 days.

The study doctor and medical microbiologists communicated daily and met every week to determine the clinical significance of isolated organisms on the basis of clinical presentation, specimen site, and sample quality. The clinical significance of NB-BALs were based on white cell count, organisms seen on gram stain, and culture (mixed or pure).

**Statistical analysis**

Data were analysed with SPSS (version 12.01). χ² for trend test was used to compare categorical variables across three groups by HIV status. For 2x2 tables, χ² test was used, except when the expected cell count in one of the cells was less than five when a Fisher’s exact test was used. Student’s *t* test was used for comparison of the means of normally distributed continuous variables, and Mann-Whitney *U* test to compare substantially skewed variables. All continuous variables are expressed as mean (SD) or median (IQR). Multiple logistic regression models used forward variable selection with an inclusion rule of p≤0.05.

**Role of the funding source**

The funder had no role in study design, data collection, analysis, interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

358 children were enrolled. 254 (71%) had WHO defined very severe disease. 356 children were black and two were Indian. Median age was 4.8 months (IQR 2.7–13.0) with 260 (73%) children younger than 1 year. 242 (68%) were
Articles

HIV-1 infected, 41 (11%) were HIV-exposed, uninfected, and 75 (21%) were HIV-1 uninfected. Table 1 shows other baseline characteristics. HIV exposed, uninfected infants had less splenomegaly (p=0·0003), less oral candida (p=0·0002) and better mean weight for age (p<0·0001) than did HIV-infected infants. 86% (207/242) of HIV-infected children either had a provincial HIV test during their admission or were known to be HIV infected before admission.

126 (35%) children failed treatment by 48 h. A further 29 (8%) failed subsequently, mostly because of nosocomial or comorbid infections. 54 (15%) children died during their admission; 13 within 48 h of admission. Median hospital stay was 8 days (IQR 4–13) and median duration of oxygen requirement was 4 days (2–8).

The strongest predictors of poor outcome were age younger than 1 year, HIV-1 status, maternal tuberculosis status, polymicrobial disease, and very severe disease (table 2). Infants younger than 1 year had higher 48 h treatment failure rates (109/260 [42%] vs 17/98 [17%], p<0·0001), cumulative treatment failure rates (126/260 [49%] vs 29/98 [30%; p=0·001), and higher in-hospital mortality rates (48/260 [19%] vs six of 98 [6%], p=0·004) than did children aged 1 year or older. Both number of children admitted to hospital and poor outcomes were highest for the youngest children, and values fell throughout the first year of life. 201/358 (56%) of admissions and 43/54 (80%) of deaths were in children under 6 months.

Both HIV-infected and HIV-exposed, uninfected infants had higher 48 h and cumulative treatment failure rates than did HIV-uninfected infants, with χ² for trend (48 h treatment failure, HIV infected, vs HIV uninfected: OR 5·3, 95% CI 2·5–13·25; HIV exposed, uninfected, 2·66, 0·89–8·11; p<0·0001; cumulative treatment failure, HIV infected, vs HIV uninfected, 6·54, 2·82–15·55, HIV exposed, uninfected, 2·3, 0·79–6·8; p<0·0001). There was also a strong association between HIV status and in-hospital mortality (figure 2). When only two groups were compared, there was a trend for HIV-infected infants to have higher 48 h treatment failure rates (p=0·05), cumulative treatment failure rates (p=0·0022), and in-hospital mortality rates (p=0·0007) than HIV exposed, uninfected infants but not more paediatric intensive-care unit admissions (figure 2). HIV-exposed, uninfected infants had higher 48 h treatment failures (p=0·05) and a trend for higher cumulative treatment failures (p=0·088) than did HIV-uninfected infants but not higher in-hospital mortality (figure 2). For children 1 year or older, there was no difference in outcomes between HIV-infected and HIV-uninfected children.

Outcomes were worse in children with WHO-defined very severe disease than in those with severe pneumonia

Table 1: Admission characteristics by age and HIV status

<table>
<thead>
<tr>
<th>All</th>
<th>Age</th>
<th>HIV Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger than 1 year</td>
<td>1 year or older</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Patient groups</td>
<td>358</td>
<td>260 (73%)</td>
</tr>
<tr>
<td>Male</td>
<td>196 (55%)</td>
<td>145 (56%)</td>
</tr>
<tr>
<td>Cough (days)</td>
<td>5.0 (0.0–7.0)</td>
<td>5.0 (0.0–7.0)</td>
</tr>
<tr>
<td>Fever (days)</td>
<td>4.0 (0.0–7.0)</td>
<td>4.0 (0.0–7.0)</td>
</tr>
<tr>
<td>Difficulty breathing (h)</td>
<td>72 (24.0–120.0)</td>
<td>72 (24.0–120.0)</td>
</tr>
<tr>
<td>Loose stools</td>
<td>101 (28%)</td>
<td>76 (29%)</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>2.86 (0.67)</td>
<td>2.8 (0.66)</td>
</tr>
<tr>
<td>Weight for age (mean Z score)</td>
<td>-1.85 (1.5)</td>
<td>-1.6 (1.48)</td>
</tr>
<tr>
<td>Clubbing</td>
<td>54 (15%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
<td>66.9 (14.2)</td>
<td>68.4 (14.1)</td>
</tr>
<tr>
<td>Clinical cyanosis</td>
<td>196 (55%)</td>
<td>152 (55%)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.4 (1.0)</td>
<td>37.3 (1.0)</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>164 (24.1)</td>
<td>168.2 (22.9)</td>
</tr>
<tr>
<td>Use of neck muscles</td>
<td>236 (66%)</td>
<td>176 (68%)</td>
</tr>
<tr>
<td>Notable to drink</td>
<td>134 (37%)</td>
<td>116 (45%)</td>
</tr>
<tr>
<td>Oral candida</td>
<td>181 (51%)</td>
<td>151 (58%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>314 (88%)</td>
<td>227 (87%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>232 (65%)</td>
<td>175 (67%)</td>
</tr>
</tbody>
</table>

Data are number (%) unless, median (IQR), or mean (SD). HIV-1 = HIV uninfected. HIV-1 EU = exposed to HIV but uninfected. HIV-1+ = HIV infected. TB = tuberculosis.
(48 h treatment failure p<0·0001; cumulative treatment failure p<0·0001; and in-hospital mortality p<0·0001; figure 2). HIV status affected outcome only in children with very severe disease. 124 (35%) children had a family history of tuberculosis within the past 2 years, with 18 cases (5%) of maternal tuberculosis. Only maternal tuberculosis was associated with worse outcomes (48 h treatment failures: 13/18 [72%] vs 113/340 [33%], p=0·0007; cumulative treatment failures 13/18 [72%] vs 142/340 [42%], p=0·011; in-hospital mortality seven of 18 [39%] vs 47/340 [14%], p=0·001).

304 (85%) children had all admission investigations. 106 (35%) had no organism, 141 (46%) had one, 53 (17%) had two, and four (1%) had three clinically significant different organism types isolated. The number of organisms isolated was not predicted by heart rate, respiratory rate, or temperature. Polymicrobial infections were not more common in HIV-infected children, infants younger than 1 year, or malnourished children. The number of different organism types isolated was linearly associated with all outcome measures—48 h treatment failures (none in 18 [17%]; one in 41 [29%]; two in 32 [62%]; three in four [100%]; p<0·0001); cumulative treatment failures (23 [22%]; 55 [39%]; 35 [67%]; four [100%]; p<0·0001); and in-hospital mortality (nine [9%]; 17 [12%]; 23 [18%]; one [25%]; p=0·012).

To adjust for severity of illness on admission, duration of cough (days), fever (days), and difficulty breathing (h), heart rate, respiratory rate, temperature, Z-score weight for age, age younger than 1 year, HIV status, WHO defined very severe disease, and the number of different organism types were included in logistic regression analysis. Age under 1 year (adjusted OR [AOR] 6·38, 1·23–35·14, p=0·011), HIV-ELISA-positive (0·94 for 1% rise, 0·91–0·97, p=0·0002) predicted 48 h treatment failure. HIV ELISA positivity, oxygen saturations, inability to drink, but not age under 1 year, predicted cumulative treatment failure and death.

79 (22%) children were bacteraemic, 116 (38%) had virus identified on admission nasopharyngeal aspirate, 53 (15%) culture proven tuberculosis, and 33 (9%) P jirovecii pneumonia. 79 (22%) children had bacteraemia, but there was no association with outcome (48 h treatment failure rate 34/92 vs 99/279, p=0·098; cumulative treatment failure rate 40/92 vs 115/279, p=0·136; in-hospital mortality rate 13/92 vs 41/279, p=0·70). HIV status did not affect bacteraemia rates (HIV infected 6·53 [1·93–27·97] vs HIV exposed, uninfected 4·36 [1·42–13·24], p=0·18; but not in-hospital mortality two [6%] vs four [5%], p=0·56). For children younger than 1 year, bacteraemia had no effect (data not shown). This result was not attributable to increased antimicrobial

<table>
<thead>
<tr>
<th>Predictors of poor outcome on univariate analysis</th>
<th>48 h treatment failure</th>
<th>Cumulative treatment failure</th>
<th>In-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age younger than 1 year</td>
<td>3·44 (1·78–6·40)</td>
<td>2·24 (1·32–3·82)</td>
<td>3·37 (1·41–10·25)</td>
</tr>
<tr>
<td>HIV-1 ELISA positive</td>
<td>2·55 (1·33–4·96)</td>
<td>3·22 (1·73–6·07)</td>
<td>8·06 (2·02–69·74)</td>
</tr>
<tr>
<td>Very severe disease</td>
<td>3·52 (1·94–6·49)</td>
<td>3·55 (2·05–6·17)</td>
<td>6·13 (2·05–23·93)</td>
</tr>
<tr>
<td>Maternal tuberculosis</td>
<td>6·52 (1·93–27·97)</td>
<td>4·53 (1·36–19·4)</td>
<td>4·36 (1·42–13·24)</td>
</tr>
<tr>
<td>Loose stools</td>
<td>1·55 (0·94–2·56)</td>
<td>1·68 (1·03–2·74)</td>
<td>1·47 (0·76–2·83)</td>
</tr>
<tr>
<td>Seen health-care worker</td>
<td>2·02 (1·11–3·72)</td>
<td>2·09 (1·19–3·7)</td>
<td>2·59 (1·04–7·68)</td>
</tr>
<tr>
<td>Weight for age &lt;2 SD</td>
<td>1·28 (0·81–2·03)</td>
<td>1·66 (1·06–2·60)</td>
<td>1·40 (0·75–2·59)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>3·28 (1·81–6·0)</td>
<td>3·02 (1·89–4·84)</td>
<td>6·02 (2·1–23)</td>
</tr>
<tr>
<td>Clinical cyanosis</td>
<td>3·02 (1·84–4·97)</td>
<td>3·02 (1·89–4·84)</td>
<td>4·92 (2·12–11·19)</td>
</tr>
<tr>
<td>Oral candida</td>
<td>2·04 (1·28–3·25)</td>
<td>2·49 (1·58–3·91)</td>
<td>4·15 (2·02–6·7)</td>
</tr>
<tr>
<td>Clubbing</td>
<td>0·42 (0·19–0·88)</td>
<td>0·61 (0·32–1·17)</td>
<td>0·29 (0·07–0·97)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>6·35 (2·24–24·97)</td>
<td>5·72 (2·31–9·66)</td>
<td>8·73 (1·41–35·37)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>2·84 (2·6–7·65)</td>
<td>3·74 (2·24–6·25)</td>
<td>2·71 (2·16–6·0)</td>
</tr>
<tr>
<td>Gross developmental delay</td>
<td>1·52 (0·9–2·61)</td>
<td>2·08 (1·23–3·52)</td>
<td>1·68 (0·88–3·21)</td>
</tr>
<tr>
<td>Increased tone</td>
<td>2·61 (1·49–4·54)</td>
<td>3·48 (1·95–6·23)</td>
<td>3·75 (1·93–7·29)</td>
</tr>
<tr>
<td>Unable to drink</td>
<td>3·26 (2·02–5·28)</td>
<td>3·24 (2·03–5·19)</td>
<td>4·18 (2·17–8·1)</td>
</tr>
<tr>
<td>Use of neck muscles</td>
<td>1·65 (1·27–2·3)</td>
<td>1·95 (1·23–3·16)</td>
<td>1·41 (0·74–2·8)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&lt;60</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>61–80</td>
<td>1·39 (0·83–2·33)</td>
<td>1·56 (1·25–2·56)</td>
<td>2·87 (1·25–6·72)</td>
</tr>
<tr>
<td>81–100</td>
<td>1·80 (1·83–3·99)</td>
<td>1·82 (1·84–3·97)</td>
<td>3·81 (1·35–10·4)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>6·08 (0·86–4·55)</td>
<td>4·56 (0·77–49·08)</td>
<td>9·83 (1·41–66·29)</td>
</tr>
<tr>
<td>No chest signs audible</td>
<td>3·36 (1·83–5·8)</td>
<td>2·61 (1·47–4·66)</td>
<td>2·76 (1·39–5·45)</td>
</tr>
<tr>
<td>WCC &lt;4 5 or &gt;20 1</td>
<td>1·58 (0·97–2·57)</td>
<td>1·61 (1·06–2·59)</td>
<td>0·51 (0·82–8·5)</td>
</tr>
<tr>
<td>Urinary antimicrobials</td>
<td>1·27 (0·6–2·37)</td>
<td>1·33 (0·73–2·43)</td>
<td>2·64 (1·56–12)</td>
</tr>
</tbody>
</table>

Table 2: Predictors of poor outcome on univariate analysis
Articles

organism identified from admission blood culture than did children younger than 1 year (13/21 organisms sensitive to both gentamicin and penicillin resistance since children 1 year or older had more strains) vs 14/16 [88%; p=0.0003], and in-hospital mortality (six of 16 [38%] vs 48/342 [14%; p=0.021). All S aureus isolates were penicillin resistant, 50% were methicillin resistant, and six of 14 were gentamicin resistant. All children with methicillin resistant S aureus had urinary antibiotic activity on admission.

In the 16 children with a previous diagnosis of lymphocytic interstitial pneumonitis, there was a trend towards higher rates of both S pneumoniae (four of 16 [25%] vs 20/224 [9%; p=0.062] and S aureus (two of 16 [13%] vs nine of 224 [4%; p=0.09) bacteraemia than in other HIV-1 infected children.

206 children had urine antimicrobial activity assessed on admission (table 4). About 40% of children were positive, indicating recent antimicrobial use. There was no association between positive urinary antimicrobial activity and maternal recall of antibiotic use, HIV status, or bacteraemia, but there was an effect on the organisms isolated. S pneumoniae was cultured less often and S aureus more often in children with positive urinary antimicrobial activity than in those who were negative. Positive urinary antimicrobial activity was also associated with increased in-hospital mortality rates.

53 children had culture-proven tuberculosis. There was no association with HIV status (HIV infected 38/242 vs HIV uninfected 15/116; p=0.49), age (younger than 1 year 34/260 vs 1 year or older 15/98; p=0.13) or mortality (tuberculosis 11/53 vs no tuberculosis 43/305; p=0.21). M tuberculosis was cultured more often in those with a maternal history of tuberculosis than in those without maternal history, but this result was not statistically significant (four of 17 vs 49/340; p=0.32). Culture-proven tuberculosis was not more common in children with other family tuberculosis contacts (14/109 vs 39/246, p=0.46). Only eight of 53 (15%) children had had symptoms for more than 2 weeks. 22 (6%) children had admission pleural effusions tapped. Ten (45%) were sterile, six cultured S pneumoniae (all HIV infected), five cultured S aureus (two HIV exposed, uninfected, three HIV uninfected), one cultured

Streptococcus pneumoniae was the most common organism identified from admission blood culture (table 3). 11/26 infants failed treatment during their hospital admission. All S pneumoniae isolates were penicillin susceptible (minimum inhibitory concentration ≤1 µg/mL), but eight of the children who failed therapy had a co-infection including four bacterial, one tuberculosis, and five viral co-infections. Only four of the S pneumoniae isolates were susceptible to trimethoprim-sulfamethoxazole although susceptibility was not dependent on whether the child was taking trimethoprim-sulfamethoxazole prophylaxis or not (trimethoprim-sulfamethoxazole resistance: six of eight on prophylaxis vs ten of 12 off prophylaxis; p=1.0).

16 had Staphylococcus aureus bacteraemia that was associated with increased 48 h treatment failure (13/16 [81%] vs 113/342 [33%; p<0.0001], cumulative treatment failure (14/16 [88%] vs 141/342 [41%; p=0.0003], and in-hospital mortality (six of 16 [38%] vs 48/342 [14%; p=0.021). All S aureus isolates were penicillin resistant, 50% were methicillin resistant, and six of 14 were gentamicin resistant. All children with methicillin resistant S aureus had urinary antibiotic activity on admission.

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both *S aureus* and *Haemophilus influenzae* (all HIV uninfected), and three *M tuberculosis* (all also cultured bacteria).

110/155 children who failed treatment during admission underwent further investigations (97 NB-BAL, seven lung aspirates, and six pleural aspirates). The remaining 45 children were excluded from this phase of the study because they were too ill for further investigation (23), because there was no intensive-care unit bed available (18), or the patient subsequently needed antimicrobials for presumed nosocomial comorbid disease (four).

There were no complications from lung or pleural aspiration. Of the 97 children who had a NB-BAL, 88 (91%) had no complication. Of the remaining nine, three had an increased oxygen requirement for less than 6 h after the procedure, three had an increased requirement for more than 6 h after the procedure, and three had temporary bronchospasm responsive to bronchodilators. None needed ventilatory support after the procedure. Only two had a NB-BAL for a presumed nosocomial infection. All other investigations done after 48 h were due to a lack of improvement in oxygen requirements.

Table 5 details the organisms isolated and thought to be clinically significant (ie, not contaminants) from children investigated for treatment failure. 102/110 (93%) had an organism isolated from at least one site. Significant bacterial pathogens were isolated from 28 admission blood cultures, nine subsequent blood cultures, seven pleural aspirates, and 38 NB-BAL specimens. A virus was isolated from 56 nasopharyngeal isolates and 47 NB-BAL specimens. Two cases of tuberculosis were diagnosed by NB-BAL alone, and the others from a combination of induced sputa and gastric washings.

The most common organisms were cytomegalovirus (44 children), *P jirovecii* (29), and *M tuberculosis* (24). Pathogens isolated from HIV-exposed but uninfected and HIV-infected non-responders were similar, including cytomegalovirus, *P jirovecii*, *Klebsiella pneumoniae* and *Escherichia coli*, but numbers were small. No children 1 year or older had *P jirovecii*, *K pneumoniae*, or *E coli*.

<table>
<thead>
<tr>
<th>Younger than 1 year</th>
<th>1 year and older</th>
<th>All children (n=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+ (n=170)</td>
<td>HIV- (n=61)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>12 (7%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>7 (4%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><em>Viburna group streptococci</em></td>
<td>6 (4%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td><em>Streptococcus millen</em></td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Other streptococci</em></td>
<td>5 (3%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>2 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>1 (&lt;1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1 (&lt;1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>1 (&lt;1%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><em>Campylobacter coli</em></td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Salmonella spp</em></td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>No significant organism</strong></td>
<td>133 (78%)</td>
<td>32 (78%)</td>
</tr>
</tbody>
</table>

All data are number (%). HIV-1=HIV uninfected. HIV-1=HIV exposed, uninfected. HIV-1=HIV infected. *Eight children had two organisms isolated from their admission blood culture. Therefore numbers do not add up to 358.

Table 3: Admission blood culture results by HIV status and age*
103/110 children investigated for treatment failure had all admission and non-responder investigations. No organism was isolated in seven (6%), 24 (24%) had one organism, 41 (40%) two, 22 (21%) three, and nine (9%) four. Therefore, more than one organism was isolated from 72 (70%) children. There was no association with HIV status or timing of investigation after admission (>two organisms and investigation <48 h, 62/88; investigation >48 h, nine of 13; p=0·85). All nine children with four organisms identified were investigated within 48 h of admission. 66/97 had no bacteria identified on NB-BAL, but 59 of these 66 had a virus, *M tuberculosis* or *P jiroveci* isolated.

### Discussion

The results of our study can be used to assess WHO treatment guidelines published in 2003 for the treatment of severe pneumonia and HIV in low-resource countries. In children older than 1 year the WHO guidelines are effective, irrespective of the child’s HIV-status. However, for those aged younger than 1 year these guidelines are inadequate since 42% of infants failed therapy by 48 h and a further 6% failed subsequently. This result is especially important because over 70% of children in our study were younger than 1 year. Predictors of treatment failure included HIV status (both HIV infected and HIV exposed, uninfected), age younger than 1 year, WHO-defined very severe disease, maternal tuberculosis, and polymicrobial disease.

79% of all children admitted to hospital with severe pneumonia were HIV-infected or HIV-exposed, which is higher than reported in similar South African studies. Unlike other studies of HIV-associated paediatric pneumonia, children were recruited irrespective of their suspected HIV status. Therefore, in areas with high antenatal seroprevalence (40% in Durban), around 80% of children admitted to hospital with severe pneumonia will be at risk of failing recommended treatment strategies.

There was a significant trend in our study for those who were HIV infected or HIV exposed, uninfected to have a worse outcome than those who were HIV uninfected. HIV-exposed, uninfected infants had an increased risk of treatment failure and paediatric intensive-care unit admission. The high reported sensitivities of HIV RNA and DNA testing make false negative molecular results unlikely. Additionally, HIV-exposed but uninfected infants had fewer clinical signs of HIV infection and were better nourished than HIV-infected infants.

There are several biologically plausible explanations for the increased risk of treatment failure reported for HIV-exposed, uninfected infants. There is reduced transplacental transfer of protective antibodies from HIV-infected mothers to their children and HIV-

### Table 5: Organisms isolated from children who were investigated for failing to respond by HIV status and age

<table>
<thead>
<tr>
<th></th>
<th>Total (n=90)</th>
<th>Infected (n=74)</th>
<th>Exposed uninfected (n=9)</th>
<th>Uninfected (n=7)</th>
<th>Total (n=20)</th>
<th>Infected (n=13)</th>
<th>Uninfected (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P jiroveci</em></td>
<td>29 (32%)</td>
<td>26 (35%)</td>
<td>3 (33%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>15 (17%)</td>
<td>13 (18%)</td>
<td>0</td>
<td>2 (29%)</td>
<td>9 (45%)</td>
<td>5 (39%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td><em>Cytomegalovirus</em></td>
<td>40 (45%)</td>
<td>37 (51%)</td>
<td>2 (22%)</td>
<td>1 (14%)</td>
<td>4 (20%)</td>
<td>3 (23%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>9 (10%)</td>
<td>7 (9%)</td>
<td>0</td>
<td>2 (29%)</td>
<td>3 (15%)</td>
<td>3 (23%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>13 (14%)</td>
<td>11 (15%)</td>
<td>2 (22%)</td>
<td>1 (14%)</td>
<td>6 (30%)</td>
<td>4 (31%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Other gram positive</td>
<td>6 (7%)</td>
<td>5 (7%)</td>
<td>0</td>
<td>1 (14%)</td>
<td>3 (15%)</td>
<td>3 (23%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>5 (6%)</td>
<td>3 (4%)</td>
<td>1 (11%)</td>
<td>1 (14%)</td>
<td>4 (20%)</td>
<td>2 (15%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>9 (10%)</td>
<td>8 (11%)</td>
<td>1 (11%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>8 (9%)</td>
<td>7 (9%)</td>
<td>1 (11%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Salmonella spp</em></td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Legionella spp</em></td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other gram negative</td>
<td>10 (11%)</td>
<td>8 (11%)</td>
<td>1 (11%)</td>
<td>1 (14%)</td>
<td>3 (15%)</td>
<td>2 (15%)</td>
<td>1 (15%)</td>
</tr>
<tr>
<td><em>Adenovirus</em></td>
<td>6 (7%)</td>
<td>4 (5%)</td>
<td>0</td>
<td>2 (28%)</td>
<td>3 (15%)</td>
<td>2 (15%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td><em>Respiratory syncytial virus</em></td>
<td>11 (12%)</td>
<td>8 (11%)</td>
<td>3 (33%)</td>
<td>0</td>
<td>2 (10%)</td>
<td>0</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Other virus</td>
<td>8 (9%)</td>
<td>6 (8%)</td>
<td>1 (11%)</td>
<td>1 (14%)</td>
<td>3 (15%)</td>
<td>3 (23%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Aspergillus spp</em></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (15%)</td>
<td>1 (5%)</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Streptomyces spp</em></td>
<td>1 (&lt;1%)*</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sacchromyces spp</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

All data are number (%). *Only children who had all study investigations and failed therapy are included (admission and non-responder blood culture; admission nasopharyngeal aspirate and NB-BAL or lung aspirate for viral immunofluorescence; and culture, induced sputum, and NB-BAL or lung aspirate for *P jiroveci* pneumonia and tuberculosis; gastric washings for tuberculosis; NB-BAL, lung aspirate, or pleural aspirate for bacteria). Bacteria isolated from nasopharyngeal swabs or induced sputa are not regarded as significant and therefore not included.
exposed, uninfected infants have altered CD4 immunity during the first year of life. These infants also have increased exposure to pathogenic organisms from their immunosuppressed mothers. There were two mother-infant pairs diagnosed with P jirovecii pneumonia. A Malawian study has shown that trimethoprim-sulfamethoxazole prophylaxis in HIV-infected adults reduces both hospital admissions and mortality in HIV-uninfected children, and a Zambian study reported increased 4 month admisions and mortality rates in HIV exposed, uninfected infants, associated with maternal immunosuppression. As prevention of mother-to-child transmission strategies of HIV become more widespread, the number of HIV-exposed, uninfected infants will increase—a matter of great public-health concern.

The poor outcomes associated with maternal tuberculosis in our study could be the result of occult tuberculosis in the child or from advanced HIV-1 disease in the mother. Contact with other family members with tuberculosis did not predict poor outcome. 15% of children had culture proven tuberculosis, but 85% of these children had had symptoms for less than 2 weeks. The tuberculosis rate is higher than in other studies of acute pneumonia in South Africa, possibly because we investigated all children for tuberculosis irrespective of whether it was clinically suspected or not. Very severe disease, defined by WHO as clinical cyanosis or inability to drink because of breathlessness, predicted poor outcome even in HIV-infected children. Indeed, the increased risk in HIV-infected and HIV-exposed children was only seen in those admitted to hospital with very severe disease.

The high rates of HIV infection, very severe disease, and death could possibly make this study unrepresentative of children routinely admitted to secondary level health-care facilities in HIV-endemic areas. However, we excluded all patients who were being referred for tertiary level care or who had a pre-existing chronic condition other than HIV. Since over 40% of pregnant mothers were HIV infected at the time of the study and at least 70% of HIV-infected patients will have an admission for pneumonia before the age of 1 year, the fact that most children were HIV infected is not surprising. The high rates of HIV infection have led to increased hospital admission rates, and the pressure on the medical services has led to only the very sickest children being admitted, hence the high rates of very severe disease. Only two HIV-uninfected patients died, one from group B Streptococcus and the other from tuberculosis. We therefore conclude that the high case-fatality rates are attributable to HIV and not the admission of children who are usually admitted to hospital for tertiary care.

The rates of bacteraemia on admission (22%) were higher than those reported in most other paediatric pneumonia studies. As in studies from both Cape Town and Malawi, there was no relation between HIV status and bacteraemia from all causes. S pneumoniae was the most commonly identified pathogen on blood culture and most positive cultures were from HIV-infected children (24/26), which accords with the increased risk of invasive S pneumoniae disease in HIV infection. 39% of tested children had urinary antimicrobial activity before starting study antimicrobials. Since the rates of pneumococcal isolation were ten times higher in children who were urinary antimicrobial positive than in those who were negative, the true rates of pneumococcal bacteraemia are probably higher than we reported. The basis for this increased susceptibility could be the poor immune response to the capsule of S pneumoniae in HIV-infected children, as shown in studies of the response to the pneumococcal conjugate vaccine, although the nine-valent pneumococcal conjugate vaccine is clearly able to protect HIV-infected children in Soweto, South Africa.

Despite all pneumococci being penicillin susceptible, 11 children with pneumococci subsequently failed therapy. Eight of these patients had another organism subsequently isolated, emphasising the importance of dual infections in children who fail first-line therapy. Only four of 26 S pneumoniae were sensitive to trimethoprim-sulfamethoxazole. Although resistance was not more frequent in HIV-infected children receiving prophylaxis than in those who did not receive prophylaxis, these high resistance rates are probably because of high trimethoprim-sulfamethoxazole prophylaxis rates as reported from other African countries.

S aureus bacteraemia was associated with poor outcome. Despite appropriate treatment once the blood culture results became available, six of the 15 children died. Six children had MRSA, and all had urinary antimicrobial activity on admission. The rate of MRSA was not higher in children who had had a previous hospital admission than in those with no previous admissions.

Mortality was higher in children with positive urinary antimicrobial activity on admission than in those who were negative, possibly because the children were sicker or had been ill for longer. Additionally, S aureus was more common in these children and was an independent predictor of poor outcome. Children could therefore have failed outpatient therapy, which usually does not include antistaphylococcal cover. Previous South African studies might have over-represented the role of S aureus since urinary antimicrobial activity was not measured. However, in children older than 1 year there were more S aureus infections than gram-negative infections. For these children possibly either penicillin alone would have been sufficient or first-line therapy should include β-lactams that cover S aureus.

Cytomegalovirus was isolated from 37 (49%) HIV-infected, two of nine (22%) HIV-exposed, uninfected infants, and one HIV-uninfected infant investigated for
treatment failure. The role of this virus in the cohort is unclear, since neither histology nor cytomegalovirus viral load was done. Previous data for cytomegalovirus in HIV-1 related respiratory infections have been contradictory.11,12 All infants received high-dose trimethoprim-sulfa-methoxazole, and therefore \( P. jirovecii \) was probably under-diagnosed. Despite this underestimation, \( P. jirovecii \) was isolated from 26/74 HIV-infected and three of nine HIV-exposed, uninfected infants investigated for treatment failure. \( P. jirovecii \) pneumonia was not diagnosed in any HIV-uninfected child nor any child older than 6 months. None of the children with such infection had other risk factors, such as malnutrition or primary immunodeficiency, which emphasises the risk for an HIV-exposed, uninfected infant.

Polymicrobial infections predicted poor outcome and were present in 70% of children investigated for treatment failure irrespective of HIV status. Polymicrobial disease might restrict the effectiveness of any revised empiric treatment strategies, especially since it could not be predicted by clinical presentation. The majority of children investigated for treatment failure with NB-BAL had organisms unlikely to respond to a change in antibiotics—two-thirds had no bacteria identified on NB-BAL, but 59 of these 66 had a virus, \( M. tuberculosis \), or \( P. jirovecii \) pneumonia isolated.

Our findings have several important public-health implications. For children younger than 1 year, the present guidelines for treatment of severe pneumonia are inadequate because of high failure rates in infants born to HIV-infected mothers, and these guidelines need to be revised. The widespread roll-out of prevention of mother-to-child transmission strategies and antiretrovirals will reduce the number of HIV-infected children admitted to hospital with pneumonia, but the raised risk in HIV-exposed, uninfected infants will assume increasing importance. Polymicrobial disease is a key predictor of treatment failure and there is a need for rapid low-cost diagnostic methods to assist clinicians. Further studies are urgently needed to address these issues.

**Contributors**

All authors contributed to conception and design of the study. LMM, PMJ, KG, A WS, HMC, AMT, and DG obtained funding for the study.

**Conflict of interest statement**

LMM has moved to GSK Biologicals, Rixensart, Belgium since submission of the paper and currently does not hold any GSK shares. The company had no involvement in the original study. No other conflicts of interest declared.

**Acknowledgments**

The study and LMM’s salary were funded through a Wellcome Trust Clinical Tropical Medicine Training Fellowship (grant number GR05669MA). We thank M Adhikari and all the staff of the Department of Paediatrics at the University of KwaZulu-Natal; S Ramji and his staff from the Paediatric Resuscitation Unit; Nisha Naidler and the study nursing team for study recruitment; and all the study participants and their families.


37 Heresi GP, Caceres E, Atkins JT, Reuben J, Doyle M. *Pneumocystis carinii* pneumonia in infants who were exposed to human immunodeficiency virus but were not infected: an exception to the AIDS surveillance case definition. *Clin Infect Dis* 1997; 25: 739–40.


Summary

Background Dengue viruses are a major cause of morbidity and mortality in tropical and subtropical areas. Our aim was to assess prospectively the burden of dengue-related illness in children in Thailand.

Methods We did a prospective study in a cohort of children at primary school in northern Thailand from 1998 to 2002. We assessed the burden of dengue illness as disability-adjusted life years (DALYs) and patient costs per illness.

Findings Dengue accounted for 328 (11%) of the 3056 febrile cases identified in 2114 children during the study period. The mean burden of dengue was 465.3 (SD 358.0; range 76.5–954.0) DALYs per million population per year, accounting for about 15% of DALYs lost to all febrile illnesses (3213.1 [SD 2624.2] DALYs per million per year). Non-hospitalised patients with dengue illnesses represented a substantial proportion of the overall burden of disease, with 44–73% of the total DALYs lost to dengue each year due to such illness. The infecting dengue serotype was an important determinant of DALYs lost: DEN4 was responsible for 1% of total DALYs lost, DEN1 for 9%, DEN2 for 30%, and DEN3 for 29%.

Interpretation Use of prospective data to estimate the burden of disease shows that most DALYs lost to dengue illness were the result of non-hospitalised illnesses of long duration. Thus, inclusion of non-hospitalised cases is critical to accurately assess the total burden of dengue illness.

Introduction Dengue fever and dengue haemorrhagic fever are important causes of morbidity and mortality in tropical and subtropical regions of the world.1, 2 Since there is no effective treatment for dengue infection, prevention efforts rely on mosquito control and the development of tetravalent dengue vaccines.3, 4 Several population-based studies have assessed the burden of disease due to dengue and found the effect of dengue on both financial and other factors to be substantial.5–11 These studies mainly used surveillance data derived from hospitalised cases, reported cases of dengue haemorrhagic fever, and deaths attributed to dengue; data on non-hospitalised cases and less severe dengue disease were not available. Therefore, these calculations probably underestimate the true burden of disease, given that classic dengue fever represents about 90% of symptomatic dengue cases and most of these are non-hospitalised cases.12

Use of disability-adjusted life years (DALYs) facilitates the assessment of the effect of illness and premature death on an individual and societal level in a manner that does not necessitate financial valuations of life and health.13, 14 Previous endeavours to describe DALYs lost to dengue have been variable with respect to source population, case ascertainment, parameter estimates, and geographical region. Nonetheless, these studies have concluded that dengue is associated with a sizeable burden of illness, relative to other diseases.

Our aim was to use prospectively collected data to assess the burden of dengue illness in children at primary school in Thailand. Such an approach captures and includes data for all febrile illnesses, thus permitting the comparison of dengue and non-dengue cases as well as hospitalised and non-hospitalised cases; these data should therefore represent the full burden of dengue illness in this cohort.

Methods

Participants The study methods and determination of acute, symptomatic dengue virus infections in the cohort have been described previously.12, 21 Briefly, the study was done in Kamphaeng Phet province in northern Thailand. In January, 1998, 2214 children were recruited from grades one to five (children aged 5 years to 15 years) at 12 local primary schools. Enrolment criteria for study participation were attendance at a study school, enrolment in first to sixth grades thereafter, and parental written informed consent. New participants were enrolled from the first grade class in January of each year until they graduated from the sixth grade. Exclusion criteria included planning to move outside the study area within the first 12 months of the study and having a history of thalassaemia that required blood transfusion.

The protocol for this study was reviewed and approved by the Human Use Review and Regulatory Agency of the Office of the Army Surgeon General, the Institutional Review Board of the University of the Massachusetts School of Medicine, and the Thai Ethical Review Board of the Ministry of Public Health, Thailand.

Procedures Volunteers were assessed three times during the dengue season from June to November every year, at which time samples were collected for dengue serology. Potential
illnesses were identified on the basis of absence from school, visit to a school nurse, visit to a public-health clinic, or admission to the hospital. Absent students were visited by village health workers and assessed with an internally validated symptom questionnaire and measurement of oral temperature. Blood samples from the acute phase of illness were obtained for absent students with a history of fever within 7 days of school absence or an oral temperature of 38°C or more, as were 14-day convalescent blood samples. Children with severe disease were referred for further assessment and possible admission to the Kamphaeng Phet province hospital. A student who was absent from school and had no history of fever on examination was assessed on each day of school absence until a fever or history of fever was documented or the student returned to school. Previously described laboratory assays were used to confirm dengue infection.13,15

An acute dengue illness was defined as a documented history of febrile illness and laboratory confirmation of acute dengue virus infection. Charts of hospitalised children were independently reviewed and classified as dengue fever or dengue haemorrhagic fever and assigned a severity grade per WHO criteria by an expert in the field.16

Calculations of DALYs were done with methods described previously.13,14 The following equation was used to obtain DALYs lost per individual:13,15

$$\text{DALYs lost} = \left[ \frac{DCe^{rL}}{L(1-\beta)(1+\beta+r)(1+\beta+r+\beta)} \right]$$

where \(a\) is age in years at the time of illness and the age-weighting variables \(C\) and \(\beta\) adjust the loss of DALYs such that an illness in an adult is weighted more heavily than an illness in a child or an elderly person. The social discount rate (\(r\)) adjusts such that DALYs lost in the present are valued more highly than those lost in the future. In accordance with previous studies, the following values were applied: \(\beta=0.04, r=0.03\), and \(C=0.16243\).

The disability weight (\(D\)) represents the severity of an illness and can range from 0 to 1, where a value of 0 represents healthy life and 1 represents death. An initial publication on the use of DALYs introduced six graded classes of disease severity, based on the ability to perform so-called activities of daily living, with each class having a unique disability weight.13 Studies specific to the burden of dengue illness have often applied a disability weight of 0.81; this level of severity indicates the level at which the afflicted individual needs assistance with instrumental activities of daily life. A subsequent publication on the use of DALYs for the Global Burden of Disease project presented revised disability weights and included weights specific for dengue haemorrhagic fever for the first time.14 Importantly, these revised weights incorporate the probability of death and represent the disability weights for one full year (with an estimated duration of illness for dengue haemorrhagic fever of 29 days).15 As the cohort data used here permitted estimation of the duration of illness in days and there were no deaths attributed to dengue during the study period, we decided that the initial disability weight of 0.81 was more appropriate for these analyses. Specific diagnoses for non-dengue illnesses were not available; a disability weight of 0.81 was therefore applied to all non-dengue febrile illnesses as well.

The duration of illness (\(I\)) in days was derived from home visit data and hospitalisation records. If a child was hospitalised, the duration of illness was the pre-hospitalisation time (from date of school absence or weekend visit to a clinic) plus the time in the hospital. If a child was not hospitalised, the duration of illness was the length of time from the date of school absence or clinic visit to the date of the last home visit at which the child was not febrile. The average length of time between acute-stage visits was 2–6 days, with an average of 3.3 visits per febrile illness.

Each illness was treated as an independent event, irrespective of whether two or more illnesses occurred for a child during a 1-year period. DALYs lost for each individual illness were calculated and summed, either in total or by stratum, then divided by the number of children in that stratum. Sensitivity analyses were done to assess the effects of varying the disability weights for both dengue fever and dengue haemorrhagic fever illnesses and of removing the parameters for age weighting and discounting. Total DALYs lost during the years of maximum and minimum dengue burden and the 5-year average of the disease burden were compared against the values computed by WHO for other diseases in the region.20

Several assumptions were used for the economic analyses, on the basis of local expert opinion, previous analyses in the region,21,22 and discussion with a subset of families of children who had previously had a diagnosis of dengue infection in the province. The health-seeking behaviours for dengue and non-dengue febrile illnesses were presumed to be similar, especially since there was a high level of awareness and concern regarding dengue haemorrhagic fever as a possible and severe outcome of a paediatric febrile episode. Health-care costs were therefore estimated by use of the same assumptions for both dengue and non-dengue illnesses.

The population in Kamphaeng Phet province commonly used private clinics when severe dengue illness was suspected but tended to use public facilities for hospitalisation. A child was assumed to have visited a private clinic if the duration of illness was 3 days or longer, if the child was vomiting or had haemorrhagic manifestations, or if the child was eventually hospitalised for the illness. The cost of a visit to a private clinic was estimated to be 200 baht (about US$5). A family member was assumed to have lost 1 day of household income if the child visited a clinic, and the family lost 1 day of income for each day of a hospitalisation. Daily income was based on government-reported averages for Kamphaeng Phet.23 We assumed
that children were hospitalised only at public facilities; under Thailand’s 30 baht public insurance system, treatment is free at public clinics and hospitals for those aged under 12 years and is 30 baht for those over 12 years. The cost of hospitalisation therefore did not depend on the diagnosis, the clinical course, or the treatment received. The cost of food for an attendant family member was estimated to be 50 baht per day of hospitalisation. Transport costs were deemed to be negligible since most families interviewed had personal transport or lived near a public or private clinic. Nearly all families with children who had a recent febrile illness reported purchasing paediatric medicines or antipyretics at the onset of the sickness; all illnesses were therefore assumed to have incurred pharmaceutical costs of 50 baht. For non-hospitalised cases, only medication costs and clinic costs with the associated expense of lost income contributed to the cost per illness.

The costs for each illness were calculated and summed, either in total or by stratum. Currency conversions were done with the reported exchange rate for each year, with $1 roughly equal to 40 baht. Sensitivity analyses were done for cost calculations by varying the costs associated with medications, clinic visits, and transportation.

### Statistical analysis

Analyses were done with SPSS for Windows version 10.0 and SAS version 9.1. Non-parametric Mann-Whitney U tests were used to compare costs and DALYs across strata, because the data did not have a normal distribution. Significance was set at the α<0.05 level.

### Role of the funding source

The funding source had no role in study design, data collection, analysis, interpretation, or writing of the report. The manuscript was reviewed by the Walter Reed Army Institute of Research before submission. The corresponding author had full access to all the data and final responsibility for the decision to submit the paper for publication.

### Results

Between 1998 and 2002, 3056 cases of febrile illnesses were seen in 2119 children, of which 328 (11%) were confirmed dengue infections (table 1). Of these dengue infections, 52 cases progressed to dengue haemorrhagic fever. There were no deaths attributable to dengue infection during this period. The incidence of dengue infection in the cohort ranged from 0.9% in 2000 to 8.4% in 2001. The number of dengue and non-dengue febrile illnesses varied greatly by year, with a notable peak in non-dengue cases in 1998. The proportion of febrile illnesses that were caused by dengue ranged from 4% in 2000 to 20% in 2001.

Over the study period, the mean burden of dengue illness in the study cohort was 465.3 (SD 358.0) DALYs per million per year. 3214.1 (2624.2) DALYs per million per year were lost on average to all febrile (dengue and non-dengue) illnesses in the cohort. Dengue thus accounted for about 15% of DALYs lost to all febrile illnesses during the study period. Wide variability in the DALYs lost to dengue was observed from year to year, ranging from 76.5 DALYs per million per year in 2000 to 954.0 DALYs per million per year in 2001.

Sensitivity analyses revealed that the most influential parameter in the calculation of DALYs was the choice of disability weight; had a lower disability weight of 0.60 been applied selectively to cases of dengue fever, the average loss of DALYs to dengue would have been 374.9 (SD 265.2) DALYs per million per year (range 65.0–803.2; table 2). The removal of age weights and discount rates decreased but did not substantially change estimates.

Illnesses not requiring hospitalisation represented the greatest burden to children in the cohort, most of which was due to non-dengue illnesses (figure 1). Dengue illness represented 232 (7.9%) of 2930 non-hospitalised cases of febrile illnesses and 1296.4 (8.8%) of the 14679.1 DALYs lost to non-hospitalised febrile illness over the study period. By contrast, 96 (76.2%) of 126 hospitalised cases of febrile illnesses and 1030.1 (74.2%) of the 1388.6 DALYs lost to all...
hospitalised febrile illnesses in the cohort were attributable to dengue infection over the study period.

Non-hospitalised cases of dengue represented an average of 259·3 [SD 258·9] DALYs per million per year (ie, an average of 56% [range 44·2–73·0] of the total DALYs lost to dengue every year), and were thus an important contributor to the overall disease burden. DALYs lost to dengue in 1998 were more than twice that of 1999, despite a similar incidence of infection (figure 2). The burden of disease associated with both dengue fever and dengue haemorrhagic fever requiring hospitalisation was roughly equal for all years except in 2001, during which dengue haemorrhagic fever predominated.

The mean burden of dengue illness as calculated from this cohort, extrapolated using regional population estimates reported by WHO, accounted for about 1% of the total DALYs lost to infectious and parasitic diseases in countries in southeast Asia deemed to have low all-cause mortality in 2002 (table 3).

Of the 328 confirmed dengue illnesses, the infecting serotype was isolated in 235 (72%) cases. Of the four dengue serotypes (DEN1, DEN2, DEN3, and DEN4), DEN2 and DEN3 accounted for most of the total DALYs lost to dengue over the 5-year period, with DEN2 responsible for 709·1 (30·5%) and DEN3 for 675·5 (29·0%) of the 2327·3 DALYs lost to dengue over the 5-year study period. DEN4 was consistently associated with a very low incidence and disease burden, representing 6 (2·5%) of 235 serotyped cases and 16·3 (0·7%) of the 2327·3 DALYs lost. By contrast, DEN1 was associated with 219·0 (9·4%) of the 2327·3 DALYs lost. DEN3 was found to be more likely to cause dengue haemorrhagic fever, representing 28 (60·9%) of 46 cases of dengue haemorrhagic fever, and was responsible for most of the dengue infections in the cohort over the 5-year period (116 [49·4%] of 235 dengue infections). By contrast, DEN3 was associated with fewer cases of dengue haemorrhagic fever than DEN2, but patients infected with DEN3 tended to be ill for a longer period of time, with an average duration of illness of 7·2 days (vs 4·2 days for both DEN1 and DEN2 and 1·5 days for DEN4).

In peak burden years (1998 and 2001), most of the DALYs lost could be attributed to a single dengue serotype (figure 3). In 1998, the high loss of DALYs was mainly attributable to a predominance of non-hospitalised cases infected with DEN3, and DEN3-related illnesses were of longer duration than with other serotypes, with an average of 8·6 days of illness (vs 4·1 days for DEN1 and 4·0 days for DEN2). The duration of illness caused by DEN3 in 1998 was also longer than that observed for DEN3 in any other year, (4·3–6·5 days). The peak in disease burden in 2001 was caused by an increase in cases of dengue haemorrhagic fever compared with other years. Of the 32 cases of dengue haemorrhagic fever identified in 2001, the infecting serotype was known in 22 cases; 15 (68%) of these cases were caused by DEN2, and lasted an average of 8·2 days.

The mean cost of illness was significantly higher for dengue than for non-dengue febrile illnesses, at $16·59

Figure 1: DALYs lost to febrile illnesses by year (A). DALYs lost to illnesses not requiring hospitalisation. (B) DALYs lost to hospitalised cases.

Figure 2: DALYs lost to dengue each year and dengue incidence Error bars are SE.
and $9·77, respectively (p<0·0001; table 4). The mean duration of illness was also significantly longer for dengue, with 5·3 days of illness versus 4·0 days for non-dengue febrile illness (p<0·0001). The duration of illness requiring hospitalisation, which included the period before hospitalisation, was greater for dengue haemorrhagic fever than for non-dengue illness (8·4 days vs 7·9 days). A dose-response effect was observed for dengue disease severity with respect to the average cost per illness as well as the duration of illness. Hospitalised cases of dengue haemorrhagic fever were associated with a mean of 8·4 days of illness, which was greater than hospitalised cases of dengue fever (6·3 days) and non-hospitalised cases of dengue (4·4 days). Similarly, hospitalised cases of dengue haemorrhagic fever were associated with a mean cost of $39·09, compared with non-hospitalised cases of dengue which cost $10·15.

Sensitivity analyses showed that if transport costs as low as 10 baht per clinic visit and per day of hospitalisation were included in cost estimates, sizeable increases were observed in costs associated with dengue illness, from $16·59 on average to $23·26 (table 5). The average cost of dengue illness decreased the most when clinic expenditures were removed, for all levels of disease severity. Raising the cost of medications to 100 baht or eliminating medication expenditures altogether resulted in negligible changes in cost.

Discussion

Our estimates of the burden of dengue illness in an endemic area over 5 years confirm previous reports that suggest that dengue virus constitutes a substantial burden to the health and finances of populations living in affected areas. Most DALYs lost to dengue illness were the result of illnesses of long duration that did not require hospitalisation, suggesting that previous estimates were conservative because they excluded non-hospitalised dengue cases.

Previous studies have used surveillance data to estimate the burden of dengue illnesses; by contrast, we used prospectively collected data. This approach permits a more definitive assessment of febrile illness as well as the capture of both non-hospitalised and hospitalised cases of dengue, which allowed us to quantify the burden of disease due to less severe illnesses. The accuracy of these analyses is further enhanced in that the duration of

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>DALYs (in thousands)</th>
<th>Log₁₀ DALYs</th>
<th>Proportion of total infectious disease burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious and parasitic diseases*</td>
<td>10 915</td>
<td>4 038</td>
<td>100%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3 530</td>
<td>3 548</td>
<td>32%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1 502</td>
<td>1 277</td>
<td>14%</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>1 481</td>
<td>1 372</td>
<td>14%</td>
</tr>
<tr>
<td>Childhood diseases</td>
<td>1 464</td>
<td>1 366</td>
<td>13%</td>
</tr>
<tr>
<td>Malaria</td>
<td>502</td>
<td>2 701</td>
<td>5%</td>
</tr>
<tr>
<td>Sexually transmitted diseases, excluding HIV</td>
<td>479</td>
<td>2 680</td>
<td>4%</td>
</tr>
<tr>
<td>Dengue (maximum)</td>
<td>284</td>
<td>2 454</td>
<td>3%</td>
</tr>
<tr>
<td>Tropical diseases</td>
<td>251</td>
<td>2 399</td>
<td>2%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>219</td>
<td>2 341</td>
<td>2%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>143</td>
<td>2 354</td>
<td>1%</td>
</tr>
<tr>
<td>Dengue (average)</td>
<td>139</td>
<td>2 342</td>
<td>1%</td>
</tr>
<tr>
<td>Intestinal nematode infections</td>
<td>135</td>
<td>2 329</td>
<td>1%</td>
</tr>
<tr>
<td>Dengue (WHO estimate)</td>
<td>89</td>
<td>1 949</td>
<td>0·8%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>67</td>
<td>1 826</td>
<td>0·6%</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>29</td>
<td>1 462</td>
<td>0·3%</td>
</tr>
<tr>
<td>Dengue (minimum)</td>
<td>23</td>
<td>1 362</td>
<td>0·2%</td>
</tr>
</tbody>
</table>

*Non-dengue estimates obtained from the 2003 World Health Report, which estimates for DALYs for 2002 for low-mortality countries in southeast Asia.

Table 3: The burden of dengue in Thailand compared with other infectious diseases in the region in 2002

<table>
<thead>
<tr>
<th>Year</th>
<th>DALYs per million per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>249</td>
</tr>
<tr>
<td>1999</td>
<td>279</td>
</tr>
<tr>
<td>2000</td>
<td>309</td>
</tr>
<tr>
<td>2001</td>
<td>329</td>
</tr>
<tr>
<td>2002</td>
<td>359</td>
</tr>
</tbody>
</table>

Figure 3: DALYs lost each year to specific dengue serotypes

<table>
<thead>
<tr>
<th>Non-dengue illness</th>
<th>Dengue</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Non-hospitalised cases</td>
<td>Hospitalised cases</td>
</tr>
<tr>
<td>Number</td>
<td>2728</td>
<td>2702</td>
</tr>
<tr>
<td>Duration of illness (days)</td>
<td>3·98</td>
<td>3·94 (1·36)</td>
</tr>
<tr>
<td>Cost of illness (US$)</td>
<td>$9·77</td>
<td>$9·46 (1·10-18·14)</td>
</tr>
</tbody>
</table>

Data are n or mean (range), except for overall, where data are n or mean. *Comparison of total (overall) non-dengue with total dengue illnesses.

Table 4: Cost and duration of dengue and non-dengue illnesses
illness for each case could be estimated; this variable has been shown to be an influential parameter in sensitivity analyses of DALYs lost to dengue illness. Illness-specific data, including clinical course and infecting serotype, allowed estimation of the burden of disease at the family level and description of larger epidemiological trends within the population.

Dengue illnesses were associated with a longer duration of disease and increased costs, compared with non-dengue febrile illnesses. Our cost estimates are lower than those reported elsewhere—a study of the economic burden of hospitalised dengue illness in Thailand in 1994 found that direct patient costs (ie, for hospitalisation, clinic cost, food, and transportation) were about US$70 per hospital admission for dengue haemorrhagic fever;\(^2^2\) when indirect costs of lost income due to missed work were included, patient costs were found to be $48–118 for a child and $138 for an adult patient. Another study of hospitalised dengue in Kamphaeng Phet in 2001, reported an average cost per illness of $61.\(^2^3\) The lower costs estimated here could in part be due to the introduction of the 30 baht insurance system in Thailand, which has lowered patient costs substantially at public clinics and hospitals; further, such cost estimates are complicated by variability in health-care systems and associated expenditures. Our estimates did not include costs associated with the use of private hospitals, so true costs could be higher than those reported here. Transport costs were not included in the primary analysis but sensitivity analyses showed that such costs substantially affect cost calculations. These findings suggest that future economic analyses of dengue should routinely include a thorough investigation of transportation expenditures. Generalisation of these cost estimates to other populations is complicated by variability in health-seeking behaviours and health infrastructure. Nonetheless, with an average monthly wage of $312 in Thailand,\(^2^3\) an average cost of $39 per hospitalised case of dengue haemorrhagic fever can represent a substantial proportion of familial income. To conclude that several severe infections in a family could result in financial catastrophe is not unreasonable.

We found that the burden of dengue illness varied widely by year, with a range of 76·5 to 954·0 DALYs per million per year and an average of 465·3 DALYs per million per year. In Burma, a study of fatal and non-fatal cases of dengue haemorrhagic fever reported an average loss of 84 DALYs per million population per year for the period 1970–97, with the loss of 134 DALYs per million per year averted through prevention efforts.\(^2^4\) A study that used data derived from patients with haemorrhagic manifestations, deaths, and hospitalisations due to dengue in Puerto Rico reported an average of 580 DALYs per million per year, with a maximum of 2153 DALYs per million per year in 1994.\(^2^5\) A 2001 study of hospitalised dengue in Kamphaeng Phet, Thailand, reported a loss of 427 DALYs per million per year.\(^2^6\) Finally, the WHO World Health Report 2003, presented an estimate of 89 000 total DALYs lost to dengue in developing countries with low mortality in southeast Asia (eg, Thailand, Indonesia, and Sri Lanka) and a loss of 292 000 DALYs in developing countries with high mortality in the same area (eg, Bangladesh, India, and Nepal).\(^2^7\) Dengue illnesses that did not require hospitalisation, not reported in national dengue surveillance programmes and not captured in previous burden of disease studies, were responsible for over half the average number of DALYs lost to dengue, which suggests that in years when there are few reported hospitalised cases, the burden of dengue could be grossly underestimated. Previous studies have sought to account for unreported cases of dengue illness by assuming there were ten undetected cases for every detected case.\(^2^8\) Since non-haemorrhagic cases of dengue (ie, non-hospitalised cases of dengue fever and hospitalised cases of dengue fever) represented over two-thirds of all cases of dengue identified each year in this study on average, this crude adjustment is perhaps not that inaccurate. However, a key finding of this study is that the incidence of disease and the burden of disease in DALYs do not necessarily correlate, and that the relative contributions of dengue fever and dengue haemorrhagic fever to the total disease burden can vary considerably by year. This finding would be lost with blanket estimates of the duration of disease and the use of multiplication factors for undetected disease.

When placed in the context of the burden of other diseases in southeast Asia, as calculated by WHO, our estimate of the average burden of dengue illness falls below the burden of meningitis and hepatitis B, and above intestinal nematode infections, hepatitis C, and Japanese encephalitis (table 3). However, during the peak burden year of 2001, the burden of dengue illness ranked above meningitis, hepatitis B, and tropical diseases (including schistosomiasis, trypanosomiasis, and
leishmaniasis). The average burden of dengue illness disease as calculated for this cohort was higher than that calculated by WHO for the region (139 000 vs 89 000 DALYs).

The burden of disease associated with specific dengue serotypes is an important epidemiological finding in this study. DEN2 and DEN3 combined represented almost 60% of the total DALYs lost to dengue over the 5-year period. However, their contributions to the overall burden were quite different: whereas infection with DEN2 was more likely to result in hospitalised cases of dengue haemorrhagic fever, infection with DEN3 generally resulted in a milder illness of longer duration. The finding of increased pathogenicity associated with southeast Asian strains of DEN2 is supported by previous studies. Given the assignment of the same disability weight to all serotypes, the disproportionately high burden of DEN2 illnesses can be attributed to a greater disease incidence and the long duration of dengue haemorrhagic fever caused by DEN2. If a lower weight were applied to cases of dengue fever, the burden of disease associated with DEN2 would be higher still. However, the important contribution of milder cases of DEN3 to the burden of disease is evident in a comparison of the years 1998 and 1999: despite much the same incidence of dengue illness in the cohort in these 2 years, the burden of disease was nearly twice as high in 1998 because of the predominance of DEN3-associated illnesses that did not require hospitalisation. This effect would have been overlooked in a basic study of disease incidence or in a hospital-based burden of disease study.

DALYs are an important indicator of the burden of disease in a population and facilitate the comparison of the effect of a disease in the context of other diseases and across populations. As used in this study, DALYs have also proven to be a valuable epidemiological tool, allowing description of the burden of disease with respect to population-level effects, as well as the assessment of subgroup and temporal effects that are incompletely described with simple incidence and prevalence measures. Nonetheless, calculations of the loss of DALYs as done here are subject to some limitations. First, since this study is based on a schoolaged cohort—the population with the highest incidence of dengue infection in Thailand—extrapolation of the loss of DALYs to the general population could result in an overestimation of the true disease burden. Second, identification of the specific causes of non-dengue illnesses was not possible, and the same disability weight was therefore applied to both dengue and non-dengue febrile illnesses. If inaccurate, this assumption would probably result in an overestimation of the severity of non-dengue illnesses with a decrease in the relative burden of dengue. Finally, the adoption of some critical assumptions when calculating DALYs or the cost of illness is unavoidable. The choice of disability weight, in particular, can greatly influence the calculated burden of disease. We sought to address this issue by undertaking extensive sensitivity analyses; the results underscore the critical process of the selection of parameter estimates and the need for thorough assessment of assumptions. More long-term prospective studies are needed to place these findings in relation to different populations, different geographical regions, and to allow smoothing of trends over several years.

Our findings have important implications for dengue vaccine design and for the assessment of vaccine effectiveness. Dengue virus will continue to be an important emerging pathogen for the foreseeable future, and these data support the necessity of short-term and long-term prevention measures such as vector control and the development of tetravalent dengue vaccines.

Contributors KBA did the data analysis and wrote the manuscript. SC contributed to the implementation and conduct of the study. AN did the diagnostic assays and contributed to the implementation and conduct of the study. MPM contributed to the implementation, data analysis, and conduct of the study. ALR, SG, and DWV contributed to the implementation and conduct of the study. FAE was overall programme manager and contributed to the implementation and conduct of this study. TPE assisted in the analysis of the data and writing of the manuscript.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
We thank Martin Meltzer for his technical expertise in the calculation of DALYs. We thank the staff at the Department of Virology, Armed Forcers Research Institute of Medical Science (Bangkok, Thailand) for their careful diagnostic testing and data collection and entry. We acknowledge the support of the Office of the Provincial Public Health, Kamphaeng Phet province and the clinical research nurses at AFIRMS and the support staff at the Kamphaeng Phet Field Station for all their efforts. This project and publication was made possible by NIH Grant AI45313 and the United States Army Medical Research and Materiel Command, Ft Detrick, MD, USA. The opinions expressed in this manuscript do not necessarily represent the official views of the US National Institutes of Health, the US Department of Defense, or the US Department of the Army.

References


Clinical Picture

Fishing for worms with a nasogastric tube

Varun Dhir, Ashok Kumar

After a road traffic accident, an 18-year-old man was admitted to our unit with suspected traumatic pancreatitis. He was treated conservatively with intravenous fluids and continuous nasogastric aspiration. On the third day of admission, we noted that 12 h had passed without any fluid draining from the nasogastric tube, so the tube was removed. To our surprise, the distal end of the tube appeared bifid! A second look revealed that an *Ascaris lumbricoides* worm was lodged in the nasogastric tube, despite being very nearly the diameter of the tube (figure). Roundworms (nematodes) are estimated to infest a quarter of the world’s population: *A lumbricoides* is the commonest. By migrating into lumens, it can cause cholangitis, appendicitis, or pancreatitis. In this case, the lumen it migrated into was the nasogastric tube.

**Acknowledgment**

We thank Dr Kiran Kumar, who assisted us in the management of this case.
Hypopituitarism

Harald Jörn Schneider, Gianluca Aimaretti, Ilonka Kreitschmann-Andermahr, Günter-Karl Stalla, Ezio Ghigo

Incidence and prevalence of hypopituitarism are estimated to be 4·2 per 100 000 per year and 45·5 per 100 000, respectively. Although the clinical symptoms of this disorder are usually unspecific, it can cause life-threatening events and lead to increased mortality. Current research has refined the diagnosis of hypopituitarism. Identification of growth hormone and corticotropin deficiency generally requires a stimulation test, whereas other deficiencies can be detected by basal hormones in combination with clinical judgment. Newly developed formulations of replacement hormones are convenient and physiological. Work has shown that many patients with brain damage—such as traumatic brain injury or aneurysmal subarachnoid haemorrhage—are at high risk of (sometimes unrecognised) hypopituitarism. Thus, a much increased true prevalence of this disorder needs to be assumed. As a result, hypopituitarism is not a rare disease and should be recognised by the general practitioner.

Pituitary insufficiency was the topic of a 1998 Lancet seminar.1 Since then, new insights in the areas of epidemiology, diagnosis, and treatment of hypopituitarism have taken place that deserve to be summarised in a current seminar.

Hypopituitarism, first described clinically by Simmonds in 1914,2 is the inability of the pituitary gland to provide sufficient hormones adapted to the needs of the organism. It might be caused by either an inability of the gland itself to produce hormones or an insufficient supply of hypothalamic-releasing hormones. Figure 1 shows how changes in hormones that regulate pituitary and hypothalamic function might lead to hypopituitarism. Generally, hypopituitarism is chronic and lifelong, unless successful surgery or medical treatment of the underlying disorder can restore pituitary function. Patients with hypopituitarism have increased mortality.3,4

Causes and epidemiology

As far as we know, only one population-based study has assessed the incidence and prevalence of hypopituitarism.4 These researchers noted a prevalence of 45·5 cases per 100 000 in a Spanish population. Incidence was 4·2 cases per 100 000 per year and increased with age. The causes of hypopituitarism were pituitary tumorous (61%), non-pituitary lesions (9%), and non-cancerous causes (30%), including 11% idiopathic cases.4 Other disorders that classically have been regarded as rare causes of hypopituitarism include perinatal insults, genetic causes, or trauma.4 The panel summarises causes of hypopituitarism.

Since the beginning of the 21st century, the importance of brain damage attributable to traumatic brain injury,4 aneurysmal subarachnoid haemorrhage,5 ischaemic stroke,6 neurosurgery,7 and cranial irradiation8 as a major and formerly underestimated cause of hypothalamic-pituitary dysfunction has been highlighted. Ten systematic studies of endocrine function in a total of 749 patients in the chronic phase after admission for traumatic brain injury (most patients were studied at least 6 months after trauma)9–20 and five studies of 122 individuals with aneurysmal subarachnoid haemorrhage21–24 have been published. Tables 1 and 2 summarise the results. Taken together, 35% and 48% of the investigated patients were diagnosed with some degree of hypopituitarism after traumatic brain injury and subarachnoid haemorrhage, respectively. In most individuals, only single pituitary axes were affected. Pituitary irradiation is a well-known cause of hypopituitarism.25 Findings of a study of patients irradiated for brain tumours distant from the hypothalamo-pituitary axis showed that 41% developed hypopituitarism.26 In individuals undergoing surgery for non-pituitary brain tumours and in those with ischaemic stroke, rates of hypopituitarism were 38% and 19%, respectively.8,9 To date, traumatic brain injury and subarachnoid haemorrhage have been best characterised as causes of hypopituitarism. Respective incidences of these disorders leading to admission are 80 and 10 cases per 100 000 per year.3,27 The estimated overall incidence of traumatic brain injury in Europe is even higher than these values, at 235 cases per 100 000 per year.28 Application of the above-mentioned frequencies of hypopituitarism to these incidences would result in an estimated incidence of 31 cases of hypopituitarism attributable to traumatic brain injury and subarachnoid haemorrhage per 100 000 per year, when using the most conservative data. This number might still be an overestimate because of possible preselection of severely traumatised patients or varying definitions of pituitary dysfunction.
dysfunction used in the studies mentioned above. However, without doubt, a large amount of hypopituitarism related to brain damage remains undiagnosed. Patients with brain pathological disorders have many somatic, psychiatric, and neurological symptoms that could well mask the typically subtle signs of hypopituitarism. Additionally, clinicians who treat these patients have very little awareness of this risk, and endocrine assessment is usually not considered after brain damage.

Pathophysiology

The pituitary gland is supplied with blood by branches of the internal carotid artery. These vessels form a capillary plexus in the region of the median eminence of the hypothalamus. Blood from this area reaches the anterior pituitary by means of long and short portal veins via the pituitary stalk. The middle and inferior hypophyseal arteries supply the pituitary stalk and neurohypophysis with arterial blood. However, the anterior lobe is not included in this arterial blood supply; it is provided with oxygenated blood only through the internal and external plexus of the median eminence.

The pathophysiology of hypopituitarism is dependent on the cause of the disorder and is not understood completely in some cases. For pituitary adenomas, mechanical compression of portal vessels and the pituitary stalk, and ischaemic necrosis of portions of the anterior lobe, have been postulated to be the predominant mechanism causing hypopituitarism. Moreover, increases in intrasellar pressure have been recorded in patients with pituitary macroadenomas, which could be the cause of reduced blood flow through the portal vessels and the pituitary stalk, resulting in diminished delivery of hypothalamic hormones to the anterior pituitary. Empty sella is caused by herniation of the subarachnoid space and associated with flattening of the pituitary gland. This process is sometimes, but not necessarily, accompanied by hypopituitarism. The pathway by which radiation induces hypopituitarism is largely unresolved. Sparse data favour

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Panel: Causes of hypopituitarism

Brain damage
- Traumatic brain injury
- Subarachnoid haemorrhage
- Neurosurgery
- Irradiation
- Stroke

Pituitary tumours
- Adenomas
- Others

Non-pituitary tumours
- Craniopharyngiomas
- Meningiomas
- Gliomas
- Chordomas
- Ependymomas
- Metastases

Infections
- Abscess
- Hypophysitis
- Meningitis
- Encephalitis

Infarction
- Apoplexy
- Sheehan’s syndrome

Autoimmune disorders
- Lymphocytic hypophysitis
- Haemochromatosis, granulomatous diseases, histiocytosis

Empty sella

Perinatal insults

Pituitary hypoplasia or aplasia

Genetic causes

Idiopathic causes

*Pituitary tumours are classically the most common cause of hypopituitarism. However, new findings imply that causes related to brain damage might outnumber pituitary adenomas in causing hypopituitarism.
direct neuronal rather than vascular damage to the hypothalamus—which is assumed to be more radiosensitive than the pituitary gland itself—as one causal factor. Moreover, findings of a study undertaken in children suggest that hypothalamic dysfunction after external-beam radiotherapy is also secondary to altered neurotransmitter input from other brain centres. These factors might also have a role in other forms of brain damage associated with neuroendocrine dysfunction, such as stroke, neurosurgery, or traumatic brain injury.

Traumatic brain injury and subarachnoid haemorrhage have long been known to cause lesions in the hypothalamic-pituitary region, as shown by findings of several neuropathological studies. Haemorrhage, necrosis, and fibrosis of the pituitary gland and hypothalamus have been recorded. Stalk lesions can produce anterior-lobe infarction by damaging the portal blood supply. Hypothalamic lesions were noted in two-thirds of patients who died shortly after aneurysmal subarachnoid haemorrhage, consisting of areas of ischaemic necrosis, macrohaemorrhages, and microhaemorrhages.

Development of the pituitary gland is regulated by a complex interplay of several transcription factors, including HESX1, LHX1, PROP1, and POU1F1 (formerly PIT1). Mutations of these and other factors could cause pituitary malformation and hypopituitarism that might be accompanied by specific clinical symptoms.

### Diagnosis

#### Clinical presentation

Sometimes, signs and symptoms of underlying diseases accompany hypopituitarism. Tumoral masses in the sellar region with suprasellar extension can become manifest with visual impairment that is slowly progressive in most cases. Visual-field defects can present not only as classic bitemporal hemianopsia but also unilaterally in many cases. Usually, such defects remain unrecognised by patients until diagnosed by a doctor. Headaches can be an unspecific symptom of tumour masses. In case of lateral extension, rarely, signs of oculomotor nerve impairment and, even less common, additional damage to other cranial nerves within the cavernous sinus might arise. Brain damage can cause

### Table 1: Hypopituitarism in the chronic phase after traumatic brain injury

<table>
<thead>
<tr>
<th>n</th>
<th>Any degree of hypopituitarism</th>
<th>GH</th>
<th>LH/FSH</th>
<th>ACTH</th>
<th>TSH</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al, 2000*</td>
<td>22</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lieberman et al, 2001*</td>
<td>70</td>
<td>48</td>
<td>12</td>
<td>7</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Bondanelli et al, 2004*</td>
<td>50</td>
<td>27</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Agha et al, 2004*</td>
<td>102</td>
<td>29</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Poppovic et al, 2004*</td>
<td>67</td>
<td>23</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Aimaretti et al, 2005*</td>
<td>70</td>
<td>16</td>
<td>7</td>
<td>14</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Leal-Cerro et al, 2005*</td>
<td>170</td>
<td>42</td>
<td>15</td>
<td>6</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>Schneider et al, 2005*</td>
<td>70</td>
<td>25</td>
<td>3</td>
<td>7</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Tanriverdi et al, 2006*</td>
<td>52</td>
<td>26</td>
<td>5</td>
<td>17</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Herrmann et al, 2006*</td>
<td>76</td>
<td>18</td>
<td>5</td>
<td>6</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Total (%)</td>
<td>749 (100)</td>
<td>262 (35)</td>
<td>69 (9)</td>
<td>86 (11)</td>
<td>99 (13)</td>
<td>84 (11)</td>
</tr>
</tbody>
</table>

LH=luteinising hormone. FSH=follicle-stimulating hormone. GH=growth hormone. ACTH=adrenocorticotropic hormone. TSH=thyrotropic hormone.

### Table 2: Hypopituitarism after subarachnoid haemorrhage

<table>
<thead>
<tr>
<th>n</th>
<th>Any degree of hypopituitarism</th>
<th>GH</th>
<th>LH/FSH</th>
<th>ACTH</th>
<th>TSH</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al, 2000*</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brandt et al, 2004*</td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Aimaretti et al, 2004*</td>
<td>40</td>
<td>15</td>
<td>4</td>
<td>10</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Kreitschmann-Andermahr et al, 2004*</td>
<td>40</td>
<td>22</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Dimopoulou et al, 2004*</td>
<td>30</td>
<td>14</td>
<td>4</td>
<td>11</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total (%)</td>
<td>122 (100)</td>
<td>58 (48)</td>
<td>11 (9)</td>
<td>32 (26)</td>
<td>13 (11)</td>
<td>20 (16)</td>
</tr>
</tbody>
</table>

LH=luteinising hormone. FSH=follicle-stimulating hormone. GH=growth hormone. ACTH=adrenocorticotropic hormone. TSH=thyrotropic hormone.
neurological deficits, weight changes, depression, sleep disturbances, and loss of drive.

Hypopituitarism can be subclinical, indicated only by measurement of hormones, or its clinical onset might be acute and severe, necessitating admission and intensive-care management. Shortages of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and antidiuretic hormone (ADH) are potentially life-threatening and, thus, require particular attention to warrant timely diagnosis and hormone replacement. Gonadotropin and growth-hormone deficiencies, on the other hand, cause chronic morbidity. Raised prolactin concentrations sometimes accompany hypopituitarism because of disruption of inhibitory signals by the hypothalamus. This alteration can cause lactation, tenderness of the breast, and suppression of gonadotropins, leading to symptoms of hypogonadism. Table 3 summarises clinical features of hypopituitarism.

### Imaging

Craniat MRI should be done to exclude tumours and other lesions of the sellar and parasellar region after hypopituitarism has been confirmed. Of sellar tumours, the pituitary adenoma is the most frequent (figure 2). Careful review of high-resolution native and contrast-enhanced images is needed so that small lesions are not missed—eg, microadenomas (<10 mm). With MRI depicting the relation of tumours to adjacent vessels and the optic chiasm, it has a major role in presurgical planning. Traumatic damage can present with pituitary-stalk deviation, with signal inhomogeneity attributable to haemorrhage or infarction, or as empty sella (figure 2). However, hypopituitarism is not excluded by normal MRI of the sellar and parasellar region.

### Diagnostic tests

In principle, a combination of low peripheral and inappropriately low (below the upper level of the reference range) pituitary hormones indicates hypopituitarism. However, basal concentrations alone might not be distinctive owing to pulsatile, circadian, or situational secretion of some hormones. Table 4 provides a summary of endocrine testing for pituitary function.

### ACTH deficiency

ACTH and cortisol secretion follow a diurnal rhythm, with highest amounts in the early morning and lowest concentrations around midnight. These chemicals are stress hormones. Thus, values in the normal range might still indicate that the ability to respond adequately to stress is impaired. Secondary adrenal insufficiency can be excluded at morning cortisol concentrations greater than 500 nmol/L and is indicated at less than 100 nmol/L. Amounts between these values need a stimulation test. Hypoglycaemia (blood glucose <2.2 mmol/L) induced by the insulin tolerance test (0.1–0.2 IU insulin per kg bodyweight given intravenously as a bolus) is a strong stressor and regarded as gold standard for assessment of the entire hypothalamic-pituitary-adrenal axis. A maximum cortisol response to a peak concentration greater than 500 nmol/L generally excludes adrenal insufficiency. This test has some unpleasant side-effects, such as sweating, trembling, fatigue, and hunger, and is contraindicated in patients with heart disease or epileptic seizures. It should be undertaken only under close supervision at skilled centres. Corticotropin-releasing hormone (100 µg as a bolus) given as a stimulant for the pituitary ACTH reserve is no more predictive of adrenal function than morning cortisol concentrations.

![Figure 2: MRI of patients with different causes of hypopituitarism](image-url)

(A) 44-year-old man with total pituitary hormone deficit. Contrast-enhanced, coronal, T1-weighted MRI shows macroadenoma of the pituitary gland with compression of the optic chiasm (arrowheads). (B) 55-year-old man with deficiencies of luteinising hormone and follicle-stimulating hormone and growth hormone after severe traumatic brain injury. Native sagittal, T1-weighted MRI shows reduced pituitary volume and absence of hyperintense neurohypophyseal signal (asterisk). The arrow shows optic chiasm.

### Table 3: Clinical features and investigative findings of hypopituitarism

<table>
<thead>
<tr>
<th>Investigative findings</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticotropin deficiency</strong></td>
<td>Acute: weakness, dizziness, nausea, vomiting, circulatory collapse, fever, shock</td>
</tr>
<tr>
<td><strong>Chronic fatigue, pallor, anorexia, weight loss</strong></td>
<td>Hypoglycaemia, hypotension, anaemia, lymphocytosis, eosinophilia, hyponatraemia</td>
</tr>
<tr>
<td><strong>Acute: weakness, dizziness, nausea, vomiting, circulatory collapse, fever, shock</strong></td>
<td><strong>Thyrotropin deficiency</strong></td>
</tr>
<tr>
<td><strong>Children: delayed puberty, failure to thrive</strong></td>
<td>** Gonadotropin deficiency**</td>
</tr>
<tr>
<td><strong>Women: oligomenorrhoea, loss of libido, dyspareunia, infertility</strong></td>
<td><strong>Men: loss of libido, impaired sexual function, mood impairment, loss of facial, scrotal, and trunk hair</strong></td>
</tr>
<tr>
<td><strong>Children: delayed puberty</strong></td>
<td><strong>Children: retarded development, growth retardation</strong></td>
</tr>
<tr>
<td><strong>Gonadotropin deficiency</strong></td>
<td><strong>Decreased muscle mass and strength, visceral obesity, fatigue, decreased quality of life, impairment of attention and memory</strong></td>
</tr>
<tr>
<td><strong>Decreased muscle mass and strength, visceral obesity, fatigue, decreased quality of life, impairment of attention and memory</strong></td>
<td><strong>Increased muscle mass and strength, improved visceral obesity, increased muscle mass, improved quality of life, improved muscle mass, improved function of attention and memory</strong></td>
</tr>
<tr>
<td><strong>Children: growth retardation</strong></td>
<td><strong>Antidiuretic hormone deficiency</strong></td>
</tr>
<tr>
<td><strong>Polyuria, polydipsia</strong></td>
<td><strong>Polyuria</strong></td>
</tr>
</tbody>
</table>

**Table 3:** Clinical features and investigative findings of hypopituitarism.
Therefore, it is of limited value for diagnosis of ACTH deficiency.

ACTH deficiency causes adrenal atrophy and ACTH-receptor downregulation. Thus, the standard 250 µg 1-24 ACTH (corticotropin) test can be used to establish secondary adrenal insufficiency if done at least 4 weeks after onset of ACTH deficiency. Stimulated cortisol concentrations at 30 min of 500 nmol/L or less strongly indicate ACTH deficiency, and amounts of more than 600 nmol/L rule out the disorder. At values in between, a second test is recommended. Whether a low-dose (1 µg) corticotropin test would represent a more physiological stimulus for maximum adrenal stimulation than the 250 µg corticotropin dose is debatable. Even though findings of some reports have suggested superior sensitivity for a 1 µg test, workers on a meta-analysis reported comparable operating characteristics of both tests for diagnosis of secondary adrenal insufficiency. The low-dose test has disadvantages, including a need for dilution of the commercially available 250 µg corticotropin dose and repetitive blood sampling. These factors make the standard test more practical. In 20 studies included in the above meta-analysis, overall sensitivity of the 250 µg corticotropin test for diagnosis of secondary hypoadrenalism—with the insulin tolerance test as the gold standard at equal sensitivity and specificity—was 83·5% (95% CI 79·6–87·4). At a specificity of 95%, however, sensitivity was only 57% (44–71). Therefore, the ability of this test to detect all relevant cases of secondary hypoadrenalism has been questioned. However, in a retrospective follow-up of 148 patients with a low-normal cortisol response (510–635 nmol/L) to the 250 µg corticotropin test over a median time of 4-2 years, only two patients developed clear-cut adrenal insufficiency, another two presented with persistent diagnostic uncertainty, and seven had adrenal insufficiency after subsequent pituitary surgery or irradiation. Thus, the 250 µg corticotropin test seems to exclude clinically significant hypoadrenalism, even though—for a definite conclusion—a prospective comparison with the insulin tolerance test would be desirable.

We should bear in mind that no test—including the insulin tolerance test—classifies all patients correctly. Thus, in borderline cases, clinical judgment and follow-up are crucial for assessment of ACTH deficiency.

**TSH deficiency**

Central hypothyroidism is diagnosed when concentrations of free thyroxine are decreased and TSH amounts are low or normal. Dynamic testing is generally not necessary because it does not add to diagnostic reliability. In some cases, TSH can be even slightly raised, owing to secretion of biologically inactive TSH. Tri-iodothyronine is still at normal concentrations in most patients.

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**Luteinising hormone and follicle-stimulating hormone deficiency**

Before diagnosis of luteinising hormone (LH) and follicle-stimulating hormone (FSH) deficiency, prolactin excess should be excluded, which might be present because of disturbed hypothalamic inhibition of prolactin release. Diagnosis of female LH and FSH deficiency should be based on clinical findings, supported by laboratory values. Oligoamenorrhea along with inappropriately low LH and FSH concentrations indicates secondary hypogonadism in premenopausal women. During or after menopause, an absence of the typical rise in LH and FSH during menopause shows central hypogonadism. In men, secondary hypogonadism is shown by low testosterone concentrations in combination with inappropriately low gonadotropins. Hypogonadism in childhood causes no clinical symptoms until onset of puberty, at which time it usually presents with delayed or missing onset of puberty.

---

**Table 4:** Endocrine testing for pituitary function

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria for hormone deficiency*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticotrophic function</strong></td>
<td></td>
</tr>
<tr>
<td>Morning cortisol</td>
<td>&lt;100 nmol/L—hypocortisolism,</td>
</tr>
<tr>
<td></td>
<td>&gt;500 nmol/L—hypocortisolism excluded</td>
</tr>
<tr>
<td>Morning ACTH test</td>
<td>Below upper reference range: secondary adrenal insufficiency</td>
</tr>
<tr>
<td>Insulin tolerance test</td>
<td>Cortisol &lt;500 nmol/L</td>
</tr>
<tr>
<td>250 µg ACTH test</td>
<td>Cortisol &lt;500 nmol/L after 30 min</td>
</tr>
<tr>
<td><strong>Thyrotrophic function</strong></td>
<td></td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>Low (&lt;11 pmol/L)</td>
</tr>
<tr>
<td>TSH</td>
<td>Low or normal (occasionally slightly raised)</td>
</tr>
<tr>
<td><strong>Gonadotropic function</strong></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Oligoamenorrhea, oestradiol &lt;100 pmol/L, LH and FSH inappropriately low</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>LH and FSH inappropriately low</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Low (&lt;10–12 nmol/L), LH and FSH inappropriately low</td>
</tr>
<tr>
<td><strong>Somatotropic function</strong></td>
<td></td>
</tr>
<tr>
<td>IGF-1</td>
<td>Below or in the normal reference range</td>
</tr>
<tr>
<td>Insulin tolerance test</td>
<td>Adults: growth hormone ≤3 µg/L; Children: growth hormone ≤10 µg/L; Transition phase: growth hormone ≤5 µg/L</td>
</tr>
<tr>
<td>GHRH+arginine test</td>
<td>Underweight or normal weight (BMI &lt;25): 11·5 µg/L; Overweight (BMI ≥25 to &lt;30): 8·6 µg/L; Obese (BMI ≥30): 4·2 µg/L</td>
</tr>
<tr>
<td>GHRH+GHRP-6 test</td>
<td>Growth hormone ≤10 µg/L</td>
</tr>
<tr>
<td><strong>Posterior pituitary function</strong></td>
<td></td>
</tr>
<tr>
<td>Basal urine and plasma sample</td>
<td>Urine volume (&gt;40 ml/kg bodyweight per day)+urine osmolality &lt;300 mOsm/kg+water+hypermatraemia</td>
</tr>
<tr>
<td>Water deprivation test</td>
<td>Urine osmolality &gt;700 mOsm/kg; Ratio of urine to plasma osmolality &gt;2</td>
</tr>
</tbody>
</table>

*Hormone levels might differ to the ones indicated, dependent on the laboratory and assay used.
Table 5: Hormone-replacement regimens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monitoring and dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Use the least dose necessary to relieve clinical symptoms; Increase dose during pregnancy; Growth hormone replacement might unmask ACTH deficiency and require dose adjustment&lt;sup&gt;83&lt;/sup&gt;</td>
</tr>
<tr>
<td>TSH</td>
<td>Adjust to free thyroxine (target: middle-upper normal range) and normal tri-iodothyronine Further adjustments to cholesterol and clinical symptoms; Increase might be necessary during pregnancy or new oestrogen or growth hormone replacement&lt;sup&gt;85&lt;/sup&gt;</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>Use the least dose necessary to relieve clinical symptoms Stopped replacement at the age of menopause if possible</td>
</tr>
<tr>
<td>LH/FSH Women&lt;sup&gt;86&lt;/sup&gt;,&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Oral contraceptive (20–35 µg ethinyl oestradiol) or oestradiol valerate 2–4 mg/day or equine oestrogens 0.625–1.250 mg/day or transdermal oestradiol patch or gel (four times less risk of thrombosis); Unless hysterectomised: additional gestagen replacement necessary Induction of fertility: FSH or pulsatile gonadotropin-releasing hormone (the latter only if hypothalamic dysfunction&lt;sup&gt;88&lt;/sup&gt;)</td>
</tr>
<tr>
<td>LH/FSH Men</td>
<td>Testosterone gel 25–50 mg/day&lt;sup&gt;89&lt;/sup&gt; or testosterone undecanoate 1000 mg intramuscularly all 12 weeks&lt;sup&gt;90&lt;/sup&gt; or buccal testosterone pellet 30 mg twice a day&lt;sup&gt;91&lt;/sup&gt; or testosterone enantate 250 mg intramuscularly all 2–4 weeks (causes fluctuating testosterone concentrations); Induction of fertility: human chorionic gonadotropin, human menopausal gonadotropin FSH or pulsatile gonadotropin-releasing hormone (the latter only if hypothalamic dysfunction&lt;sup&gt;92&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Growth hormone dose after up-titration; Adults: 0.2–1 mg/day Children: 25–50 µg/kg per day;</td>
</tr>
<tr>
<td>ADH</td>
<td>Desmopressin oral (0.3–1.2 mg/day) or intranasal (10–40 µg/day) in 1–4 doses per day&lt;sup&gt;93&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Growth hormone deficiency**

In general, growth hormone deficiency needs to be diagnosed by stimulation testing, unless all other pituitary axes are defective and insulin-like growth factor 1 (IGF-I) is low. In these patients, the a-priori-likelihood of the deficiency is 99%.<sup>94</sup> Reference ranges for the growth hormone–regulated chemical IGF-I are helpful for monitoring of growth hormone substitution. However, both IGF-I concentrations and spontaneous growth hormone secretion substantially overlap between patients with both deficient and sufficient amounts of growth hormone, limiting their value for diagnosis of deficiency.

For identification of growth hormone deficiency, the insulin tolerance test is the best choice. Peak amounts of growth hormone of 3 µg/L or lower during the test suggest severe deficiency in adults.<sup>95</sup>–<sup>97</sup> In children, the secretory capacity of growth hormone is higher and, generally, an arbitrary cutoff of 10 µg/L is used.<sup>98</sup> For patients in the transition phase between puberty and early adulthood, cutoff amounts of 6–1 µg/L or 5 µg/L<sup>99</sup> have been suggested.

The growth hormone-releasing hormone (GHRH) plus arginine test (1 µg/kg of GHRH intravenously as a bolus plus 30 g arginine as an infusion over 30 min) is easy to do, well tolerated, and has been shown to reliably detect severe growth hormone deficiency in a lean adult population when a cutoff of 9 µg/L is used.<sup>100</sup>–<sup>102</sup> Further work has shown, however, that the growth hormone response to this test declines greatly with increasing body-mass index (BMI),<sup>103</sup> and use of this cutoff in obese patients causes a high proportion of false-positive results.<sup>104</sup> Findings of a study in which six different dynamic tests of growth hormone secretion were assessed in an obese study population (mean BMI 31) suggested a cutoff of 4.1 µg/L for the GHRH plus arginine test.<sup>105</sup> In the past few years, BMI-dependent cutoff amounts have become available. The values suggested for lean (BMI <25), overweight (BMI 25 to <30), and obese (BMI ≥30) patients are 11–5, 8–0, and 4–2 µg/L, respectively.<sup>106</sup> Another alternative is the GHRH plus growth hormone-releasing peptide 6 test.<sup>107</sup> This test has been shown to distinguish well between growth hormone-deficient and healthy individuals, although it seems to be of limited sensitivity for hypothalamic disease.<sup>108</sup> A cutoff of 15 µg/L showed the best balance of sensitivity and specificity, and specificity was 100% at a cutoff of 10 µg/L. The glucagon test (1 mg glucagon intramuscularly, growth hormone measurements every 30 min until 240 min after administration) has been shown to separate growth hormone-deficient and healthy patients with a sensitivity and specificity of 100% at a peak amount of 3 µg/L.<sup>109</sup> However, it is dependent on age and BMI<sup>110</sup> and is more time-consuming than other stimulation tests.

We should bear in mind that no test for assessment of growth hormone deficiency is 100% reliable. The likelihood of this chemical deficiency rises with increasing numbers of additional defects in pituitary axes. Normal concentrations of IGF-I in the blood do not exclude a diagnosis of growth hormone deficiency, but such a diagnosis can probably be excluded if low amounts of
this hormone are measured. These aspects, along with clinical signs of growth hormone deficiency and safety considerations, should be taken into account for the decision to start growth hormone substitution.

### ADH deficiency

ADH deficiency causes polyuria and polydipsia. Before testing, diabetes mellitus as a typical cause of polyuria should be excluded. Diabetes insipidus is possible if polyuria (≥40 ml/kg bodyweight per day) in combination with urine osmolality less than 300 mOsm/kg water and hypernatraemia is present. If normal amounts of sodium are present in plasma, a water deprivation test will be necessary. This test should be done at a skilled centre and signs of exsiccosis should be monitored closely. Generally, diabetes insipidus can be diagnosed if no clear increase is seen in urine osmolality (maximum <700 mOsm/kg) or the ratio of peak urine to plasma osmolality is less than 2.73 Glucocorticoids can suppress ADH secretion and, thus, diabetes insipidus might be precipitated by glucocorticoid replacement.79

### Management

#### Screening for hypopituitarism

Endocrine assessment of pituitary function is usually prompted by presence of ophthalmological, neurological, or other symptoms, leading to suspicion of pituitary disease. In some disorders, however, pituitary dysfunction should be actively searched for. After pituitary surgery, glucocorticoid replacement should be given to avoid undetected hypoadrenalism until deficits of ACTH and other pituitary hormones are excluded about 4 weeks after surgery.74 In patients with traumatic brain injury or subarachnoid haemorrhage, a high risk exists for hypopituitarism, but symptoms are usually masked by the sequelae of brain injury. In these individuals, endocrine assessment should be done routinely, particularly in severe or moderate cases15,70 or if the brain injury has led to prolonged admission.28

#### Treatments of cause

If caused by a tumour, pituitary function might be restored after successful surgical or medical removal of the lesion. The ability to restore pituitary function depends on accessibility, aggressiveness, and size of the tumour, skill of the surgical team, and the chosen operative pathway. In a study of 721 patients undergoing surgery for non-functioning pituitary adenomas, pituitary function improved in 50% and 11% after transphenoidal and transcranial surgery, respectively, and worsened in 2%.78 Medical treatment of prolactinomas with dopamine agonists restores pituitary function in 60–75%.47

Generally, unless contraindicated, surgery is the primary treatment for symptomatic pituitary tumours. Neurosurgery aims to prevent deterioration or manifestation of clinical symptoms such as visual disturbances and neurological signs. Particularly, visual field impairments are a serious sign and should prompt immediate surgical intervention. Prolactinomas are an exception to the rule. They respond very well to dopamine agonist treatment and should undergo primary medical treatment.

#### Hormone substitution

We should remember that hypopituitarism is sometimes accompanied by events such as diabetes mellitus, dyslipidaemia, cardiovascular complications, and osteoporosis. In addition to pituitary hormone substitution, we must treat these disorders adequately with treatments including lifestyle adaptations, lipid-lowering and antihypertensive drugs, or bisphosphonates. Table 5 gives an overview of hormone-substitution regimens.82–105 Because glucocorticoid deficiency can be life threatening, substitution should begin as soon as a deficit is confirmed. All patients should be supplied with an emergency card or bracelet with information about their steroid dependence and instructions on stress-related dose adjustments. Thyroid hormone substitution with T-thyroxine is necessary if hypothyroidism is identified. Because thyroid hormone replacement increases the rate of metabolism of glucocorticoids, which can lead to an adrenal crisis, replacement therapy should begin after hydrocortisone substitution has been initiated.15 Female sex hormone substitution can return libido, well being, and bone mass to normal levels. Findings of large studies of sex hormone replacement in non-hypopituitary postmenopausal patients have shown an increased risk of cardiovascular and neoplastic diseases.106,107 Thus, stopping sex hormone substitution in hypogonadal women after menopause is recommended.

In hypogonadal men, testosterone substitution returned bone and muscle mass, sexual function, and haematocrit to normal levels.158 Growth hormone substitution enhances body composition, lipid variables, and quality of life.159 Growth hormone deficiency has been assumed to contribute to the excess cardiovascular mortality seen in hypopituitarism, even though other factors such as cranial radiation, surgery, and other chemical deficits might also have an important role.160 In some studies, researchers have recorded an improvement of cognitive function,160,161 although others have noted no effect.162,163 Findings of long-term studies have shown no increased overall risk of malignant disease or tumour regrowth.164 However, the recorded numbers of patients are still too small for a final conclusion, and surveys on tumour growth are ongoing.
Follow-up
Once hypopituitarism has been diagnosed, adequate hormone replacement should be monitored at regular intervals. After the initial titrating phase, intervals of 6–12 months are usually recommended. If a tumour is the cause, regular ophthalmological controls and MRI should be undertaken. Endocrine assessment after brain injury should be done initially in the rehabilitation phase (3–6 months after trauma). Since pituitary dysfunction can recover after this phase, but sometimes new deficiencies might become manifest, assessment should be repeated in the chronic phase (about 1 year after trauma). Adequate replacement of pituitary hormones can greatly enhance quality of life, morbidity, and mortality associated with hypopituitarism. Research has shown that many groups of patients previously not considered for endocrine assessment are at high risk for hypopituitarism. In these individuals, the disorder should be actively searched for. Current research has not only refined the diagnosis of hypopituitarism but also emphasised the importance of clinical judgment. Many questions about need for and best dose of hormone replacement and clinical follow-up, particularly in patients with post-traumatic hypopituitarism, are still unanswered and need further research.

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Clinical, educational, and epidemiological value of autopsy

Julian L Burton, James Underwood

The autopsy is now often regarded as of marginal use in modern clinical practice. In this Review we contend that the autopsy remains an important procedure with substantial, if largely underused, potential to advance medical knowledge and improve clinical practice. Many doctors lack familiarity with autopsy practices, and are insufficiently aware of the benefits for not only bereaved families but also present and future patients. In this Review, which has an international perspective, we consider the ascent and decline of the autopsy, the legal frameworks that govern its use, the value and potential pitfalls of alternatives to the conventional method, and the autopsy’s role in undergraduate medical education. We also draw attention to the continuing ability of autopsies to improve the completeness and reliability of death certification, which is important for public-health strategies and for some bereaved families.

Trends in autopsy rates

Until the 1960s, the autopsy was regarded as central to medical research, education, and professional development. However, many studies have shown the decline of autopsy in adults in most developed countries in the latter half of the 20th century and beyond (table 1).

The fall in autopsy rates is not universal and can be reversed. In Nova Scotia, Canada, although the clinically indicated autopsy rate fell in the 13 years before 1999, the medicolegal autopsy rate rose by around 50%. In Montreal, Canada, although overall autopsy rates declined the autopsy rate in patients enrolled in haemopoietic stem cell transplant programmes remained stable at 32% between 1992 and 2002. Lugli and colleagues in Switzerland showed that simple measures—such as inclusion of the attending physicians in the discussion with the relatives, training in communication with relatives, and clinicopathological conferences that include autopsy findings—increased the autopsy rate from 16% in 1997 to 36% in 1998. The rate fell sharply to 6% when these measures were discontinued, but rose again when they were reintroduced. Several other institutions have been able to achieve autopsy rates of 80–96%, within the context of specific autopsy related studies. The panel shows some factors that determine autopsy rates.

<table>
<thead>
<tr>
<th></th>
<th>Initial autopsy rate (period)</th>
<th>Subsequent autopsy rate (period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>21.0% (1992–93)</td>
<td>12.0% (2002–03)</td>
</tr>
<tr>
<td>France</td>
<td>15.4% (1988)</td>
<td>3.7% (1997)</td>
</tr>
<tr>
<td>Hungary</td>
<td>100.0% (1938–51)</td>
<td>68.9% (1990–01)</td>
</tr>
<tr>
<td>Ireland</td>
<td>30.4% (1990)</td>
<td>18.4% (1999)</td>
</tr>
<tr>
<td>Jamaica</td>
<td>65.3% (1968)</td>
<td>39.3% (1997)</td>
</tr>
<tr>
<td>Sweden</td>
<td>81.0% (1984)</td>
<td>34.0% (1993)</td>
</tr>
<tr>
<td>UK</td>
<td>42.7% (1979)</td>
<td>15.3% (2001)</td>
</tr>
<tr>
<td>USA</td>
<td>26.7% (1967)</td>
<td>12.4% (1993)</td>
</tr>
</tbody>
</table>

Autopsy rate is expressed as a percentage of all deaths. Figures in brackets denote the years in which the data were reported. *Data summarised from a meta-analysis that included reports on all overall rates and on clinically indicated autopsy rates.1*

Table 1: The worldwide decline in autopsy rates

Attitudes to autopsy

The reasons for the fall in autopsy rates are multifactorial and complex. The general public, medical professionals, and pathologists all have a vested interest in the autopsy, and knowledge of the attitudes of these interested parties is essential to understand the present status of the procedure.

Public attitudes

Public attitudes to autopsy are based usually on secular (emotional and cultural) or religious considerations, or often a combination of both. Secular attitudes are perhaps more amenable to influence according to the clinical desirability of an autopsy in individual cases. Some faiths are strongly opposed to autopsy and anatomical dissection, partly because of the inevitable delay in burial, but a few are taking a more permissive stance (table 2).

Public attitudes to autopsy are heightened when consent is being requested in individual cases. The decline in the autopsy rate is commonly attributable

Search strategy and selection criteria

We searched Medline (January, 1966–January, 2006). We used the search terms “autopsy”, “necropsy”, and “post-mortem examination”, in combination with the terms “attitudes”, “consent”, “education”, “endoscopic autopsy”, “histology”, “history”, “needle autopsy”, “pathologist”, “rates”, “regulation”, “training”, “trends”, “undergraduate”, and “verbal autopsy”. The search was limited to articles relating to work in people. We concentrated on publications in the past 5 years, but did not exclude frequently cited or highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Several review articles were included because they provide comprehensive overviews that are beyond the scope of this Review.

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more to the fact that relatives are not being given the opportunity to give consent than to their outright refusal. In a study from Jamaica, the consent rate was 65%, although the actual autopsy rate was much lower because consent was requested in only 35% of eligible deaths.8 Reasons for refusal were exposed in a survey of autopsies on Zambian children, in which the overall consent rate was 25%.29 Most parents and guardians declined an autopsy because they were unconvinced of any benefit; only 9% cited that mutilation of the body was forbidden by so-called ancestral spirits. A refusal rate of 38% was reported in neonatal deaths in the Scotland, with disfigurement and a wish for the infant to “be left in peace” cited as reasons.30

Public attitudes to autopsy could become more positive if the benefits—to the individual family and to future patients—were made more evident. In the northern region of England, where there is a 60% late fetal and neonatal autopsy rate, parents who had consented to the autopsy of a child cited the following reasons to explain why the procedure had been beneficial: the autopsy had helped to explain what happened; helped to plan future pregnancies; and helped them to come to terms with what had happened.31 Other surveys, although small, lend support to the benefits potentially experienced by family members’ consideration of autopsy consent.32

To realise these benefits and make them accessible to family members who consent to an autopsy (or accept that a medicolegal autopsy has to be done), pathologists should play an active part in next-of-kin clinics.33

Clinicians’ attitudes

The reasons most commonly cited by clinicians for the decline in autopsy rate include an increasingly onerous consent process, an assumption that bereaved families are hostile to the idea of autopsy, and advances in premortem diagnostic techniques.13 There is an understandable reluctance to discuss the possibility of an autopsy with bereaved relatives, especially in legislative regimes that require long complex consent forms to show that the authority provided is valid.

A Norwegian study investigating the attitudes of hospital clinicians and family doctors concluded that most clinicians recognised the value of autopsies, especially as a means of quality assurance.34 However, 82% felt that advances in medical imaging, particularly CT, had reduced the value of autopsy.

Whether consent will be granted depends greatly on the strength of the requesting clinician’s recommendation that an autopsy is needed.35 Although a high degree of persuasiveness is unlikely to affect those with immutable

| Panel: Determinants of the clinically indicated autopsy rate and influential factors |  |
|---|---|---|
| Law |  |
| • Statutory requirement for consent |  |
| • Penalties for breach of law |  |
| Request rate |  |
| • Clinical specialty and seniority of initiating clinician |  |
| • Perceived benefits of autopsy |  |
| • Premortem investigations |  |
| Consent rate |  |
| • Religion |  |
| • Ethnic origin |  |
| • Cultural attitudes |  |
| • Media portrayal of autopsies |  |
| • Public (secular) perceptions |  |

<table>
<thead>
<tr>
<th>Autopsy</th>
<th>Tissue retention</th>
<th>Disposal of the body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atheism</td>
<td>No prohibition</td>
<td>No prohibition</td>
</tr>
<tr>
<td>Baha’i</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Buddhism</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Christianity</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Christian Scientist</td>
<td>No religious prohibition but usually not acceptable</td>
<td>No religious prohibition but usually not acceptable</td>
</tr>
<tr>
<td>Church of Jesus Christ of Latter Day Saints</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Hinduism</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Islam</td>
<td>Usually only if required by law</td>
<td>Returned to the body or, if released after the funeral, buried</td>
</tr>
<tr>
<td>Jainism</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Jehovah Witness</td>
<td>No religious prohibition but usually not acceptable</td>
<td>No religious prohibition but usually not acceptable</td>
</tr>
<tr>
<td>Judaism</td>
<td>Usually only if required by law</td>
<td>Returned to the body or, if released after the funeral, buried</td>
</tr>
<tr>
<td>Rastafarianism</td>
<td>Only if required by law</td>
<td>Only if required by law</td>
</tr>
<tr>
<td>Shintoism</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Sikhism</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
<tr>
<td>Taoism</td>
<td>No religious prohibition</td>
<td>No religious prohibition</td>
</tr>
</tbody>
</table>

Where there is no religious prohibition, there may be cultural, secular, or personal objections.26–28

Table 2: Religious attitudes to autopsy, retention of tissues and organs, and disposal of the body
religious objections, those with cultural or emotional reservations might be prepared to consider a sensitively explained argument for autopsy. However, clinical enthusiasm could wane if those who request autopsies are not notified when they are done, or do not receive the findings in a timely manner. The UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) surveys have revealed the infrequency with which clinicians are informed of the time and place of autopsies and the substantial number of cases in which a report is never sent to them.46

Pathologists' attitudes
The attitudes of the public and clinicians towards autopsy are perhaps unsurprising when we consider that many histopathologists share similar views. The low value some pathologists put on the autopsy is perhaps shown by the number of criticisms levelled against autopsy reports that are incomplete, delayed, incoherent, internally inconsistent, and inconsistent or poorly correlated with the clinical presentation.37,39 The autopsy is regarded by some pathologists as an unpleasant, expensive, and time-consuming task, which is secondary to their primary duties, and best delegated to a junior trainee.2,11,38 Some pathologists undoubtedly think autopsy is of little clinical value because the clinicians who cared for the patient often refuse to attend the mortuary to witness and discuss the results. Therefore, closer liaison between pathologist and clinician before the autopsy would enable agreement on when both parties would be available to attend.

Few studies have explored the attitudes of pathologists towards autopsy. Although there is not complete consensus, most pathologists who have participated in such studies value autopsy practice. The procedure teaches the inherent uncertainty that still persists in medical practice, despite advances in evidence-based health care.39 Start and colleagues39 reported over a decade ago that senior pathologists regarded the autopsy as an important part of their work, which had not been diminished by modern medical advances. Moreover, autopsy was regarded as an integral component of training and continual professional development (for both pathologists and clinicians), and was thought to have a substantial role in clinical audit and medical research.39 Similarly, most trainee pathologists who were surveyed reported that they enjoyed doing autopsies, and regarded them as an important component of their work with a substantial role in clinical audit, and of educational value.40 Most surveyed trainees reported that they would provide consent for an autopsy to be done on one of their own relatives.39 Pathologists' belief in the value of the autopsy declines as various restrictions imposed on the scope of the examination increase.40 Studies that assess the educational value of autopsies have shown that pathologists (and other educators) believe firmly in the educational value of the autopsy (independent of its clinical value) and would be willing to consent to their own body or that of a deceased close relative for autopsy.41,42

Legal aspects
Autopsies can be undertaken only with appropriate consent or other authorisation, which defines the limits of the procedure. In most cases nowadays, authorisation comes from the relevant medicolegal officer, and is restricted to an examination that allows that officer to establish the cause and circumstances of death.

An international perspective
The relevance of law to autopsies is manifold. First, many jurisdictions require suspicious and unnatural deaths, including those from unknown or uncertain causes, to be referred to an appropriate authority, such as a medical examiner or coroner, who can request an autopsy if they think it is necessary to establish reliably the cause and circumstances of death—consent is not needed. Second, legislation decrees whether consent or absence of objection is required before doing an autopsy, unless the procedure is being done for medicolegal purposes. This agreement has to come from an appropriate individual, either the deceased person during their lifetime, their next-of-kin, or other close relative. Third, the law can prescribe non-diagnostic uses of tissue removed at autopsy, unless consent or some other lawful authorisation has been obtained.

In some countries and autonomous regions—eg, Austria, Hungary, and Trieste (Italy)—the law allows autopsies to be done without consent for medical, scientific, or educational reasons. As a result, autopsy rates in these areas are much higher than in countries where legislation requires valid consent. On the one hand, changes in law to require consent for autopsy invariably result in a decline in autopsy rates45,46 but, on the other hand, these changes acknowledge the interests and rights of the bereaved family.

Not surprisingly, there has been much debate over who should seek consent, since consent can only be provided if the custodian is appropriately informed.47 Clinicians might be insufficiently informed about autopsy practice to obtain valid consent.48 A study in the USA revealed that 45% of chief residents had received no training in autopsy consent practice and 82% had received no training on the religious and cultural issues that surround autopsy practice.49 Furthermore, over 90% of chief residents did not know how organs were disposed of, or for how long they were retained, and more than 50% did not know what investigations were done on such retained tissue.50

Some have argued that, just as the surgeon is expected to seek consent for an operation, so the individual with the greatest understanding of the procedure—namely, the pathologist—should obtain consent for autopsy.45,46 Some pathologists have strongly opposed this view, since they claim to have overwhelming commitments to diagnostic work for living patients, and they suggest that the request is likely to be better received from a clinician who has developed a personal rapport with the family.
before death occurred than from a pathologist. Rosenbaum and colleagues (none of whom are pathologists) have suggested that this issue be solved by education of clinicians and nurses about the nature of the autopsy.

Authorisation and consent

In the UK, authorisation of an autopsy that gathers information about the identity of the deceased person, the location and time of death, and the circumstances that led to death—including cause of death—is required from a coroner (England, Wales, and Northern Ireland) or procurator fiscal (Scotland). Consent from the next-of-kin or other relative is not needed for a medicolegal autopsy, which is essential if justice is not to be thwarted by those who might have played a part in the events that led to death. Medicolegal authorisation includes the retention of bodily material that is only directly related to the cause of death. The retention of tissue for educational or research purposes still requires consent.

Clinically indicated autopsies not required by law are undertaken with consent obtained from the individual—usually the next-of-kin or other relative—who has responsibility for the disposal of the body. In the UK, such consent has been obtained under the Human Tissue Act 1961 and extended to the retention of tissue for education and research. The Human Tissue Act 2004, and the Human Tissue (Scotland) Act 2006, which replaced the 1961 Act in September, 2006, required that consent (authorisation in Scottish legislation) be obtained for autopsies not done for a medicolegal authority. The new Acts require that consent be obtained for the retention of tissue for purposes such as education and research and, unlike the 1961 Act, there are penalties for those who transgress the legislation.

In view of the invasive and sensitive nature of autopsy, some recommend that students should only be allowed to witness the examination if specific consent has been obtained, as is the case for intimate examinations of living patients. However, this recommendation is not a requirement of the new UK legislation.

In cases in which there is no medicolegal requirement for autopsy, the deceased person’s family is free to refuse consent. Such refusals are frequently claimed to be the main reason for the fall in the clinically indicated autopsy rate. As already noted, the family might refuse for cultural or religious reasons, because of misconceptions that the autopsy will delay the funeral or prevent viewing of the body, or because of a belief that the deceased person has already suffered enough. As a result, clinically indicated autopsies in the UK are done infrequently on those whose faith or ethnic origin is customarily associated with objections to dissection of the body. However, Burton and co-workers reported no relation between the religion, sex, marital status, or educational attainment of the deceased person and the likelihood that consent would be granted for autopsy. Studies suggest that clinicians’ unwillingness to seek consent, rather than relatives’ refusal, contributes greatly to the drop in the hospital autopsy rate. Reluctance to seek consent for autopsies could deny the deceased person’s and relatives’ wishes to be altruistic. Almost all those asked will grant consent, but most relatives are never asked or they are asked in a way that deters them from consenting. Consent is most likely to be granted when the clinician very strongly recommends an autopsy and when the deceased person dies before the age of 50 years.

Tissue retention and autopsy

Authorisation for tissue retention at autopsy

Tissue is retained from autopsies most often for histological confirmation or refinement of the macroscopic findings. Such is the value of histology that routine sampling of major organs and lesions is regarded as an integral part of the autopsy in protocols issued by many professional pathology organisations. The subsequently archived tissue can be re-examined for clinical reasons to reinterpret the findings and perhaps revise the cause of death in view of new information. Archived tissue is also used for clinical audit, medical education, and research, provided that such uses have been lawfully authorised. The value of archived autopsy tissue was emphasised by the characterisation of the 1918 influenza virus that was recovered from frozen lung samples. The unauthorised or, more commonly, undisclosed retention of tissue (including organs) became the subject of widespread concern in the UK as a result of evidence provided to the Bristol Inquiry into local death rates during and after paediatric cardiac surgery. This evidence led to several other inquiries, the formation of the Retained Organs Commission (disbanded in March, 2004), the Human Tissue Act 2004 (and similar legislation in Scotland), the Coroners (Amendment) Rules 2005, and the formation of the Human Tissue Authority. Adverse and misleading reports in the media and the introduction of more complex consent forms undoubtedly steepened the decline in autopsy rates in UK hospitals. New legislation has also been introduced in other countries—eg, bioethics legislation was introduced in France in 1994 and is thought to explain the drop in autopsy rates.

Tissue retention has particular relevance to the investigation of unexpected deaths in infancy. A full autopsy, with histological examination of retained tissue, is essential before an infant’s unexpected death can be attributed to sudden infant death syndrome. Only by autopsy can specific natural and unnatural explanations for the death be excluded with acceptable reliability. Since a small proportion of deaths attributed initially to sudden infant death syndrome are subsequently suspected, alleged, or proven to be caused unnaturally, many argue that there should be a longer retention of tissue samples for audit and diagnostic review. However, in England, Wales, and Northern Ireland, tissue can be retained...
Role of histology at autopsy

The histopathological examination of lesions seen macroscopically is regarded by most pathologists as an integral component of the autopsy. Failure to undertake histological examination was noted as a substantial deficiency in 28% of reports analysed by NCEPOD in 2004. However, in Scotland, the Human Tissue (Scotland) Act 2006, enables the tissue samples (but not organs) to be associated with the deceased person’s medical record on completion of the procurator fiscal’s investigation; consent is required only if the tissue is to be used for research or education.

A report commissioned by the Royal Colleges of Pathologists and Paediatrics and Child Health recommended a standard UK national protocol, which includes tissue retention, for the investigation of unexpected deaths in infancy. The aim is to ensure that the thoroughness and quality of the investigation, and the appropriateness of the pathologist who does the autopsy, are of a consistently high standard. The report seeks to keep the risk of unnatural infant deaths being attributed to sudden infant death syndrome to a minimum, and avoid unwarranted incrimination of parents and miscarriages of justice.

Needle autopsies

Although not as reliable as complete autopsies, needle autopsies are undertaken when consent can be obtained for only the most limited of examinations, when the body poses a high risk of serious infection, or when there are neither the time nor conditions needed for a complete autopsy. Almost every organ and soft tissue can be examined post-mortem by use of a biopsy needle without or, less commonly, with, ultrasound guidance (so-called echopsy). Such autopsies are uncommon but can provide tissue for histopathological and microbiological examination. Although these autopsies provide valuable information that confirms or refutes a specific cause of death, the disadvantage is that not all information usually obtained from the direct inspection and dissection of the internal organs is ascertained. Thus, any lesion identified in this way might have contributed to the cause of death but is not necessarily the only cause of death. Moreover, the focal nature of much pathology means that in many instances the needle sample is non-contributory. The technique is most useful for the assessment of diseases that diffusely affect large viscera, such as pulmonary, renal, or hepatic disorders. Random biopsy of
the brain, although technically possible through burr holes or via the cribriform plate, is of little value. Nonetheless, needle autopsy shows 83–85% agreement with complete autopsies. Endoscopic autopsies, done with either an endoscope or a laparoscope, have not been widely adopted, possibly because of the specialist equipment and expertise needed. Nonetheless, they have been used to advance research into specific lesions, and in cases in which consent for a more complete autopsy has not been obtained. As for needle autopsies, endoscopic autopsies can provide tissue for further examination and moreover can allow visualisation of the body cavities. Avrahami and co-workers reported that endoscopic autopsies show a 60–100% agreement with complete autopsy examinations, but are of little value in the assessment of diseases affecting the relatively inaccessible posterior mediastinum or retroperitoneum.

Imaging autopsies
MRI has been used for some time to study organs, especially the brain, which are removed at autopsy. The use of MRI instead of autopsy dissection has taken longer to gain acceptance, and only few institutions have developed experience in post-mortem cross-sectional imaging. Early studies in the UK, pressured by requests to coroners from the Jewish community for an alternative to standard autopsy procedures, were small, flawed, and inadequately evidence based compared with conventional autopsy techniques. Bisset and colleagues reported the use of MRI for post-mortem examination in 53 sudden natural deaths, and noted that a cause of death could be confidently diagnosed in 87% of cases. A standard autopsy was done in only six cases, when the MRI results were inconclusive. Substantial pathological changes were not detected by MRI in two cases. Although MRI-determined causes of death have been accepted by some coroners in lieu of standard autopsies, many concerns are raised about the use of this technique. First, the coroner is an independent judicial officer, and many question whether people who might have played a part in the events that led to death should be able to influence how the cause of death is established. Second, MRI has lower resolution than the conventional autopsy and so is able to provide only coarse or imprecise diagnoses—eg, ischaemic heart disease rather than acute myocardial infarction caused by coronary artery thrombosis. In the cases reported by Bisset, MRI was limited to the head, thorax, and upper abdomen, and seemed to miss the neck, lower abdomen, and pelvis, which are all sites of common and substantial pathological changes. Moreover, the non-invasive MRI autopsy does not include the sampling of tissues for histological, microbiological, or chemical analysis. Third, we should consider that, although acceptable to some, MRI autopsy is up to five times more expensive and is dependent on equipment that is already in high clinical demand.

<table>
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<tr>
<th>Advantages compared with conventional autopsies</th>
<th>Disadvantages compared with conventional autopsies</th>
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<tbody>
<tr>
<td>Needle autopsy: Rapid</td>
<td>High false-negative rate</td>
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<tr>
<td>Minimally invasive</td>
<td>No opportunity to examine internal organs macroscopically</td>
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<tr>
<td>Most organs and tissues can be sampled for laboratory investigation</td>
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<tr>
<td>Increased acceptability to relatives</td>
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<tr>
<td>Low risk to health and safety of mortuary staff</td>
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<tr>
<td>Low cost</td>
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<tr>
<td>Endoscopic autopsy: Minimally invasive</td>
<td>Specialist equipment and expertise needed</td>
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<tr>
<td>Increased acceptability to relatives</td>
<td>Of little use for examination of the posterior mediastinum and retroperitoneum</td>
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<tr>
<td>Most internal organs and tissues can be examined and sampled</td>
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<tr>
<td>Echopsy: Non-invasive</td>
<td>Specialist equipment and expertise needed</td>
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<tr>
<td>Increased acceptability to relatives</td>
<td>No opportunity to sample tissues for further investigation</td>
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<tr>
<td>Low risk to health and safety of mortuary staff</td>
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<tr>
<td>MRI/MSCT autopsy: Non-invasive</td>
<td>High cost</td>
</tr>
<tr>
<td>Increased acceptability to relatives</td>
<td>Specialist equipment and expertise needed</td>
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<tr>
<td>Low risk to health and safety of mortuary staff</td>
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<tr>
<td>Can assist in the determination of the direction of traumatic forces</td>
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<tr>
<td>Valuable adjunct for the examination of CNS disease</td>
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<tr>
<td>Verbal autopsy: Low cost</td>
<td>Indirect and retrospective</td>
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<tr>
<td>Non-invasive</td>
<td>Low sensitivity</td>
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<tr>
<td>No specialist equipment needed</td>
<td>Low specificity</td>
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<tr>
<td>Acceptable to relatives</td>
<td>Doubtful reliability and validity</td>
</tr>
<tr>
<td>Data can be obtained by non-medical personnel</td>
<td>No opportunity to sample tissues for further investigation</td>
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<tr>
<td>No risk to health and safety of mortuary staff</td>
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Table 3: Comparison of the conventional autopsy with minimally invasive and non-invasive autopsies.
Further studies have so far failed to resolve these issues. Roberts and colleagues confirmed that although MRI could indeed identify some abnormalities associated with common causes of death, better imaging resolution and experience in the correlation between MRI and conventional autopsies are needed before MRI alone can be accepted as a standard autopsy option. Jackowski and co-workers examined 80 human corpses by MSCT and MRI before a standard autopsy was done. MRI examination was limited to the head, thorax, abdomen, and to any other area of special interest. The researchers reported that a limitation to the head, thorax, abdomen, and to any other area of special interest. The researchers reported that a combination of MRI and MSCT is beneficial in the examination of the post-mortem heart and can provide valuable additional morphometric data that is helpful in the study of complex cardiac abnormalities. Conversely, Huisman and others regard MRI autopsy as helpful in the assessment of the CNS in neonatal death investigations, but not as useful as standard autopsies in the study of complex cardiac malformations.

MRI and MSCT have been used with success as adjuvant techniques in forensic autopsy practice, but detailed discussion of criminal investigations is outside the scope of this Review. Nonetheless, there are those who favour the use of these imaging techniques to enhance conventional autopsy practice, possibly as an adjunct to needle autopsies. Thali and colleagues have suggested that magnetic resonance microscopy might eventually be used as a non-invasive alternative to post-mortem histological examination. However, experience with this technique is limited to isolated case reports and there is insufficient evidence to support adoption of magnetic resonance microscopy into routine practice.

In summary, non-invasive autopsy techniques represent a valuable adjunct to the standard autopsy, and they could lend support to the minimally invasive autopsy. These non-invasive techniques should be undertaken as soon as possible after death, to keep decomposition-induced artifacts to a minimum. At present, there is insufficient evidence to lend support to the use of MSCT or MRI autopsies as an alternative to standard autopsy practice. However, in the UK, studies financed by the Department of Health (England) have started to gather the evidence by which these alternative methods can be judged.

**Verbal autopsy**

The so-called verbal autopsy has emerged as an indirect retrospective method to identify the probable cause of death. This approach has largely been confined to developing countries where resources are restricted and to countries where there are strong religious objections to human dissection. No examination of the body is undertaken in this method. Indeed, we contend that the term verbal autopsy is an oxymoron, and suggest that post-mortem clinical case review is more appropriate. The relatives or other associates of the deceased person are questioned, often months or years after the death took place, about medical events that preceded the death.

Such interviews are usually undertaken by non-medical personnel who have received some training in the use of algorithmic protocols to guide their questioning. The results of such interviews are then reviewed by a doctor (who might or might not be a pathologist). Boule and others have shown that artificial neural networks can be used to classify the data obtained by a verbal autopsy to establish a cause of death. Verbal autopsies have been used to find the cause of adult deaths in rural areas, and deaths from homicide. Verbal autopsies have also been used to record the frequency and causes of maternal deaths, neonatal deaths, and deaths that occurred in childhood and deaths attributable to epilepsy.

The value of such autopsies is debatable. We recognise that in many developing countries most deaths are not attended by a doctor and no medical certificate of the cause of death is issued. Verbal autopsies need “neither the administrative nor the medical infrastructure of death certification”. As a result, there are few epidemiological data on causes of death, and those that are available are unreliable. In such circumstances, any data could be better than none at all. Gajalakshmi and Peto reported that verbal autopsies reduced the proportion of deaths from unknown causes from 54% to 23% in urban areas and from 41% to 26% in rural areas of Tamilnadu, India. Moreover, the verbal autopsy had a 95% sensitivity for the identification of deaths caused by cancer when compared with records held in a cancer registry. Elsewhere, the sensitivity of verbal autopsies has been as low as 30%.

However, the validity of the data obtained from verbal autopsies is questionable. The autopsy, as done by the pathologist, is widely regarded as the optimum method to establish cause of death. Several studies have confirmed that the discrepancy rate between the cause of death identified by the clinician who cares for the patient and that recorded at autopsy is between 10% and 30%. Such discrepancies arise even though the clinician had attended the patient in life, had access to radiographic and laboratory investigations when establishing the cause of death, and had made a diagnosis in the immediate post-mortem period. We are not aware of any robust study in which the causes of death made by verbal autopsy have been validated against those from a pathological autopsy; typically such procedures are validated only by physician review.

Many studies that assessed verbal autopsies have focused on maternal or paediatric deaths, which are often associated with complex pathological changes. The method used in such studies is often not stated. In view of the inaccuracies in causes of death made by clinicians closely associated with the care of the deceased person, we question the validity and reliability of data obtained years after death by non-medically trained personnel. However, although the time between death and verbal autopsy ranged from 1 month to 7-8 years (mean 2-4 years), Höj and colleagues...
reported that the length of the recall period did not greatly affect the verbal autopsy results.

Rutty and colleagues\(^a\) have shown that pathologists provided with the deceased person’s clinical history and an opportunity to examine the body externally were able to predict autopsy findings accurately in only 61–74% of cases. The accuracy of verbal autopsy is probably substantially lower than this result. Indeed, although Gajalakshmi and Peto\(^a\) achieved a sensitivity of 95% for cancer deaths, the specificity of these diagnoses was around 50% when compared with data obtained from cancer registries. Since the data obtained in such studies are used to inform the provision of public health measures, we challenge the value of replacement of the absence of data with data that has such low specificity and sensitivity.

**Role of autopsies in medical education**

Autopsy epitomises problem-based learning for students. Despite curricular reform, a decline in autopsy rates, and adverse media attention to autopsy, medical educators regard this technique as valuable but underused in medical education.\(^a\)\(^4\)\(^2\)\(^1\) Provided that adequate consent has been obtained,\(^a\) students can either be invited to the mortuary to witness autopsies, from external examination to reconstruction of the body, or they can be called once the examination has been completed to discuss the clinical history of the patient and view the gross (macroscopic) findings. In centres with a low autopsy rate, students can gain some understanding of the autopsy by watching a series of specially produced videos.\(^a\)\(^2\)

As a result of diminished clinical interest in the autopsy, and because reduced autopsy rates mean fewer opportunities to experience procedures and results, many students remain poorly educated about the autopsy and are unaware of the indications for its use.\(^3\)\(^5\)\(^4\)\(^2\)\(^4\) Not surprisingly, some students find autopsies unpleasant, with concerns ranging from the minor—such as the unpleasant smell—to those suggesting the students were in great distress: “...attending a PM [post mortem] is the worst thing I have ever done...”, “...I was overtaken with pain, grief and palpitations and burst into tears...”.\(^3\)\(^5\) Some students raise objections to the autopsy on religious grounds, or because they believe the autopsy to be an unnecessary mutilation, which does not show proper respect for the deceased person.\(^6\)\(^5\)\(^6\)\(^7\)

Despite students’ objections to the autopsy, early studies in the USA showed that the autopsy had various uses in undergraduate medical education.\(^a\) Further research has revealed that, in the modern medical curriculum, the autopsy can be used to teach not only anatomy but also gross (macroscopic) pathology, skills in clinicopathological correlation, the fallibility of medicine, a holistic approach to medicine, medical ethics, the process of dying and handling of the dead, invasive clinical procedures, medical law, and the importance of health and safety at work.\(^6\) The autopsy satisfies these functions because of its visual nature and the systems based, problem oriented approach adopted by many pathologists during the procedure.\(^4\)\(^2\) Moreover, the autopsy is important in delivering the hidden curriculum because students are encouraged to develop a sense of clinical detachment, which acts as a rite of passage into medicine. Students are provided with an opportunity to meet pathologists and are encouraged to treat patients, their families, and deceased people with respect. The autopsy engenders a sense of one’s own mortality, emphasises the importance of teamwork, and increases the credibility of clinical teachers.\(^6\) Students should be actively encouraged to witness autopsies. The autopsy is a memorable experience that exposes students to pathology and could encourage them to enter into the specialty.\(^6\)

Several disadvantages associated with use of the autopsy for teaching pathology (and other specialties) to medical students should be considered. Autopsy could encourage students to view the body as an object,\(^4\)\(^2\)\(^9\) and discourage students from choosing pathology as a career and from requesting autopsies after graduation.\(^4\)\(^2\) It is unarguably physically unpleasant for some, time consuming if done to an adequate standard, and poses serious health and safety hazards. The autopsy demonstration might present students with an inappropriately sanitised view of the procedure. Furthermore, some regard it as an unsophisticated approach that has the potential to teach a biased view of the prevalence of disease.\(^4\)\(^2\)\(^6\)

**Conclusions**

We cannot support the assertion, published in *The Lancet*, that “the autopsy has lost much of its authority and now has a marginal role in contemporary medical practice”.\(^8\)\(^5\) Despite intensive modern clinical investigations, autopsies continue to reveal major ante mortem diagnostic errors in around 30% of cases;\(^9\) thus, autopsies improve the completeness and reliability of national mortality data on which health-care strategies are based. Autopsy is also a decisive factor in the discovery of deaths caused by adverse drug events.\(^5\)\(^6\) It continues to be vital for advancing our knowledge of diseases not readily accessible to biopsy, such as those of the cardiovascular and CNS and especially those for which novel therapies are emerging.\(^1\)\(^0\)

**Conflict of interest statement**

JU was an observer on the Retained Organs Commission, is a member of the Human Tissue Authority, and is Chairman of the Management Board of the Multiple Sclerosis Society’s Tissue Bank and of the Board of Trustees of the National Bereavement Partnership, but the opinions expressed in this review are those of the authors. JU and JLB receive statutory fees for performing autopsies authorised by HM Coroner for South Yorkshire (West).

**Acknowledgments**

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In this review, we aim to focus attention on the interaction between adolescents with chronic conditions and the health systems that support them. At least 12% of adolescents live with a chronic condition. Some conditions are characterised by increasing incidence (eg, diabetes) or improving survival rates (eg, cystic fibrosis), while others are concerning because of differentially poorer outcomes in adolescents in comparison to both children and adults (eg, cancer). Growing evidence suggests that young people with chronic conditions are doubly disadvantaged—engaging in risky behaviours to at least similar if not higher rates as healthy peers, while having the potential for greater adverse health outcomes from these behaviours. In addition to efforts at improving survival, in order to improve their life chances, we need to better understand how the social and emotional outcomes of young people with a chronic disease can be improved, and better support young people’s emerging capacity for self-management.

Increasing appreciation of the growing burden of chronic illness in adults is based on estimations that at least 80% of heart disease, stroke, and type 2 diabetes could be avoided through the combination of healthy diet, regular physical activity, and refraining from use of tobacco. This appreciation has led to integrated policy responses that focus on prevention, such as the WHO Global Strategy on Diet, Physical Activity and Health,1 together with calls for innovative, cost-effective models of care in adults with chronic disease that focus on self-management.2 However, children and adolescents with chronic disease have been remarkably absent from this discourse. Most chronic conditions of childhood, unlike those of adults, are not preventable by lifestyle changes, but there is every reason to suppose that the socially-mediated co-morbidities experienced by adolescents with chronic conditions can be modified.

Numbers of young people with chronic conditions are growing. Improvements in survival typify many previously fatal conditions of childhood, such as cystic fibrosis, congenital heart disease, and spina bifida. Increasing incidence in adolescence is a feature of other conditions such as diabetes, mental disorder, HIV/AIDS, and cancer. Not only is cancer in young people on the rise, but also improvements in outcomes in adolescents and young adults for this disease lag behind advances that have been achieved for children and older adults.3,4 The health issues of adolescents with chronic conditions are reported to be “linked to the illness they suffer from, to adolescence in general, and to psychosocial problems generated by the interaction between the illness, the adolescent and his immediate environment”.5,6 Certainly, many health professionals report that managing the complexity and range of health concerns in adolescents is more challenging than for other age groups.6,7

In this review, we aim to focus attention on the interaction between adolescents with chronic conditions and the health systems that support them. Following a description of the epidemiological challenges of measuring chronic conditions in adolescents, we review the value of measuring health and developmental burdens, and investigate the benefits and challenges of self-management support in adolescents with chronic conditions. We wish to bring attention to what is common in young people’s journey through adolescence with different chronic conditions, by contrast with the many disease-driven divisions that characterise much current practice, policy, and research.

Challenges in definition and epidemiology

The shortage of age-specific epidemiological data is one factor limiting more focused policy and planning considerations for adolescents with chronic conditions. Many surveys and reports of chronic disease fail to recognise adolescence as a developmental stage by grouping adolescents with children (0–14 years) or with adults (15–34 years).8,9 When adolescence is recognised, the choice of lower and upper age limits is variable. This inconsistency limits national, let alone international, comparability. For example, even within the USA, where health surveys of relevance to adolescents are most advanced, the National Centre for Health Statistics defines “adolescence” as the “period from the beginning of puberty to the end of their 18th birthday”.5

Search strategy and selection criteria

We searched MEDLINE (2000–06) and the Cochrane Library (any age or date) using the search terms “chronic illness”, “adolescence” or “adolescents” (“ado1””), “risk factors”, “psychosocial outcomes”, “self-management”, “self-efficacy”, “adherence”, “compliance”, and randomised controlled trial interventions in various combinations. No language restriction was used. Key references published before this period were identified through scrutiny of commonly cited papers and review articles that showed particular insight into the area of psychosocial wellbeing for young people with chronic conditions.
Health Interview Schedule Child Health Supplement defines adolescents as individuals aged 10–17 years, the National Health and Nutrition Examination Survey as those aged 12–17 years, the National Adolescent Hospital Discharge Survey groups 15–24-year-olds together, whereas the National Longitudinal Study of Adolescent Health explores the causes of health-related behaviours of adolescents in school grades 7 through 12, who range in age from 12 years to 20 years.

Prevalence data have typically been derived from one of three sources: checklists of medical disorders or disease types (eg, diabetes) have been used to identify chronic illness; functional status assessment has been used to identify chronic conditions that cause impairment in basic functions (eg, vision, hearing, activities of daily living); and limitation in socially defined roles (eg, schooling) has identified children with disabilities. Sources of data will affect prevalence results. For example, reports from doctors and parents differ as to the presence of a chronic condition, whereas doctors’ and adolescents’ reports differ in relation to the importance of physical symptoms. Comparison of parents’ and adolescents’ report suggests greater congruence between parents with older (age 15–17 years) rather than younger (age 12–14 years) adolescents and less similarity between parents and adolescents for reports of mental health and behavioural needs. Checklists commonly vary between surveys and include only the most common conditions. With few exceptions (such as asthma and allergy), most individual chronic conditions of adolescence are uncommon but together comprise a substantial proportion (31%) of all US children. Many less common conditions, such as achondroplasia, are likely to cause major limitations in daily activities, which further highlights the importance of accurate ascertainment. Importantly, checklists identify children with several chronic conditions who have increased morbidity across a range of measures. However, many checklists do not include mental, behavioural, or cognitive disorders, resulting in an underestimation of chronic conditions in adolescence. The extent of co-morbidity makes this omission relevant, especially in older adolescents, in view of the relatively large contribution of mental illness to their burden of disease and the complex ways that mental disorder can affect the experience and expression of chronic disease.

The limitations of disease-specific checklists have produced interest in generic or non-categorical approaches. These approaches are predicated on the many similarities in the lived experiences of young people with different chronic conditions, with many of the consequences being independent of a specific disease or disorder. Stein and colleagues proposed a framework based on three definitional concepts that must coexist for a child or adolescent to be classified as having a chronic condition (panel 1).

A similar non-categorical approach has been used to define children and young people with special health-care needs as those who “have or are at increased risk for a chronic physical, developmental, behavioural or emotional condition and who also require health and related services of a type or amount beyond that required by children generally”. This definition identified 12% of people younger than 18 years in the USA with a chronic condition, with an additional 6% having a presumed need for increased services.

Prevalence of special needs increases from childhood through adolescence (figure), but we have remarkably little understanding of how the functional needs of the young change across childhood, through adolescence, and into adulthood, let alone how young people respond to such changes or how they can best be supported. To improve consistency in age criteria and approaches to prevalence estimates, including mental health and behavioural comorbidities, would focus policy efforts on adolescents with chronic disease, and provide a valuable platform from which clinical interventions could be more rigorously tested.

**Effect of chronic conditions: disease-specific or generic understandings?**

A large amount of disease-specific published work describes the effect of individual diseases and disabilities on adolescents and their families, whether framed in terms of adjustment or coping, comorbid depression and anxiety, or more recently, in terms of health-risk behaviours. Appreciation of the similarities and differences between specific diseases and groups of disorders could inform practice and policy. However, the traditional separation of health-care research, practice, and policy in relation to
individual chronic physical diseases, and the common separation of these conditions from mental and behavioural disorders and disability, has effectively downplayed our understanding of young people with such problems. The difficulty of this approach is that the extent of chronic disease in this age group is unclear and underappreciated. More widely, these traditional separations have reduced our appreciation of how different groups of conditions can differentially affect young people. For example, results of a study of the relation between medically attended chronic conditions and functionally defined disability showed that functional disability was most common in children with learning-behavioural conditions (88%), followed by those with neurodevelopmental conditions (61%) and physical conditions (32%).

Increasing acknowledgment that chronic conditions affect a young person’s global developmental processes has led to increased measurement of co-morbid conditions, psychosocial adjustment, and quality of life. However, cross-referencing is strikingly uncommon between studies of different disorders and groups of disorders. For example, remarkably little cross-referencing has taken place between publications on diabetes and cystic fibrosis, even though both are severe, lifelong disorders that necessitate daily medication, regular personal monitoring, and medical review. Although this tendency is consistent with the disease-specific orientation of clinical services, the risk of this approach is that we fail to capitalise on understanding the common challenges for adolescents, parents, and clinicians—and equally fail to capitalise on efficiencies of scale that could facilitate systems and supports that transcend traditional clinical groupings. For example, experience from peer support groups emphasises the extent to which many problems and issues are shared by young people with different chronic diseases.

Much previous research has emphasised that adolescents with chronic conditions are an at-risk group, although the assumptions underlying the nature of these risks have changed with time. Attempts to identify the degree to which physical and psychosocial wellbeing might be compromised fall broadly into two categories: studies that focus predominantly on risk factors and risk-taking behaviours, and those focusing more broadly on health-related quality of life.

**Health-related quality of life**

The past 20 years has seen an explosion of studies of health-related quality of life in people with chronic conditions, reflecting a widening of focus from biomedical outcomes to include psychological and social dimensions of health. Measurement of health-related quality of life in young people with chronic conditions is still at an early stage of development with issues relating to proxy reporting by parents and clinicians still unresolved. Parents and their children often differ in their assessments of function, behaviour, and quality of life. In particular, young people report higher rates of physical health and better quality of life than do their parents. These discrepancies are not consistently accounted for by proxy characteristics such as sex, socioeconomic status, or cognitive ability. Appreciation of age-related understandings about health and illness as well as age-related notions of quality of life are urged. Importantly, the mother’s health also seems to affect her ratings of her child’s health—the worse the mother reports her own health, the lower her assessment of her child’s health.

However, whether in relation to decision-making about choice of treatment, measurement of outcomes of clinical trials, or comparison of results across studies, differing assessments of quality of life are problematic. Eiser suggests focusing on areas in which parents and young people are likely to make more dependable assessments. For example, whereas parents might be best placed to comment on the effect of illness on family and sibling relationships, adolescents will be better placed to comment on experience of symptoms, peer relations, and worries about the future. Children’s perceptions will change with time, emphasising the importance of measures for quality of life that accommodate usual changes that would be expected to occur during childhood and adolescence.

The choice of generic versus disease-specific instruments is as relevant for adolescents with chronic conditions as other populations. Generic measures facilitate comparison between adolescents with different conditions and comparison with population norms. That a study of obese children and adolescents showed lower health-related quality of life than in young people of a similar age who had cancer shows the power of this approach. Disease-specific measures can more sensitively measure differential effects of specific aspects of a disease or its treatment which might, for example, facilitate comparison of outcomes between children and adolescents, and between adolescents and adults.

How are these measures being used? In a systematic review of the measurement of health-related quality of life in clinical trials in patients aged up to 20 years, Clarke and Eiser found little evidence that these measures are

![Figure: Prevalence of children with special health-care needs by age](https://example.com/image.png)
routinely used in clinical trials, identifying only 18 published trials using standardised instruments. Few studies have compared health-related quality of life across adolescents with different disorders (eg, asthma, epilepsy, attention deficit hyperactive disorder) or groups of disorders (eg, physical, behavioural). Even fewer have determined changes in this factor over time as a function of disease stability (where age and maturational effects could be explored) or instability (where interactions of changing health status and age could be assessed and explanatory mechanisms could be investigated).43,45

Risky behaviours
Poor adherence to treatment is commonly viewed by doctors and parents as risky behaviour in adolescents with chronic illness.43 While worse health outcomes can result from poor adherence, the question of how to promote better adherence with treatment is increasingly conceptualised within the notion of self-management, rather than of risk behaviours.43

Although experimental behaviours such as sexual activity and substance use can be understood as a normal part of teenage development, they have historically been viewed differently in young people with chronic conditions. Suris and Parera28 stated that for a long time chronic conditions were assumed to serve as a protective factor in young people, restricting opportunities for enacting risky behaviours. A recent summation of published work has changed this understanding, suggesting that “young people with a chronic condition are not less likely to undertake risk behaviours than their healthy peers”.43 Others are more emphatic, suggesting that they are “as likely or more likely to undertake risky behaviours than their healthy peers”.43

Methodological limitations are a feature of many studies of psychosocial outcomes in adolescents with chronic conditions.41 In addition to small sample size, absence of appropriate population-based representation, omission of control groups, and lack of standardised measures of severity of illness and outcome are common. With this caveat, Valencia and colleagues6 reviewed two decades of publications on risky behaviours in adolescents with chronic conditions. They prioritised studies that took a non-categorical approach to sample inclusion. Focusing on sexual health, higher rates of sexual activity are reported by young people with chronic conditions than healthy peers.41,44 Additionally, lack of knowledge and reduced use of contraception was also described in these young people.41 Unsurprisingly, more sexually transmitted infections were reported.44,45 The visibility of the condition did not seem to affect rates of sexual activity.45

Findings about substance use in young people with chronic conditions are inconsistent. Tobacco use is at least as common in young people with asthma and diabetes as in healthy peers.46,47 Alcohol is thought to be the substance most frequently used by young people with chronic conditions, with little variation by diagnosis.44,45 Rates of use of other substances (eg, marijuana) and delinquent behaviour seem to be lower in young people with chronic conditions than in comparison groups46,47 although these behaviours have been less frequently studied and data are again inconsistent.46,47 One explanation might be that, as in adults, self-reporting of risky behaviours by adolescents is less reliable in clinically recruited samples compared with population-based studies, underscoring the importance of using objective measures (eg, urinary cotinine) in clinical studies when possible.46,47

In summary, growing evidence suggests that adolescents with chronic conditions are likely to engage in risky behaviour to at least similar if not higher rates as healthy peers. However, a worrying feature of such behaviours in chronic illness is the increased potential for adverse health outcomes. For example, adolescents with asthma and cystic fibrosis who are exposed to tobacco are at increased risk of pulmonary deterioration,48 those with sickle-cell disease are at increased risk of acute chest syndrome.49 Tobacco use accelerates the development of cardiovascular disease in individuals with diabetes and lupus.49–51 Alcohol use potentiates the hepatotoxicity of methotrexate, which is used to treat various autoimmune diseases.52 Many conditions and therapeutic regimens necessitate careful planning to maximise pregnancy outcomes;53–55 unprotected sexual intercourse in adolescents with these conditions thus carries additional risks.

Young people with chronic conditions are thus doubly disadvantaged by an increased prevalence of risky behaviours and increased risk to health from these behaviours. At the very least, a stronger focus on preventive efforts seems to be needed. In a health-care system where health professionals report less confidence and competence in dealing with adolescents than with other age groups,56–58 investment in generic training about behaviours and increased risk to health from these chronic conditions was assumed to serve as a protective factor in young people, restricting opportunities for enacting risky behaviours. A recent summation of published work has changed this understanding, suggesting that “young people with a chronic condition are not less likely to undertake risk behaviours than their healthy peers”.43 Others are more emphatic, suggesting that they are “as likely or more likely to undertake risky behaviours than their healthy peers”.43

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Social and emotional resilience
A chronic health condition in adolescence can represent a major psychosocial burden. Initial stresses associated with diagnosis, ongoing stresses from treatments and social disruption, social stigma and marginalisation, and changes in plans and expectations about the future can be a substantial challenge to social and emotional wellbeing.59,60 Although many young people adjust well to the challenge of a chronic condition, psychological comorbidity in US samples is estimated at about 20%, twice that of healthy young people (panel 2).59,60

The nature of the relation between chronic illness and mental health conditions remains unclear. Vessey57 suggests that the disruption of social roles by chronic
disease is especially important, rather than particular aspects of individual disorders. This idea is consistent with those of social capital theorists, who increasingly stress the value of social connectedness and support on health and wellbeing.72–74

Beyond consideration of risk factors, more recent work has focused on the emerging notion of social and emotional resilience in young people with chronic conditions to explain why many negotiate adolescence in productive and effective ways, despite the risks they face.75–77 However, many important questions are unanswered. Does having a chronic illness affect the social and emotional resilience of young people? Might some protective factors (eg, family, peers) have a different capacity to influence young people with chronic conditions than in healthy adolescents? And how might educational and health systems facilitate greater social support for these young people?

Quality health care
Despite having more frequent contact with health-care services than do healthy young people,79 adolescents with chronic conditions receive suboptimal general and preventive care. In the USA, the National Ambulatory Medical Care Survey queries doctors about their counselling of adolescents about tobacco use. Asthma is the only chronic condition with adequate sample size to analyse the effect of the condition on counselling rates. In the 1991 and 1996 surveys, notwithstanding the greater risk of smoking effect of the condition on counselling rates. In the 1991 and 1996 surveys, notwithstanding the greater risk of smoking, those with asthma, counselling took place in only 4.2% of visits.79 In this survey, primary-care providers were more likely to report counselling than specialists. As early as the 1970s, youth with chronic conditions were found to receive suboptimum preventive care.77,80 Reports of preventive service delivery in adolescents with chronic conditions are sparse, with data derived mainly from clinical samples. Apart from within specialised adolescent health units, broader screening of health-risk behaviours and mental health in adolescent inpatients is uncommon.81 Immunisation rates of children with spina bifida are worse than in the general population.82 Findings of a population-based study of adolescents with cystic fibrosis and sickle-cell disease showed that despite the greater attributable risk of tobacco smoking in both these groups, only 27% of those with cystic fibrosis and 37% of those with sickle-cell disease reported discussion of tobacco use.83 Similarly, despite greater sexual and reproductive health complications in adolescents with spina bifida, only 39% of youth with spina bifida and 30% of their parents reported they had ever discussed aspects of sexuality with a doctor.84 Perhaps not surprisingly, 95% of these young people and 59% of their parents reported inadequate knowledge about sexual and reproductive health.

How can the health-care system best serve the needs of adolescents with chronic conditions? Defining and measuring quality of care for adolescents is more complex than for adults for several reasons. The most prevalent chronic conditions in childhood tend to be mild, whereas more severe diseases tend to be rare. This small segment of the population is most likely to be affected by variations in quality of care, yet most sampling strategies are unlikely to capture them well.84–86 Mangione-Smith and McGlynn87 provide a framework for addressing quality of care in children and adolescents. First, developmental considerations must be taken into account in determining outcomes of care for adolescents. Extensive variation exists in normal adolescent development, and to ascertain when development has been adversely affected by disease is difficult. Second, developmental outcomes of care received earlier in childhood may not manifest themselves until adolescence. Third, many adolescents receive care outside of traditional health-care systems, such as schools and family planning centres. These services will not be represented in payor or institutional record systems. Finally, as described, many studies of health-related quality of life or other family-based outcomes have relied on proxy reporting. Developing measures of quality of care for adolescents with chronic conditions is a challenging but critical undertaking for this burgeoning area of measurement.

Comprehensive system-based models, such as the chronic care model developed by Wagner and colleagues,86 have shown value in improving outcomes for children and adults with various chronic conditions. The key elements of the model include the community (including resources and policies), the health-care system and its design, support for family and self-management, decision support, and clinical information systems. The model is postulated to improve outcomes by improving interactions between a “prepared proactive practice team” and an “informed, activated patient.”88 Analyses of elements of the chronic care model and of disease management programmes in general reveal that strong institutional leadership, support for quality improvement, presence of adequate information technology, and external incentives are important at the organisational level.89–91 A meta-analysis that investigated specific aspects of the chronic care model showed that interventions related to self-management support and delivery system

Panel 2: Young people’s descriptions of the effect of a chronic condition in adolescence65,76

• “Whenever I had epileptic fits, I would get angry all the time, frustrated” (16-year-old boy)
• “My management is probably medium right now. Not the best it could be, but not the lowest either. I get sick of doing all the things I have to do” (15-year-old boy)
• “I really only have one friend that I can talk to as he has the same thing as me” (17-year-old girl)
• “I’m managing well, but I feel that I don’t have a social life at all” (17-year-old girl)
• “I feel confident I can do what I want” (15-year-old girl)
design were the most powerful in improving quality of life and clinical outcomes."

To date, interventions have tended to focus on one or a few conditions, usually those that require day-to-day management by patients, such as diabetes or depression. System-based interventions in paediatrics have shown improvements in process and outcomes of care for asthma and some process outcomes for attention deficit hyperactivity disorder. While some studies included adolescents, the unit of analysis was typically the practice, so it is not possible to examine differential effects among adolescents.

Self-management

For adolescents with disorders that need daily attention (ie, adherence with recommended treatments), the individual’s and family’s ability to manage the condition is crucial. The notion of transition to adult health care is implicitly based on the need to help actualise young people’s emerging capacity for self-management. However, rather than self-management, much of the focus of work on this transition has been to explicitly support young people in the physical transfer from paediatric to adult-oriented health-care services. The shortage of adult expertise in caring for survivors of childhood conditions (eg, congenital heart disease) is now being recognised and rectified in the developed world, but will increasingly affect the developing world as they too experience improved survival of young people with chronic conditions. In the absence of appropriate primary care or specialised adult services, adolescents with complex chronic conditions risk dropping out of health care altogether, with dire health consequences.

A key tenant of self-management support is education and coaching in problem-solving, in addition to more traditional information-giving and technical skills training. The ability to self-manage, at least among adults and parents of children with chronic conditions, is correlated with self-efficacy, that is, confidence in one’s ability to implement the necessary behavioural changes. Unfortunately, although adolescents have been participants in many of the paediatric and adult trials of self-management support, age-specific analyses have not been done. Developmental considerations in adolescence, including the transition from the parent having primary responsibility for care to the adolescent assuming that responsibility, are likely to require modification of approaches to achieve the best results.

The largest numbers of studies of self-management support have focused on patients with asthma and diabetes. A systematic review of 36 randomised controlled trials for asthma that included some combination of knowledge provision, self-monitoring, regular practice review, and a written action plan, determined that these interventions reduced unscheduled health-care use (including hospital admission), enhanced quality of life, and reduced numbers of missed school or work days. Most patients in these trials were adults; a hand review of abstracts from that review revealed no stratification of outcomes by age. Similarly, a meta-analysis assessed 32 randomised controlled trials that enrolled only children and adolescents with asthma and used interventions designed to enhance knowledge, skills, and feelings of self-control. The pooled effect of the interventions was increased lung function and self-efficacy and decreased school absences, days with restricted activity, and unscheduled use of health-care services. 15 trials enrolled adolescents, but none stratified by age. By contrast with the efficacy of self-management support interventions, studies that included only knowledge-based education, written management plans, or psychological treatment generally showed no significant effect.

In epilepsy, self-management has been conceptualised as medication management (behaviours to manage medications), strategies to control seizures and their consequences (behaviours to manage seizures), and techniques to manage situations arising from having epilepsy (behaviours to manage life). A systematic review of self-management interventions is underway within the Cochrane Collaboration and might provide the opportunity to investigate outcomes for children and adolescents separately.

Diabetes is perhaps the most obvious model of a common condition that requires daily medication and lifestyle (diet and exercise) management, with evidence that intensive treatment reduces complications in adolescents. A Cochrane review of self-management education for adults showed sustained, clinically important improvements in metabolic control and complication rates. Gage and colleagues systematically reviewed studies of education, psychological, self-management, or combined interventions in adolescents with type 1 diabetes. Although these studies typically did not include sufficient follow-up to ascertain the effect of specific interventions on physical complications, almost all 62 studies reported at least one positive outcome. Incorporating parents into interventions generally had a positive effect. The authors noted, however, that none of the studies directly addressed the transition from parentally-controlled diabetes management to independent management by the adolescent.

Implications and future directions

Despite these developments, more consistent and rigorous monitoring of health status, including quality of life, mental health, and risk-taking behaviours, would provide stronger evidence for clinical and preventive efforts that aim to mediate the effect of chronic conditions on the lives of young people, and their families. We were unable to identify any longitudinal generic cohorts that had tried to identify the effect of social, economic, educational, and pubertal transitions on health outcomes and risk behaviours—and vice versa—in young people.
with major chronic disease or disability. Clarification about the distinct and common features of adolescents with specific disorders and groups of disorders would inform clinicians and health-care planners about models of adolescent-friendly health-care services.

The importance of understanding and facilitating the transition of responsibility for self-care during adolescence cannot be overstated. Well-designed theoretical and empirical studies are needed to understand the timing, speed, and nature of the shift in responsibilities. In addition to age effects, other critical developmental variables such as the timing of puberty, which can be greatly affected by chronic disease, are important. Again, models that transcend specific conditions would be especially valuable, as is understanding how structural elements of paediatric and adult health-care systems can both facilitate and hinder transitions.

More broadly, deeper understanding of the social aspects of growing up and becoming an adult with a chronic condition is needed, as well as the role of peers, both healthy and ill, in supporting adolescents’ self-care. How does the experience of adolescence with a chronic condition affect young peoples’ capacity to engage in age-appropriate social activities? How are efforts to develop a robust personal identity affected by such conditions, and how in turn, do efforts at developing a satisfactory identity and self-story affect health-related behaviours of young people with chronic conditions? Innovative approaches to qualitative data collection are providing valuable insights into some of these important questions.

Although most chronic conditions of adolescence are not preventable by lifestyle changes, many comorbidities should be highly modifiable. Engaging peer support and positive social interactions can be challenging, especially for adolescents in less populated areas or with rare conditions. However, an evidence base is emerging about the value of face-to-face peer support, whether school-based and disease-specific (eg, Triple A [Adolescent Asthma Action], a peer-led asthma health promotion programme for secondary schools) or community-based and generic (eg, ChIPS, the Chronic Illness Peer Support programme, a model of peer support and leadership training for young people with different chronic diseases). Evidence is also growing that internet-based support and self-management programmes and other technologically-mediated methods can improve outcomes for people with chronic conditions. In view of young people’s enjoyment of communication technologies, these methods seem especially promising for assisting adolescents with varying developmental and disease-related needs without the constraints of geography.

Growing investment in cancer services for young people is an example of how identification of differentially worse survival data can affect various structural elements of the health-care system. However, beyond survival data, increasingly focused assessment of health, developmental, and psychosocial outcomes in adolescents with chronic conditions will broaden our understanding of the complex issues experienced by so many of them. This knowledge in turn will provide a platform to both challenge the orientation and nature of existing services, and to strengthen the response from health-care systems to better support young peoples’ progress towards adult life.

Conflict of interest statement
We declare that we have no conflict of interest.

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In May, 2006, on a Bank Holiday weekend, an 18-year-old woman presented to an inner-city London emergency department. She had been at a nightclub with friends and purchased tablets, which she understood to be ecstasy or amfetamines, from a dealer. After ingesting five tablets, she collapsed in the nightclub and appeared to have a seizure lasting 10 min. On arrival in the emergency department, she was agitated and had dilated pupils (8 mm), sinus tachycardia (156 bpm), and a blood pressure of 150/51 mm Hg. Her score on the Glasgow coma scale was 15 and she was afebrile (35·9°C). She had no significant past medical history and was on no regular medication.

She was one of seven patients to attend the department that night with a similar presentation. We therefore considered it possible that she had taken a contaminated drug, or a substance not previously sold in the area; and we considered it possible that she had taken a contaminated pill purchased by the patient (figure) was also analysed, with strongly suspected or reported ingestion of 1-benzylpiperazine. In initial clinical trials of 1-benzylpiperazine, adverse effects similar to those of amfetamines were noted.3 A prospective study in New Zealand identified adverse effects including nausea, vomiting, tachycardia, hypertension, anxiety, and agitation among 80 patients presenting to emergency departments after 1-benzylpiperazine ingestion.4 Seizures were reported in 15 (19%), at up to 8 h after ingestion. Three patients had potentially life-threatening recurrent seizures; ingestion of 1-benzylpiperazine by these patients was confirmed by toxicological screening of their urine. Other potentially serious adverse effects included QTc prolongation (QTc duration 430–490 ms in 32 patients) and hyponatraemia (serum sodium concentration 118 mmol/L and serum osmolality 242 mmol/kg) in one patient. Clinicians should be aware of the potential presenting features of piperazine toxicity, particularly because commercially available urine toxicological screening kits for drugs of abuse may not detect piperazines. All patients with strongly suspected or reported ingestion of 1-benzylpiperazine should have an initial baseline ECG, to seek features of cardiotoxicity. They should be observed for up to 8 h after ingestion, because the onset of seizures can be delayed. Initial treatment should be based on the clinical presentation. Further management can require the advice of a clinical toxicologist.

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