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The direct-to-consumer advertising genie

European commissioners are considering proposals to loosen Europe’s ban on direct-to-consumer advertising for prescription drugs. But before they proceed, they should look carefully at the US experience. Direct-to-consumer advertising has been allowed in the USA since 1997. The pharmaceutical industry claims the advertisements educate patients about health, inform them about new treatments, and encourage them to talk to their doctors about important health concerns. Opponents, however, argue the advertisements are simply that: advertisements, most of which push expensive new drugs even when less expensive and often safer treatments, or even no treatment at all, would suffice.

A new US government report suggests such concerns are warranted. The report was published by the US Government Accountability Office (GAO), a non-partisan investigative and research agency of the US Congress. The report reviews direct-to-consumer advertising in the USA and examines how well the US Food and Drug Administration (FDA) oversees these advertisements. The investigators found the oversight was lax. But their report also raises questions about the value of direct-to-consumer advertising and shows just how hard it is to regulate once this genie is out of the bottle.

The investigators showed that from 1997 to 2005, industry spending on direct-to-consumer advertising grew on average nearly 20% per year, twice as fast as spending on drug promotion to doctors, reaching US$4·2 billion in 2005. By comparison, industry spent $31·4 billion on research and development, according to the GAO report. More than 50% of the direct-to-consumer spending went to advertisements for just 20 drugs, most for chronic conditions such as hyperlipidaemia, asthma, and allergies. Not surprisingly, these are the same drugs that drug companies are promoting directly to doctors with advertising in medical journals, drug-representative visits, and free samples. It’s a smart dual-pronged strategy, because a doctor is more likely to provide a particular drug when a patient asks for it and when the doctor has free samples on hand.

Now, this is not to say that direct-to-consumer advertising does not help some patients. In many cases, patients may have been well served by advertisements that led them to discuss their concerns with their physicians. But the primary purpose of direct-to-consumer advertising remains clear: to sell lucrative, on-patent, brand-name drugs. Claims to the contrary just do not pass the straight-face test.

How well, then, does the FDA oversee this advertising? Not well, the GAO showed. Under the law, advertising materials must contain a “true statement” of information that includes a brief summary of effectiveness, side-effects, and contraindications. Broadcast materials may present only major effects and contraindications, but must provide information about where consumers can get more details. When material is shown to be in violation, FDA officials issue a regulatory letter that might call for the advertisement to be stopped or, in more serious cases, for new advertisements to correct misinformation that may have been disseminated.

In general, the FDA only reviews material after it is disseminated, although in some cases companies bring their materials to the agency for comment before dissemination. Because the FDA can review only a small proportion of advertising put out each year, FDA officials told the GAO investigators that they used informal criteria to select what to review. But the GAO investigators showed that the FDA had no written documentation detailing these criteria, no system for applying the criteria, and no record for tracking what it had reviewed. In addition, the FDA issued relatively few regulatory letters, between eight and 11 per year between 2002 and 2005. However, once the FDA began drafting a letter it took on average 4 months before it was issued. In many cases, by that time the advertising campaigns had often run their course.

Part of the FDA’s performance is probably due to the influence of an industry-friendly administration that has made its antipathy towards government regulation clear. This should serve as a warning to European regulators that unless done very carefully, relaxation of direct-to-consumer advertising regulations risks creating a tidal wave of marketing that will be difficult to control.

It would be better to fund independent information sources, free of industry influence, to provide the public with unbiased evidence-based information. If industry truly wants to inform the public, it should supply no-strings-attached funds to support such efforts. Even a small portion of the $4·2 billion being spent each year in the USA on direct-to-consumer advertising would do nicely. ■ The Lancet
Bulgaria and Romania join the European Union

The next time European leaders sit down to discuss the future of the EU there will be two new faces at the summit table. For on Jan 1, 2007, Bulgaria and Romania formally became members of the EU. The road to accession has not been straightforward. It has taken 5 years for these two new countries to meet the conditions for entry set by the European Council, which has been closely monitoring the countries’ progress in a series of reports. Under this watchful eye, both Romania and Bulgaria have taken great strides in the past few years, including introducing several measures aimed at improving public health.

Romania—which had earned dubious international renown for the poor conditions prevalent in its numerous state institutions housing prisoners, orphans, and those with mental disorders—has improved its child-protection services. Bulgaria has increased social support for people with disabilities. Both governments have enacted legislation to improve the health of people with mental and physical disabilities. And the two countries have developed National Action Plans for the surveillance and control of communicable diseases, a specific prerequisite for EU membership.

But according to the European Commission, several health-related issues require “increased efforts”, particularly the poor conditions in psychiatric institutions. Bulgaria was criticised for its child-welfare provisions in a May, 2006, progress report, which also criticised both countries for failing to address discrimination against vulnerable groups, particularly the Romany gypsy communities of central and eastern Europe.

The fact that accession has been completed as planned this year, rather than being delayed until 2008, is testament to the capacity for positive change both countries have shown. But it remains crucial that issues of concern for health are not neglected in the aftermath of accession success. The European Commission can help by making sure its watchful gaze does not move elsewhere. ■ The Lancet

Undermining TRIPS: protectionism at its worst

Two international campaigns are currently defending the legal rights of the world’s poorest people to access the essential medicines they need. Both campaigns are calling for the rules of Trade Related Aspects of Intellectual Property (TRIPS), a binding World Trade Organisation agreement, to be upheld and are targeting the pharmaceutical industry and the US Government.

Novartis is taking the Indian Government to court over its decision last year not to grant a patent for the cancer drug imatinib mesylate. The patent was rejected under the conditions of the TRIPS legislation that India implemented 2 years ago. Section 3(d) stipulates that patents should only be granted on medicines that are truly new and innovative but Novartis is challenging this rule. Despite mounting opposition from civil society groups and non-governmental organisations, including a campaign organised by Médecins Sans Frontières, at the time of going to press Novartis still plans to take the Indian Government to court later this month.

On the other side of the Indian Ocean, Thailand recently announced that it is making use of its rights under TRIPS flexibilities to protect public health by authorising the Government Pharmaceutical Organization of Thailand to make a cheaper generic version of the second-line antiretroviral drug efavirenz. But according to the pressure group Intellectual Property Watch, the US Government has joined Merck, and other US pharmaceutical companies, in saying that the Thai Government should have asked Merck’s permission first, a stipulation that is not necessary under TRIPS. To date, 140 organisations and individuals have signed a letter to the US Secretary of State, Condoleezza Rice, asking the USA to stop interfering with the Thai efforts.

Both these cases take international law into unchartered territory. If Novartis and the US Government (and Merck) get their way, this will have grave implications for the rights of poorer countries to protect public health, which TRIPS flexibilities are supposed to protect. It will also be a further blow to the authority of the World Trade Organisation which is already drastically undermined by the repeated failure of the Doha round of trade talks where the imbalance of power allows some countries to put their own interests before the rules of international trade agreements. ■ The Lancet
Questions about adjuvant trastuzumab still remain

In today’s *Lancet*, Ian Smith and colleagues present the latest findings from HERA, one of five trials assessing the addition of trastuzumab (Herceptin) to anthracycline-containing polychemotherapy (table). The latest results show that the addition of trastuzumab reduced the absolute risk of death by 1.8% over 2 years and, at that stage, one extra woman will be alive for every 55 treated. However, an eighth of women randomised to trastuzumab died or relapsed over an average of 2 years. Some women will not be fit to receive the antibody after anthracycline treatment. For the remainder, trastuzumab will raise the absolute risk of symptomatic congestive heart failure by 2% at 2 years (up 0.4% from 1 year), and by 5% if subclinical harms are included. For symptomatic congestive heart failure, the number needed to harm is 51 (95% CI 37.2–80.1). For the risk of all (including subclinical) cardiac harms, the number is 20 (16.0–25.7).

During our work on trastuzumab for the UK’s National Institute for Health and Clinical Excellence (NICE), the cardiologists we contacted were uncertain whether damage caused by trastuzumab is, as has been claimed, essentially short-term and reversible. Side-effects of the drug are additional to those caused by anthracyclines, drugs that by themselves can have serious outcomes 20 years after treatment. With anthracyclines, a statistically significant increase in harms is not enough to reduce the survival benefit at 15 years, but trastuzumab is from a different therapeutic class, with unknown long-term effects. Most adjuvant trials of the drug, including HERA, are now confounded by mass crossover of participants from the control arm and will never adequately address whether trastuzumab prevents rather than delays recurrence and whether long-term harms will overturn early survival benefits.

While there is cause for concern, perspective is needed: over 2 years, the risk of cardiac damage seems trivial compared with that of breast cancer recurrence. Unless catastrophic long-term side-effects emerge for trastuzumab, HERA is good news for women with HER-2-positive early breast cancer and adequate cardiac function.

Our work for NICE, with the 1-year median follow-up data, suggested that the HERA schedule also represented value for money. We estimated that the regimen had an incremental cost-effectiveness ratio of around £18 500 per quality-adjusted life-year (QALY) gained, with two assumptions. First, survival benefits accrue over 5 years and are sustained thereafter (as with

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial size</th>
<th>Median follow-up (years)</th>
<th>Trastuzumab schedule*</th>
<th>All-cause mortality (%)</th>
<th>Recurrence or death from any cause (%)</th>
<th>Serious, life-threatening, or fatal cardiac events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA (Europe)</td>
<td>3387</td>
<td>1</td>
<td>110 mg/kg over 1 year after anthracyclines± taxanes</td>
<td>29 (1.7) 37 (2.2) 0.76 (0.47–1.23)</td>
<td>127 (7.5) 220 (13.0) 0.54 (0.43–0.67)</td>
<td>9 (0.5) 1 (0.1) 9.04 (1.15–71.25)</td>
</tr>
<tr>
<td>HERA (Europe)</td>
<td>3401</td>
<td>2</td>
<td>110 mg/kg over 1 year after anthracyclines± taxanes</td>
<td>59 (3.5) 90 (5.3) 0.66 (0.47–0.91)</td>
<td>218 (12.8) 321 (18.9) 0.64 (0.54–0.76)</td>
<td>10 (0.6) 1 (0.1) 9.97 (1.18–77.80)</td>
</tr>
<tr>
<td>N9831 and NSABP combined analysis (USA)</td>
<td>3351</td>
<td>2</td>
<td>106 mg/kg over 1 year with anthracyclines and taxanes</td>
<td>62 (3.7) 92 (5.5) 0.67 (0.48–0.93)</td>
<td>133 (8.0) 261 (15.5) 0.48 (0.39–0.59)</td>
<td>51 (3.1) 5 (0.3) 10.38 (4.15–25.91)</td>
</tr>
<tr>
<td>BCIRG 006 (USA)</td>
<td>2148</td>
<td>2</td>
<td>106 mg/kg over 1 year with anthracyclines and taxanes</td>
<td>20 (1.9) 36 (3.4) NR</td>
<td>77 (7.2) 147 (13.7) 0.49 (0.37–0.65)</td>
<td>25 (2.3) 10 (1.0) 2.46 (1.19–5.09)</td>
</tr>
<tr>
<td>FinHer (Finland)</td>
<td>231</td>
<td>3</td>
<td>20 mg/kg over 9 weeks with anthracyclines and taxanes</td>
<td>6 (5.2) 14 (12.1) 0.41 (0.16–1.08)</td>
<td>12 (10.4) 27 (23.3) 0.42 (0.21–0.83)</td>
<td>0 0 ..</td>
</tr>
</tbody>
</table>

*Adjusted to give yearly comparable regimens. NR=not reported.
anthracyclines); second, that no cardiac events result in death (unlike with anthracyclines). If society were willing to pay £20 000 for an additional life-year with full quality of life, \( ^{16} \) trastuzumab could be judged cost effective. With finite resources, the UK’s National Health Service (NHS) would have to stop funding other treatments to provide trastuzumab (the opportunity cost), but the NHS could consider these cuts justified.

The survival benefit with the HERA schedule was greater (in absolute and relative terms) with the 2-year observed data than with the previous 2-year estimates that had informed our calculations. \(^2\) However, compared with the earlier estimates for disease-free survival, the observed findings were worse: the new central estimate is barely within the previous 95\% CIs. As a result, if trastuzumab were evaluated today, we would expect the incremental cost-effectiveness ratio to rise above NICE’s threshold of £20 000 per QALY and for there to be a greater probability of it rising above £30 000 per QALY. This finding might make no difference to the conclusions reached by NICE’s appraisal committee, because NICE often recommends interventions that cost between £20 000 and £30 000 per QALY gained. However, their judgments about the acceptability of trastuzumab as an effective use of NHS resources would now have to make explicit reference to the degree of uncertainty surrounding the data, the innovative nature of the treatment, the particular features of HER2-positive breast cancer, and wider societal costs and benefits. \(^{16} \) Health trusts have been told that they have to cancel services for populations who might be less vocal and well-organised than the breast cancer lobby. \(^{15} \) The cancellation of treatments by health trusts was not underpinned by the same kind of analysis as that which informed NICE’s decision to fund trastuzumab, something that NICE’s new disinvestment initiative (which helps the NHS identify and stop ineffective treatments) \(^{11} \) has to change if resource allocation is to be underpinned by procedural justice. \(^{13} \)

However, NICE might never have deemed the HERA schedule to be cost effective if the FinHer study \(^{8} \) had been assessed as a comparator (table). This publicly funded Finnish trial scheduled just a fifth of the amount of trastuzumab used in other trials over a shorter period. Addition of the drug did not produce statistically significant differences between arms for overall survival or cardiac events. These findings could be due to the small sample size, but the noted improvement in disease-free survival in FinHer would be attributable to chance alone once in 100 times. The results of this trial are not as robust as those of HERA, but many treatments are funded with a lesser degree of certainty.

New Zealand’s drug-governing body, PHARMAC, is the first to suggest that the uncertainty surrounding the HERA schedule remains too great to justify the expenditure, and has commissioned a feasibility study to evaluate whether it should fund the FinHer regimen. \(^{14} \) NICE could not ask us to evaluate the FinHer schedule because its remit is restricted to licensed indications and Roche sought marketing authorisation for a 1-year schedule only. We could speculate that Roche has little desire to develop a regimen that would reduce the use of trastuzumab significantly. Instead, by contrast, HERA is investigating whether more, rather than less, treatment is beneficial. In England and Wales, a schedule that might be as good and “may facilitate lower cost, greater patient convenience, and reduced risk of cardiotoxicity” \(^{10} \) is not considered further.

NICE now recommends the HERA schedule for early-stage HER2-positive breast cancer following surgery, chemotherapy, and radiotherapy (if applicable), providing cardiac function meets the inclusion criteria for the HERA trial and cardiac functional assessments are repeated every 3 months during treatment. \(^{15} \) The US Food and Drug Administration authorises the B-31 and N9831 schedules for women whose cancer is both HER2-positive and node-negative. They also recommend baseline and subsequent assessments of cardiac function, but set no threshold for the use or cessation of trastuzumab. \(^{17} \)

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We declare that we have no conflict of interest.

Newborn screening for inherited metabolic disease

In today’s Lancet, Bridget Wilcken and colleagues provide important new evidence about newborn screening with tandem mass spectrometry for medium-chain acyl-CoA dehydrogenase (MCAD) deficiency.1 This recessively inherited disorder is caused by mutations on the ACADM (acyl-coenzyme A dehydrogenase, C-4 to C-12 straight chain) gene that cause enzyme deficiency or inactivity, and can result in severe acute metabolic decompensation episodes during fasting or in association with infection or catabolic stress. The aim of newborn screening is to prevent such episodes, which can lead to sudden death or neurological disability. For those patients with acute episodes, the risk of death is about 25%.2,3 However, because some affected children remain asymptomatic, overall cohort mortality is lower, at 12–20%.4 5 Although detection of MCAD deficiency is a primary justification for the expanded screening programmes that are being implemented in some countries, there are no population-based data for long-term outcomes. As the first study to provide such data in screened and unscreened birth cohorts in the same country, Wilcken and colleagues’ findings lend support to an important health-policy question.

Wilcken and colleagues studied almost 2.5 million children born in Australia between 1994 and 2004, a third of whom were screened at 2–3 days of age for MCAD deficiency. In an analysis confined to those born before 2003 and for whom there was at least 4 years’ follow-up, the researchers report deaths in six (17%) of 35 children with the disorder diagnosed through clinical presentation or after diagnosis of a sibling, compared with one (4%) of 24 in those diagnosed through screening. The combined outcome of rates of death or episodes of severe decompensation was lower in the screened cohort than in the unscreened (relative risk 0.19, 95% CI 0.06–0.60). However, the cohorts are not directly comparable, because the frequency of MCAD deficiency in the screened cohort was less than half that in the unscreened cohort (relative risk 0.19, 95% CI 0.06–0.60). Importantly, Wilcken and colleagues report preliminary results of cognitive testing in 25 (48%) of 52 surviving children of at least 4 years of age. Test scores were normal in both screened and unscreened children with MCAD deficiency. In a previous study, normal developmental scores were reported for screened children with the disorder, but most assessments had been done in infants or toddlers.6 7 Previous studies of children diagnosed clinically, including one from Australia, typically reported serious disability in about 5% of survivors and milder impairments in up to 30%.2,6 Wilcken suggests that their finding shows improved clinical awareness of
MCAD deficiency in Australia in recent years. Further studies of clinical outcomes in screened and unscreened populations from other countries are needed, not least because children who are hard to follow up might be more likely to be disabled than those who have been successfully traced and contacted.

One important question that remains unanswered is the extent to which children who are not homozygous for the common severe mutation benefit from screening and clinical management. Combination of the systematic identification of ACADM mutations with outcomes data in larger samples of such children, from diverse populations in different countries with much the same screening and diagnostic criteria, will allow this issue to be addressed.

Wilcken and colleagues’ study provides the best evidence so far of MCAD deficiency outcomes in screened and unscreened populations. The findings suggest that screening for this disorder is associated with fewer episodes of decompensation and deaths, although no difference in hospital admissions or cognitive impairment was reported. On the basis of these results, newborn screening seems to prevent death in around one in ten children with MCAD deficiency in Australia, which is about half as many deaths prevented as cost-effectiveness analyses of screening for this deficiency have generally predicted, although consistent with Feuchtbaum and Cunningham’s analysis. Most cost-effectiveness analyses assumed that 8–20% of surviving children with the disorder would have neurological impairment, and one analysis assumed 60% impairment. Those analyses probably overstate the benefits of screening for MCAD deficiency in populations with health care similar to that of contemporary Australia. Finally, we urge that high-quality studies of long-term outcomes be started for the many other disorders for which newborn screening with tandem mass spectrometry has been introduced, and for which evidence of effectiveness is less clear than that for MCAD deficiency.

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The findings and conclusions in this Comment are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the UK Department of Health (UK). CD is lead investigator in the UK Collaborative Study of Newborn Screening for MCAD deficiency, and strategic co-director of the UK Newborn Screening Programme Centre, both funded by the UK Department of Health (UK). We declare that we have no conflict of interest.

Decrease in frequency of cerebral palsy in preterm infants

The frequency of cerebral palsy, a major clinical marker of brain injury, increased during the early years of the introduction of neonatal intensive care, concomitant with the decreased mortality of very-low-birthweight (<1500 g) preterm babies. Treatment with steroids in the antenatal period and with surfactants in the postnatal period was introduced in the early 1990s and led to further reductions in neonatal mortality, particularly for less-mature infants of birthweight less than 1000 g.

Until the late 1990s, cerebral palsy was defined as a non-progressive disorder of movement, posture, or both; there was no reliable measure of the severity of motor disability or consideration of other cognitive or neurosensory problems. In 1997, Pallisano and colleagues developed a reliable system to quantitatively classify gross motor function in children with cerebral palsy. In 2004, an international workshop on the definition and classification of cerebral palsy proposed a new definition, which includes not only the motor disorders associated with cerebral palsy but also disturbances of sensation, cognition, communication, perception and behaviour, and seizure disorders. These important advances in diagnosis and assessment improved the classification of children with cerebral palsy. Furthermore, the 2004 classification includes anatomical and radiological findings, and causation and timing of the lesion. This classification aids comparison of the frequency of cerebral palsy and its correlates, and enables a multidisciplinary approach to treatment.

Cerebral palsy in preterm infants is associated most commonly with periventricular leucomalacia, with or without severe periventricular haemorrhage or infarction. Many factors may cause cerebral palsy, including perinatal ischaemia, anoxia, perinatal infections, and the iatrogenic effects of drugs such as steroids in the postnatal period; it also occurs more commonly in multiple births. The frequency of cerebral palsy, especially in infants of less than 28 weeks’ gestation, mainly reflects the aggressiveness and quality of perinatal care, and thus in the 1990s there was concern that the frequency of cerebral palsy would continue to increase.

In today’s *Lancet*, the Surveillance of Cerebral Palsy in Europe (SCPE) group report an encouraging decrease in the frequency of cerebral palsy. This group found that the prevalence of cerebral palsy in very-low-birthweight infants and those born at less than 32 weeks’ gestation decreased significantly, from 6% of livebirths (60·6 per 1000) in 1980 to 4% (39·5 per 1000) in 1996. This improvement occurred despite an increase in livebirths at very low birthweight, a decrease in neonatal deaths, an increase in multiple births, and, in children with cerebral palsy, a decrease in mean birthweight and gestational age. However, the decline in cerebral palsy occurred mainly in very-low-birthweight infants (1000–1499 g). The prevalence of cerebral palsy for infants of very low birthweight who weighed less than 1000 g did not change, although its incidence decreased for survivors born after 1990. Assessment of outcome by gestational age showed no change in the frequency of cerebral palsy between 1980 and 1996 for infants born at less than 28 weeks’ gestation, but showed a decrease for infants born at 28–31 weeks’ gestation.

The major strengths of the SCPE study include: follow-up of children to age 4 years, when diagnosis of cerebral palsy is fairly reliable; diagnosis according to agreed definitions, which were similar to the classification of the 2004 international workshop; assessment by neurological subtypes and severity, as measured by functional abilities such as intelligence, vision, hearing, and walking; analysis of time trends in the prevalence of cerebral palsy for all livebirths in the regions studied, which gives a perspective of the contribution of increased survival to the prevalence of cerebral palsy; and...
analysis of the incidence of cerebral palsy in survivors, enabling assessment of special health-care needs and the potential burden to the health-care system and to families.

Despite the encouraging decrease in the prevalence of cerebral palsy reported by the SCPE group, which is consistent with findings from our institution for infants of less than 1000 g birthweight born between 2000 and 2002, there is no cause for complacency. Cerebral palsy is associated with major disabilities: in the SCPE study, 35·2% of children with bilateral spastic cerebral palsy were unable to walk and 23·5% of children had severe mental retardation (ie, intelligence quotient <50). Furthermore, both the SCPE study and data from the USA have recorded an increase in the number of livebirths of very low birthweight, which might lead to an increase in the number of children with cerebral palsy. Therefore every effort needs to be invested in the prevention of preterm birth and its associated brain injury.

Early childhood development: the global challenge

In 1978, WHO and UNICEF made immunisation and the prevention and control of endemic disease key elements of primary health care and Health for All, set up a new programme for the promotion of oral rehydration therapy (ORT), and supported their widespread adoption and promotion in developing countries. Within 15 years, the practice of ORT had multiplied exponentially, reaching all continents and most countries of the world. By 1990, WHO estimated that the number of children aged under 5 years who died from diarrhoea and dehydration each year had fallen from 5 million to 4 million. The expansion of immunisation was saving a further 3 million, if not more.4

Three Lancet papers, one in today’s issue and the others in the following two issues,2–4 if taken seriously, could have an impact hardly less dramatic. At least 200 million children aged under 5 years fail to reach their potential in cognitive and socioemotional development, because of four causes: malnutrition that leads to stunting, iodine and iron deficiency, and inadequate stimulation in their first 5 years of life. This lost potential is preventable. There are effective and mostly low-cost actions that can be taken to prevent the damage and remedy the deficiencies. Just as with ORT (and immunisation, growth monitoring, and the promotion of breastfeeding), the problem is not the lack of knowledge about what to do but the lack of professional and political commitment to mobilise action on the scale required—and for poorer communities in countries throughout the world.

The third paper in the series4 sets out the strategic actions required: mobilise awareness, among parents as well as professionals; implement interventions for childhood development in infancy through families and caregivers, particularly for disadvantaged children; expand preschool education programmes, with components linked to health and nutrition; incorporate early childhood development into existing services and systems; and reach full coverage of programmes to eliminate iodine and iron deficiency in all countries. The call for such action is not to whistle in the wind. This paper provides hard evidence from countries in all regions of the world where such programmes are successfully underway and at an affordable cost. Moreover, programmes of iodine and iron fortification have, since 1990, shown the possibilities for rapid expansion, even in some of the poorest countries. In
Comment

Panel: Child development priorities: Jim Grant’s ten commandments

- Articulate your vision with inspiring goals
- Break goals down into doable, time-targeted actions
- Demystify techniques and technologies
- Generate and sustain political commitment
- Mobilise a grand alliance of all social forces
- Go to scale
- Select your priorities and stick to them
- Institute public monitoring and accountability
- Ensure relevance to broader development goals
- Unleash full potential of the UN

1990, less than a fifth of households in developing countries were using iodised salt; by 2000, the proportion was about 70%.

The first and second papers review a mass of recent material which leaves no doubt about the widespread nature of the major causes of these failures in early childhood development. They underline how any one of these four deficiencies leads to a serious effect on childhood development. When two or more of the deficiencies are found together, the combined impact is even more severe. These two papers also draw attention to related problems: malaria, violence and maternal depression, diarrhoea, exposure to heavy metals, and HIV/AIDS. These problems also cause severe setbacks to childhood development no less serious than those resulting from the basic four causes, although, as the authors make clear, remedial actions for the others are more difficult to implement and less evidence is available about costs and effectiveness.

We can learn how to respond to the challenge today by remembering the lessons of expanding ORT and immunisation in the 1980s and 1990s. Jim Grant, the legendary executive director of UNICEF, summarised the approach in his ten commandments (panel).

UNICEF working with WHO and many others—governments, civil society, Christian, Islamic, and other religious groups, and non-governmental organisations such as the Rotarians—showed that applying these principles on a global scale could achieve rapid results in more than a hundred countries, rich and poor. UNICEF described the results in the 1980s as a “child survival and development revolution.” The bottom line was that child deaths were reduced over the 1980s from 15 million to 12 million a year, despite the fact that economically these years were a lost decade for economic development in most of Latin America and Africa.

What is the chance that early childhood development could experience a similar surge in awareness, commitment, and action over the next decade? The papers in this Lancet series and the country examples show the opportunities well. Whether they are seized will depend on the response from key groups. These groups include policymakers within countries and internationally. Will they take up the challenge—and back up their response with the necessary resources? Researchers and academics also have a critical role. Will they give new attention to the issues, provide the professional leadership and guidance required, help document experience, and explore outstanding research questions, especially to identify low-cost approaches which can be implemented by poor families and communities? Another key group is the medical and public-health community. Will they agree that these critical issues of early childhood development can and need to be put on the priority agenda, along with the mass challenges of reducing child mortality and poverty?

The challenge is clear. The size and nature of the problem is defined, along with the seriousness of its long-term consequences. What remains open is only the world’s response, and our own.

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I declare that I have no conflict of interest.

Comment

User fees or equity funds in low-income countries

In last week’s *Lancet*, Bruno Meessen and colleagues compared fundamentally different approaches to redress the unfairness towards poor individuals that characterises health systems in low-income countries: equity funds and abolition of user fees. In Cambodia, an equity fund was established to enable the poorest patients in hospitals to be exempted from health-care and transport fees. By contrast, user fees in Uganda were abolished at all levels of the health system for all patients.

Both experiments sharply increased attendance by poor patients. Two crucial differences merit discussion. First, the Cambodian system recognised that financial barriers in health-care access include indirect costs such as transport or opportunity costs. By only abolishing user fees, the Ugandan experiment neglected this point. Transport as a proportion of total patients’ costs can be high, especially in developing countries (28% in Burkina Faso, 25% in northeast Brazil). In Tanzania, costs of transport were so high that “the substantial costs in time and effort and the money spent on travel make it unjustifiable to introduce charges on the grounds that it would discourage frivolous use of services”. Thus the abolition of user fees does not resolve all financial barriers for poor patients. However, user fees are a major part of the reason why the poorest groups are excluded from health care, and alternatives need to be found.

Second, use of performance-based payment in Cambodia is increasingly advocated by donors such as the World Bank to improve health-care delivery. Performance-based payment has been praised for overcoming the limitations of per-capita fees (leading to under-provision of services) and fees for services (leading to over-provision of services). Meessen and colleagues point out that the removal of user fees in Uganda removed the incentive for providers to aim for quality care. This observation assumes that patients can influence quality of providers through payment. The fundamental question is why such financial incentives should come from patients, especially from those least able to pay. Since Meessen and colleagues, among many others, accept that user fees are regressive, discussion of other funding mechanisms to support incentives, such as capitation, would be useful.

Meessen and colleagues’ article sits at a crucial moment in the debate about access to health care for poor people in low-income countries. Donors and health economists have advocated user fees since the 1980s as a sustainable and cost-effective health-financing mechanism able to constrain health-care demand in resource-scarce countries. Individual studies claiming to show benefits of user fees, such as curtailing frivolous demand for health care, encouraging individuals to take responsibility for their health (including preventive behaviour), and reducing inappropriate use of referrals, have been repeatedly contradicted. Rice and Morrison and Sepehri and Chermonas, among others, have shown that problems with efficiency and equity persist with user fees. User fees are not always cost effective: national systems have generated an average of only 5% of total recurrent health-system expenditure, and necessary as well as unnecessary demand for care is constrained. The RAND Health Experiment—a large...
randomised study in the 1970s in the USA—showed that health-service use fell as cost-sharing increased. However, there were reductions in both ineffective and effective services, and poorer health outcomes overall.11 Also, supply-side incentives (ie, for health workers) might be more efficient at restraining demand than demand-side incentives (ie, for patients).12 For equity, because health care has been argued to be an essential good, the demand for it will not fall with price (ie, price inelasticity), and people in the lowest income quintile have shown to be highly responsive to even small changes in price.13 Hence, even very small fees can reduce their access, and exemption mechanisms for these groups have repeatedly failed.9 Médecins Sans Frontières studied prices paid in several sub-Saharan African countries at public-health centres that applied user fees for primary care,14–16 and found that the fees represented a substantial share of household expenditure (equivalent to 12–30 days of expenses), forcing many families to borrow money or sell goods.

All this information begs the question of why we still need to argue about user fees. The discussion is an old one,17 but unfortunately still relevant. The debate has regained interest in view of the international agenda for poverty alleviation and the Millennium Development Goals, and Meessen and colleagues’ article is a useful addition. Several donors have acknowledged the failings of user fees, some at least rhetorically (World Bank), and others are adapting their aid-policy implementation (UK Department for International Development). Some countries have recently abolished user fees fully (Uganda, Zambia) or partly (Burundi, Niger). Yet, user fees remain in most of sub-Saharan Africa, often publicly denounced by donors but privately accepted as the only viable option if poor countries are not to spend more than their domestic resources allow.

Health economists and donors are now focusing on community-based health insurance, which is defined as any scheme with voluntary membership that uses prepayment for health care by community members.18 However, the fundamental question remains—who will pay for those unable to afford it?

Meessen and colleagues rightly conclude that no one solution can improve access for poor individuals worldwide. However, they point out that context-specific solutions are attainable. It is time to learn from the accumulated evidence from the past two decades and follow up with action to effectively overcome financial barriers for the world’s poorest populations.

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Vote buying in the UN Security Council

In an increasingly globalised world, health is ever more affected by international institutions. Over the past 25 years, the World Bank, the International Monetary Fund (IMF), and the World Trade Organization (WTO) have increasingly dominated policymaking in developing countries, leading to substantial effects on health. Furthermore, global threats to health, such as HIV/AIDS, severe acute respiratory syndrome, avian influenza, and climate change, need effective collective action at the international level. Therefore the system of global governance is of central, and growing, importance to health.

However, global governance is becoming increasingly controversial, particularly in the case of global economic institutions. Controversies have included: the World Bank's and IMF's undemocratic weighted-voting structures; the so-called tradition by which the USA and European Union (EU) effectively appoint the respective heads of these organisations; and the abuse of economic and political power by the USA and EU to pressurise developing countries to accept potentially damaging concessions in WTO negotiations. By comparison, the UN has tended to be seen as relatively democratic, neither sharing the IMF's and World Bank's weighted-voting structures; the so-called tradition by which the USA and European Union (EU) effectively appoint the respective heads of these organisations; and the abuse of economic and political power by the USA and EU to pressurise developing countries to accept potentially damaging concessions in WTO negotiations.5,4

By comparison, the UN has tended to be seen as relatively democratic, neither sharing the IMF's and World Bank's weighted-voting system nor showing the routine circumvention of democratic and transparent processes that characterise the WTO. The UN and its specialist agencies have been criticised as being starved of resources; increasingly dependent on discretionary funding; compromised in their neutrality; and sidelined by the major powers in favour of the World Bank, over which these powers exert greater control. However, criticism of the UN's democratic processes has been more limited, and has focused mainly on the selection processes for agency heads, notably those of WHO.6,6

Ilyana Kuziemko and Eric Werker recently highlighted systematic use of aid from the USA and resources from UN agencies (mainly UNICEF) to “buy” the votes of countries on the UN Security Council. These researchers reported that countries receive about 59% more US aid and about 8% more UN aid during the time that they are on the UN Security Council than at other times. These figures increase to 170% and 53%, respectively, when important issues are at stake. Overall, US$17 million in aid is diverted in a typical year, and $53 million in an important year, for each of seven or eight countries. Aid is at normal levels in the years immediately before and after UN Security Council membership. The additional UN aid is almost entirely attributable to UNICEF, an agency with close links to the US administration and which is (by another consistently observed tradition) headed by a US citizen (currently, former US Agriculture Secretary, Ann Veneman). Kuziemko and Werker’s conclusion that these findings are evidence of an attempt by the USA to buy votes on the UN Security Council seems compelling. However, they have not analysed votes to assess how effective such efforts are, citing problems in the methods for trying to do so, and they have not assessed how the flow of aid from other donors is affected.

Kuziemko and Werker’s findings complement other studies that have found a significant correlation between lending by the IMF (in which the USA casts 17% of votes and wields a de-facto veto on major policy decisions) and recipient governments’ proximity to, or movement towards, US positions on votes in the UN General Assembly. Furthermore, qualitative and quantitative evidence suggests that lending by the World Bank (in which the USA enjoys a proportion of votes similar to that in the IMF and appoints the President) is used to reward countries in the Middle East that conform to US policy there. The latest, and particularly controversial, US appointee as World Bank President—former US Deputy Defense Secretary Paul Wolfowitz—stands accused of using his position to channel World Bank funds to support the US-backed administration in Iraq, setting aside the standards on corruption he is seeking to apply in other
countries and the normal World Bank policies on countries in conflict.12–14

If these analyses and events indeed reflect an attempt by the USA to influence international decision-making, it is a matter for serious concern. If successful, such attempts skew international decision-making away from the common good, resulting in outcomes that will be less favourable for those in greatest need. The credibility and legitimacy, and thus the effectiveness, of international bodies will be undermined, making it still more problematic to find effective solutions to global challenges such as poverty, health, and climate change. Decisions of the UN Security Council, whose remit extends to the legitimate use of military force and economic sanctions, may have profound effects on health, as exemplified by the experience in Iraq.12–14

Moreover, even if voting patterns are unaffected, allocation of scarce aid resources according to donors’ geopolitical agendas rather than to need or potential effect reduces the effectiveness of aid in achieving objectives such as poverty reduction and health.13–14 In few cases can the health implications be greater than in UNICEF, whose programmes are targeted strongly at health-related activities, such as immunisation and girls’ education.

The growing criticism of the system of global governance is unsurprising. This system was established in the 1940s, and has changed little. Since then, not only have the world and the roles of international institutions changed fundamentally, but so too have political standards and culture. It would be more surprising if a system of governance (developed while much of the developing world remained under colonial rule) did conform to the standards of democracy, accountability, and transparency of the early 21st century.

That governments which enjoy a privileged position in international organisations and dominant economic, political, or military power use these advantages to promote their self-interest and to protect their political privileges is unsurprising. Predictably, when a country’s leader has the wealth and power to act at will, in a national governance system that lacks effective mechanisms to ensure accountability, power will be abused and jealously guarded. There is little reason to expect a different outcome at the global level. However, that abuse of power is predictable does not make it acceptable or justifiable, and it does not exonerate the culprits. Rather, it creates an overwhelming case for fundamental reform of governance structures to prevent such abuse.

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I declare that I have no conflict of interest.


Doing the undoable: Magpie Trial long-term follow-up

Compelling evidence from the Magpie Trial1 that administration of magnesium sulphate to women with pre-eclampsia halves the risk of progression to eclampsia1 is now supported by data on longer-term outcome for both the mother1 and child.4 These data are particularly relevant for resource-poor countries, where eclampsia remains a major cause of maternal death, and where administration of magnesium sulphate to women with pre-eclampsia costs less and prevents more eclampsia than in richer developed countries.5
To do a large randomised trial is a major logistical challenge. To provide data on the longer-term outcome for participants in such studies requires particular energy and enthusiasm. The Magpie Trial follow-up was a project that everyone said needed doing, but many people thought was undoable. Finding women and children long after discharge from hospital is difficult enough in countries such as the UK, where national systems and developed infrastructure can assist researchers. In many of the places where women were recruited to the Magpie Trial, no such infrastructure exists, making follow-up even more daunting. That such a study proved possible is testament to each collaborator’s dedication and commitment to the women they recruited and their overwhelming desire to provide reliable reassurance for women and their families in the future.

When collaborators from the 19 countries participating in the Magpie Trial follow-up came together to discuss the final results, the most memorable part of the meeting for many was an afternoon during which colleagues from vastly different backgrounds and settings talked about how they had followed up the women in their country. They told about their successes and failures, how they overcame incredible barriers, and how they were touched by many of the families they contacted. They shared anecdotes illustrating humour, humanity, and heartbreak. They told powerful stories, stories that are often untold in research. We asked collaborators to write them down, and to write in their own words rather than in the language of science.

These stories are now available on The Lancet’s website. They include: an explanation of why contacting families in Tirana, Albania, was made easier by bread shops; a colourful account of a weekend of adventures finding families in the towns and villages of Santiago del Estero province in Argentina; a résumé of the difficulties in recruiting field workers in Mumbai, India; an explanation of why the geography and recent history of the North West Frontier Province in Pakistan made follow-up in the breathtaking beauty of this mountainous area particularly challenging; and how the regulations in obtaining research ethics approval nearly prevented any follow-up in Oregon, USA. Our opinion, unbiased of course, is that these are a wonderful read, regardless of whether or not you have an interest in doing randomised trials. We also hope these stories will encourage others to attempt the seemingly impossible, and do trials that stretch out way beyond our normal academic comfort zone. We applaud the many Magpie Trial collaborators—those whose experiences are highlighted on the website and those whose, equally vivid, experiences are not—for a job well done; we hope you will too.

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Nicaragua tightens up abortion laws

Doctors in Nicaragua are outraged by the removal of a legal loophole that permitted abortions for women whose health is at risk. Critics say the amendment, which was fast-tracked through the legislature without a single opposing vote, will endanger women’s lives. Jill Replogle reports.

On Nov 2, in a haphazard cemetery in the hills outside the capital city Managua, Jazmina Bojorge Rodríguez was buried in a simple grey casket. She was 19 years old. The funeral procession of fifty or so friends and relatives wound along the dirt road to the cemetery on foot. The coffin-bearers, wearing simple work clothes, passed round cheap rum to ease the pain and strain. Women shuffled along in flip-flops, carrying bouquets of wildflowers and bougainvillea to place on the grave.

Bojorge was 5 months pregnant with her second child when she went to the Fernando Velez Paiz public maternity hospital in Managua, with bleeding, pain, and a fever. She had begun to have uterine contractions. The hospital’s ultrasound machine was not working, so she was sent to another hospital to find out if the fetus was alive, which it was. Then Bojorge was taken back to Velez Paiz and put on medication to try and stop the contractions. After 12 h of waiting for the woman’s condition to improve, the doctors determined that the fetus had died. They stopped the treatment and waited for Bojorge to abort naturally. However, she began to haemorrhage and was taken to the operating room for caesarean section. It was too late; the placenta had detached and the uterus was filled with blood. Bojorge died shortly afterwards.

Women’s groups and some doctors say Bojorge was the first victim of a recent change in Nicaraguan law, which prohibits abortion in all cases, even if the mother’s life is in danger. The law puts Nicaragua among just 2% of countries worldwide that do not permit life-saving abortions. The combination of her doctors’ fear of being prosecuted under the new law, lack of diagnostic equipment, and the delay in taking medical action proved fatal in Bojorge’s case, says gynaecologist Ana Maria Pizarro, from the Nicaraguan women’s health organisation, SIMujer (Servicios Integrales de la Mujer or Integral Services for Women).

She and other doctors, along with activists for choice and human rights, fear that many other women—especially those who are poor—with complicated pregnancies will follow Bojorge to the grave. “We think this is the beginning of a long chain of maternal deaths”, says Pizarro.

The new law was passed by the Nicaraguan legislature on Oct 26, shortly before the country’s Nov 5 presidential elections. Despite appeals from the EU and the UN not to vote on the controversial legislation during election time, the bill was fast-tracked through the legislature, and was passed without a single opposing vote.

 Nicaraguan president Enrique Bolaños signed the bill into law 3 weeks later, in the presence of Catholic and Evangelical church leaders, who campaigned heavily for the law.

The legislation does not actually create a new law, but rather removes an article from the country’s penal code that permitted abortion for therapeutic reasons. Under this article, which refers to “therapeutic abortion”, the procedure had generally been allowed to protect the mother’s health, in the case of rape or incest, or when severe fetal malformation was detected. Abortion for any other reason has been illegal in Nicaragua for more than 100 years.

Doctors face up to 6 years in jail for doing an abortion; women who abort face up to 4 years’ imprisonment. President Bolaños had originally asked for an increase in abortion-related penalties—up to 20 years for doing an abortion, or 30 years if the mother on whom the procedure was done sustained psychological or physical damage.

Bishop Juan Abelardo Mata Guevara, president of the Episcopal Commission of Life and the Family, says the loophole allowing therapeutic abortion had been abused. “Abortions have been carried out that were unnecessary [for medical reasons],” says Mata. He adds that medical science has advanced and doctors should be able to save women’s lives without killing the unborn child.

The law has been hotly debated in Nicaragua over the past decade, with...
The printed journal includes an image merely for illustration

Throngs of protesters have campaigned to get the law changed to ban all abortion

both the Catholic Church and Evangelical Church hierarchies demanding a stronger antiabortion law.

Pro-choice groups have countered with a campaign aimed at convincing the mostly Catholic population that therapeutic abortion is a human right and does not contradict Church teachings.

The debate came to a head several years ago when a 9-year-old Nicaraguan girl, Rosita, was raped in Costa Rica and became pregnant. Her parents, illiterate campesinos, were working in the neighbouring country as coffee pickers when it happened. The family’s fight for a legal abortion for Rosita became an international battle between anti-abortion and pro-choice camps.

In the end, Rosita had a legal but clandestine abortion. The names of the doctors who did the operation were kept secret along with the location.

Later, a representative from an anti-abortion group filed a lawsuit against the parents and anyone else that aided or consented to the girl’s abortion, including some members of women’s rights groups. But the court dismissed the charge.

The Catholic Church, however, excommunicated the girl, her parents and all others involved in the abortion. Prior to this year’s Nov 5 presidential elections, the issue again became front-page news. Church leaders held an anti-abortion march on Oct 6, where they presented 290 000 signatures supporting a complete outlaw of abortion.

Along with posters and banners for different candidates, the streets of Managua were overhung with banners that read “don’t vote for candidates who support abortion” and, on the other side of the spectrum, “murderers of women, don’t vote for them” followed by the names of the three leading candidates for president, all of whom declared their support for a total abortion ban.

Only one candidate, Edmundo Jarquín of the left-leaning Sandinista Renovation Movement, publicly supported the right to therapeutic abortion. He won just 6.4% of total votes. Daniel Ortega—whose entire Sandinista National Liberation Party legislative bench voted in favour of the new law—won the election.

Latin American nations have taken diverging paths on the abortion issue, with some countries enacting increasingly restrictive measures, and others loosening up legislation on the matter. In 1997, El Salvador passed a law similar to the one recently enacted in Nicaragua, prohibiting abortion with no exceptions. An aggressive law-enforcement apparatus in El Salvador makes sure that those who break the law are punished, including aborting women, some of whom are serving prison sentences of up to 30 years. Whether Nicaragua will effectively enforce its recently passed legislation is yet to be seen.

In Colombia, by contrast, has loosened up its abortion law earlier this year. The country’s constitutional court ruled that abortions were legal to save the life of the mother, in the case of rape or severe fetal malformation. Nevertheless, the new legislation has caused a legal quagmire, with women’s groups suing doctors who refuse to uphold the new law, and anti-abortion groups seeking to overturn the high court’s decision.

Doctors and other opponents of Nicaragua’s new law say the new legislation responds to religious dogma without taking into account the opinions of the medical community. “It’s really the start of an inquisition”, says Marta Maria Blandon, director for Central America of Ipas, a US-based reproductive rights group. “We feel like we don’t have a lay state anymore.” She fears the law would keep women from seeking professional help in the case of a spontaneous abortion, for fear of being sent to jail.

As in most other countries where abortion is illegal, the poor will bear the brunt of the law, said Blandon. “People with money can get high quality services, legally or illegally.” It’s not uncommon for wealthy women to fly to Miami or nearby countries where laws are less restrictive to have abortions, she says.

Nicaraguan doctors say the new legislation will limit their ability to practise, and could prevent them from treating common, but potentially deadly, complications like ectopic pregnancies. Oscar Flores Mejía, member of the Nicaraguan Society of Obstetrics and Gynaecology, says the law puts him in an impossible position. If he ignores his professional obligation to give necessary care and does nothing, Flores says, he must sit back and watch the woman die and then face a lawsuit from the family. “And if I act, I go to jail—so I don’t have any option but to stop practising my profession.”

Flores says the medical associations—20 different associations have publicly expressed opposition to the new law—will present a constitutional challenge to the penal reform, on the grounds that it is a threat to human life and limits doctors’ ability to practise.

Doctor Ramiro López, head of quality control for the public-health ministry, says his office is working on a list of cases in which medical interruption of a pregnancy is necessary to save the mother’s life. He says that it may be possible for doctors and mothers with life-threatening complications to plead self-defence and avoid criminal prosecution under the new law.

Jill Replogle

Kenya’s mixed HIV/AIDS response

Government delays providing audited accounts to the Global Fund to Fight AIDS, Tuberculosis, and Malaria, could harm Kenya’s anti-AIDS efforts, say some faith-based groups. But the government insists its strict procedures ensure money is well spent. Wairagala Wakabi reports.

Kenya says though it has managed a small reduction in HIV/AIDS prevalence rate over the past year, delays by donors like the Global Fund for HIV/AIDS, Tuberculosis, and Malaria to release funds could harm the country’s anti-AIDS campaign.

In November, Kenya received an additional US$70 million from the Global Fund to support its fight against tuberculosis and HIV/AIDS. The release of the funds came after months of wrangles between government and faith-based agencies, which have accused authorities of failing to account for Global Fund monies and jeopardising Kenya’s chances of receiving more funds. Until a few years ago, the country had kept its AIDS problem under wraps for fear of scaring away tourists, given that tourism is the country’s highest foreign exchange earner.

The faith-based groups, which provide care and help in distributing antiretrovirals, with the support of the Global Fund, say delays in providing the audited accounts were likely to result in the loss of millions of dollars in funding. The Global Fund had given Kenya a deadline by which to provide the books of accounts, showing how the funds it had been allocated in two rounds of funding were utilised.

Representatives of the Global Fund said in November that Kenya had made efforts to reduce the bottlenecks it faced in having its requests processed, but added that there were real problems on the ground that needed to be eliminated. Procurement processes were slow and graft-ridden, which made purchase and distribution of drugs tedious. There were also concerns that some of the money went to briefcase organisations.

“There have been delays in receiving disbursement requests”, said Josephat Mwaura, an overseer of Global Fund finances in Kenya. “Kenya has improved institutional bottlenecks and the Global Fund encourages Kenya to continue improving and addressing the real problems on the ground.” KPMG, the accounting and auditing firm, oversees the Global Fund money in the east African country. Mwaura says progress reports on the utilisation of the funds were required regularly and on time to avoid disbursement delays.

Kenya has 1.3 million people living with HIV/AIDS and 108,000 people with tuberculosis. The country will use the new grant to scale-up voluntary counselling and testing services and to provide a range of care services including drugs for mothers, spouses, infants, and medical workers who are HIV-positive. The country has more than 350 registered Voluntary Care and Testing (VCT) sites.

The HIV/AIDS prevalence rate has declined to 5.9% from 6.1% during the past year. Alloys Orago, National AIDS Control Council (NACC) acting director, said the improvement happened against a backdrop of shortage of financial support, following delays in the release of funds by some of the funders of the country’s HIV/AIDS programmes.

Beatrice Gathirwa, NACC deputy director for finance and administration, said at the launch of the results of the national sero-status report in October that despite having fulfilled the conditionalities set by the Global Fund to address good governance, the organisation had delayed release of the money yet the government was only providing about 20% of the funds for their activities. “The Government needs to match donor funding for HIV/AIDS intervention so that we can sustain the programmes”, Gathirwa says. The council is assuring donors that it has set up a strict audit mechanism to ensure money given for fighting AIDS was not squandered by briefcase organisations.

The prevalence rate in urban areas is 9.6% and 4.6% in rural areas. Prevalence is highest among women at 7.7% compared with 4% among men. Among those aged 15–24 years, prevalence is highest among girls at
to develop an efficient supply system and national chairman, says there is need for them. Tom Aosa, the council’s coordinator, says out of the 263,000 adults who require antiretrovirals, only 90,000 are getting them. He said 1.2 million children have been orphaned from HIV and AIDS-related illnesses, but the NACC put the number of children who require antiretrovirals at 39,000.

But the National Community-Based Organisation Council says poor distribution of antiretrovirals is locking out many of those who need them. Tom Aosa, the council’s national chairman, says there is need to develop an efficient supply system so that deserving people, especially in the rural areas, could be reached.

“Patients who cannot afford to buy the drugs are forced to default on their treatment due to the shortage”, which reduced the effectiveness of the treatment. He said many health units, particularly upcountry, routinely report that they cannot cope with the high demand for antiretrovirals.

There are reports that the stigma that continues to surround AIDS in Kenya has apparently made some people living with HIV/AIDS wary of obtaining antiretrovirals through official channels, as they fear this could lead to their HIV-positive status being made public. As a result, some of those who are registered sometimes sell off some of their drugs in order to afford other basics like food. But there are also reports of some people registered to get antiretrovirals at two sites, who then sell off the extra drugs.

Patricia Asero, a member of the Kenya Treatment Access Movement, said recently that in some cases, patients who only have one source of drugs would also sell their antiretrovirals to buy food. “They will tell you that their medication got lost; others claim that their bags were snatched by thieves. But when you interrogate them keenly, you get to know the truth”, she says.

John Mwangi, a field worker with the Kenya Network of Women and AIDS, says hundreds of people living with HIV in the Central Province were discriminated against by their relatives, leaving them without proper food and shelter. These people were as a result not accessing antiretrovirals or counselling facilities. The number of people receiving antiretroviral medication has risen from 39,000 in 2005 and 24,000 in 2004.

Meanwhile, health officials say the increasing number of people living with HIV and kala-azar (visceral leishmaniasis) in Kenya poses a major health challenge. Médecins Sans Frontières (MSF) has said the new trend could cause a health crisis in the country and in other weak African economies. “HIV and kala-azar are a lethal cocktail and efforts must be taken to control the trend”, says MSF medical adviser Koert Ritmeijer, who adds that it could still be decades before a vaccine against kala-azar was found. “Kala-azar will remain a serious health threat due to the growing number of people infected with the disease as well as HIV”, he adds.

In Kenya, the disease is common in arid and semi-arid regions of North Eastern and Rift Valley provinces, where infection rates rise at national high. In Turkana district in the north of the country, poor services and low literacy have resulted in an infection rate of 11.4%. Yakish Eyapan, the Turkana AIDS and sexually transmitted infections coordinator, says: “The problem with Turkana is that it has many neglected issues that are more important to people than HIV. It has priority problems like food insecurity, water, education, and poverty. If they have no water and are hungry, how can you talk to them about HIV?”

Ruth Eripete, a nurse counsellor with Merlin, a UK-based non-governmental organisation, told PlusNews that “cultural factors like polygamy and wife inheritance [a practice in which a widow has to marry a male relative of her deceased spouse], we believe, increase the prevalence rate”. Eyapan said a lack of education, a major truck route to the southern Sudan capital of Juba and poverty, had forced girls to “use their bodies to get food or money”.

Among the nomadic communities, the shortage of condoms and the fact that the communities keep moving in search of pasture for their livestock, which means they tend to meet many new sex partners, also contributed to the high prevalence rate.

Condoms are not widely used in Turkana for reasons of access and culture, Eripete said, adding that she had heard men say that “they cannot eat a sweet while the wrapper is still on. Many also say that their penises are too long for condoms.”
Questions of identity

At least part of the reason for the world’s present discontents is that humanity is deeply divided within itself, mainly by assumed cultural differences of ideology, religion, politics, and also by economic self-interest—not that these are wholly separate things. Race and ethnicity play their part too, exacerbated by those other factors; but currently it is the apparent sharpness of a major religion-based divide that is drawing blood.

Even as the Iron Curtain was falling, marking the end of the Cold War division between two ideological monoliths, so some were predicting the approach of new and differently motivated divisions. The best known is Samuel Huntington’s “clash of civilisations” thesis, to many borne out by the contemporary appearance of a collision between “Islam and the West”. It is no use objecting to this formula on the grounds that it opposes a religion to a geography; the terms are shorthand for two contrasting identities, two sets of values, two ways of looking at the world. And to that extent it refers to a real contrast—one has only to compare the bikini on the western beach with the burka on the Afghan street to see that in many respects what the terms “Islam” and “the West” respectively denote are, in some respects, contrasting indeed.

But not in all respects. There is far more wrong with the simplistic division into two identities than this last thought allows, which is precisely the point of Amartya Sen’s brilliant reflections on identity, and especially religious identity, driving today’s increasingly acrimonious conflicts. Descending others, or thinking of oneself in terms of “a choiceless singularity of human identity” is the mistake and the danger that not only diminishes individuals, Sen says, but fuels the flames of opposition between them. The aim of Identity and Violence: The Illusion of Destiny is to debunk this error, and to force us to remember that a person is not one thing—a Muslim or a Jew only, or an Arab or an American only—but many things: a parent, a mathematician, a tennis player, a feminist, a Muslim, all of these things at once, and thus a complex being whom the politics of singular identity reduces to a mere cipher and crams into a box.

“Sen’s vigorous opposition to the politics of singular identity is both timely and right, which makes this a necessary book.”

Sen says that there is as an increasing tendency to overlook the many identities a human being has in place of a single differentiating identity. In fact this tendency has always existed, and was the norm before the days of “political correctness” taught us to avoid the errors of stereotyping on which racism, sexism, and other forms of discrimination rest. But he is right to say that this tendency is animating dangerous divisions as attitudes harden on all sides. Sen’s vigorous opposition to the politics of singular identity is both timely and right, which makes this a necessary book. In it he subjects the Huntington thesis to powerful criticisms, reminds us of the plural identities in past Islamic culture and the contributions it made to world culture, and cites Akbar, the great Mughal emperor of the 16th century, and Saladin, the prince of Islam in the 12th century, as exemplars of pluralism and tolerance. These salutary points should help to arrest the move towards ever greater divisiveness in a world that is now too small to contain it.

At the same time, the unhappy truth is that the actors most responsible for insisting on singular identities at present are Islamist radicals. Whereas fundamentalist Christians in the USA might consider their faith commitment to be their main individuating characteristic, they are also Americans, southerners (perhaps), and (in most cases) Republicans. For an Islamist it seems that the religion and the politics are one and the same. Over-riding identities are the ones people are prepared to die for; soldiers are encouraged to make their identification with the homeland complete and their sacrifice for it glorious—this is precisely the use of singular identities that proves the idea’s danger.

Sen’s main audience seems to be those in the West whose reaction to contemporary Islam, indiscriminately branded with the mark of Islamism, is to pigeon-hole it simplistically. He is right to warn them against this mistake. A problem for debates of the kind Sen here initiates is that they engage only those who read and think, and are unlikely to penetrate to the constituencies of ignorance and anger where their lessons are really needed. Because it is far easier for people to think in terms of singular identities, getting them to unlearn the habit is hard. Actual acquaintance with people—working with them, socialising with them—makes it difficult to think of them in group terms; but young men in the cities of Pakistan or Egypt watching Al Jazeera television are as far removed from that possibility as if they were on the moon—and the same for many watchers of television in the USA. Worse still is the fact that some young Muslims of Pakistani descent in the UK, or Algerian descent in France, feel alienated from the mainstream culture around them, and grasp a singular Islamic identity as a shield and staff. Sen’s book, if only they would read it, is for them too, and not just for the majority population around them.

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Photographs make the unbelievable irrefutable. Images of the execution chambers and mass graves at Auschwitz, people jumping to their deaths from the Twin Towers, or prisoners in Abu Ghraib have become engraved on our collective memory and change forever our view of the world. But with a globalised media churning out thousands of poignant images every week, is it harder today to make an image that changes the world? Is the traditional attention-grabbing tactic of shock—illustrated, for example, by the 1984 images of the Ethiopian famine that resulted in Live Aid—still as powerful today? Or have we reached saturation point and image fatigue?

During the past 21 years Reuters, one of the world’s largest international news agencies, has amassed some outstanding photographs. The State of The World, a new collection of more than 500 Reuters images with accompanying text, captures the stories and developments of this century. These pictures document a world fragmented by war, instability, and inequality, and reveal that the power of image is as important as ever. Predictably many of the images of war and conflict are from the Middle East and Central Asia, with photographs of injured and dead Iraqi civilians among the most disturbing. Yet the many forgotten wars that are being fought across Africa are hardly featured in this collection. Perhaps this omission reflects the news agenda and political priorities in western countries where such conflicts are largely unreported.

Split into nine main themes the book covers issues that range from the role of religion, the pattern of war and peace, to our increasingly technological world. The contrast between photographs of so-called celebrities—“the demigods of our age”—and the aftermath of terrorism, the Asian tsunami, and the Pakistan earthquake is horrifying. Such visual juxtaposition demands the question: what relative value do we place on real-world issues and on human life? The State of the World is a powerful reminder that our memories are etched visually, and that images often force us to confront what words allow us to deny.

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Cesar Victora thought he would be a mathematician or a nuclear physicist until he was 17 years old. But then he left Brazil on a scholarship to study at secondary school in the USA. The year he spent living just outside San Francisco at the tail end of the 1960s altered the course of his life. “It really changed my mind about a lot of things”, he said. “It was a very important year in my life.” Above all, he became interested in environmental issues, he said, and when he got back to Brazil, he thought he would study ecology, but there were no courses available. Then he read a book by the medical missionary and winner of the Nobel Peace Prize, Albert Schweitzer, who had dedicated his life to the health care of impoverished Africans. “I thought maybe that’s what I want to do”, he said. “I switched from the exact sciences to medicine because I felt I could do something more useful.”

37 years later, Victora is one of the world’s leading epidemiologists in child health and despite his frequent trips to Africa, Geneva, London, the USA, and elsewhere—and invitations to join the United Nations and prestigious universities in the wealthiest countries of the world—he lives in the small Brazilian city of Pelotas, in a house looking out onto a lagoon. “I thought I wanted something I could do where I could live in a small city and be helpful to people.” Colleagues at WHO, where he is a consultant to the department of child and adolescent health and development, say he is a leading thinker in the field, but he is also a practical man, with his feet firmly planted in his Brazilian homeland. “He is a leading epidemiologist in child health and is basically one of the big thinkers in terms of child health epidemiology”, said Elizabeth Mason, director of WHO’s department of child and adolescent health and development. “The fact that he continues to live and work in Brazil keeps him in touch with reality.”

After qualifying as a doctor at the Federal University of Rio Grande do Sul, Victoría did his residency in the slums. Like all who went to college at that time in Brazil, he was from the upper-middle classes. “It was a big shock”, he said. “I kept seeing the same kids over and over again with the same illnesses. We were not doing anything about changing the factors that cause diseases. That stuck me very much. That’s when I decided to do epidemiology.” Few of his colleagues at that time were interested in prevention of disease. During his residency, a new medical school was established in Pelotas. It was the chance he wanted to move out of Porto Alegre, the state capital, to a quieter town in the countryside. He taught at the school for 4 years before heading to the UK and the London School of Hygiene and Tropical Medicine for a PhD in health care and epidemiology. His thesis was on land tenure and child health. The children of landless parents in rural Brazil were far more likely to suffer disease and early death. “I have always been very concerned about issues of social inequity”, he said.

Victora came back to Pelotas and in 1984 set up a new research department at the university, which is now one of the best-known centres for epidemiology in Brazil. His work on breastfeeding, nutrition, and infant growth, based on research among the local children, has international respect. A birth cohort study he started in 1982 of 6000 babies born in Pelotas, which is ongoing, is one of the longest prospective studies of its kind ever undertaken. It has provided a wealth of information about the effects that conditions in early life have on adult health. In 1997, he became a senior technical adviser to WHO, helping to assess its global strategy on the integrated management of diarrhoeal and respiratory diseases and other major causes of mortality in children. Then, in 2003, he became the joint coordinator, with Jennifer Bryce, of the groundbreaking Lancet child survival series. He describes his past 10 years as “trying to raise the visibility of child health in the world”. He explains how “There are fashions in aid and global research. There was a child survival revolution, with strong leadership from UNICEF, but it has gone off the agenda since.” Other issues, such as HIV/AIDS, became the priority. That is understandable, but “we can’t just concentrate on some priorities and forget about others”, Victora insists.

If his work has a political dimension, Victora is not himself a political animal. Some of his Brazilian colleagues in public health joined the armed resistance against the military dictatorship in the 1970s and 1980s while there was no clear social agenda and then moved into politics as the regime became more liberal, but Victora said that was not for him. “I wouldn’t survive as a politician”, he said. “I find politics a bit too vague for me.” According to Robert Scherpber of WHO’s department of child and adolescent health, Victora “recognises the importance of political issues, but he is not driven by them. That makes it very pleasant to work with him. He concentrates on the technical issues and formulates them in such a way that they have political appeal.”

Victora is a researcher to whom objectivity is essential and his work is a testimony to his commitment to child health and development. Although he works prodigiously hard and is very productive, he also knows how to have fun. He goes to the beach and his greatest passion, outside of work, is windsurfing on the lagoon beyond his window. “I will always find time for my windsurfing”, he says. “If I’m home and the wind is behaving, I’m there every day. I like to go for 10 miles and come back. Just me and the ducks.”

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Obituary

David Kritchevsky

Eminent nutrition scientist and campaigner against junk science. Born on Jan 25, 1920, in Kharkov, Russia, he died on Nov 20, 2006, in Philadelphia, PA, USA, aged 86 years.

Candid and irreverent in the face what he considered junk science, David Kritchevsky was unafraid of flouting the political orthodoxy when it came to nutritional truths and myths. And during the few months leading up to his death, New York City’s plan to ban transfats in restaurant food was one of his particular vexations. “He thought the detrimental effects of transfats had been exaggerated and was worried that more saturated fats would be used as a substitute”, explains David Klurfeld, a former postdoctoral student of Kritchevsky’s, who is now the human nutrition national programme leader at the US Department of Agriculture Research Service, MD, USA. So it is something of an irony that just a fortnight after Kritchevsky’s death, the ban was approved. “That noise you just heard?”, says long-time colleague and friend Jon Story, a professor at Purdue University, IN, USA, “that’s Dave rolling over in his grave”.

Kritchevsky’s commitment to exposing pseudoscientific thinking was not the only thing that made him an unusual scientist. He was known for his brilliant communication skills. Elizabeth Whelan, President of the American Council on Science and Health, a consumer education organisation, who knew Kritchevsky for 30 years, recalls that he was so comfortable in front of a microphone that he once did an entire radio show by himself when clashing appointments meant she had to cancel their arrangements. “I said I can’t interview you, I have to run. He said don’t worry I’ll interview myself. I came back an hour later and he was still going. How many prominent scientists are there that could do that?”

Kritchevsky died while still Caspar Wistar Scholar at The Wistar Institute in Philadelphia, an institution he had been closely connected to for 50 years. His distinguished career started in the 1940s when, after earning a degree, masters, and doctorate in chemistry from the University of Chicago, IL, USA, he worked as a chemist in two laboratories in his university town. An opportunity to work for a Nobel laureate in Switzerland took him to Europe, and it was during this postdoctoral assignment that he developed an interest in cholesterol, which was to form the basis of his most important scientific contributions. With almost 30 awards and honours to his name, Kritchevsky was an eminent scientist by any measure. He had a great influence on investigations into the role of lipids, dietary fibre, and dietary protein in atherosclerosis, espoused the idea of using purified diets to model atherosclerosis in animals, and prompted much of the early work into the effect of diet on risk of cancer, including the beneficial effect of caloric restriction.

Colleagues ascribe Kritchevsky’s varied contributions to his ability to keep a broad perspective, rather than specialising on a specific enzyme or dietary pathway. He was always looking for the connections between things, says Story. And, according to Whelan, this broad view was what made him such a good communicator. “He never lost perspective about the role of cholesterol and the role of diet in heart disease. Diet is a relatively small player in causing heart disease compared with cigarette smoking, high blood pressure, and genetics. This was unique about him”, she says.

As an avid reader, with a passion for poetry and music, Story remembers Kritchevsky as having enthusiasm for almost everything. “He was what I think of as a real intellectual”, he says. He frequently used his diverse interests to entertain his students by writing songs to help them remember chemical pathways—he once set the synthesis of cholesterol to the tune of Jingle Bells and made another song about the Krebs cycle. Kritchevsky also amused his colleagues with his wit. “I have a list of Kritchevskysisms. One of my favourites is ‘We tortured the data until they confessed!’ It sums up Dave’s view that statistics should confirm the obvious”, said Klurfeld. But for Klurfeld and Story, it was Kritchevsky’s humanity and compassion for people that truly set him apart. “He believed everyone deserves to be treated with respect”, explains Story. Klurfeld adds: “I am sure that his work is going to be a lasting legacy, but I believe that his personality is going to be a separate legacy for everyone that knew him.”

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Severe acute hepatitis in a patient treated with anastrozole

A 58-year-old woman underwent quadrantectomy for a ductal breast carcinoma in June, 2005. She received six cycles of doxorubicin and cyclophosphamide from August to November, with good tolerance. She was also being treated with valsartan for essential hypertension, which had begun 2 years previously. In December, 2005, treatment with anastrozole (1 mg/day) was started, and 3 weeks later she noted severe asthenia and progressively developed jaundice and dyspnoea. Anastrozole was withdrawn and the patient was admitted to hospital.

Laboratory data showed thrombocytopenia (platelet count 65×10⁹/L), prothrombin time 22 s (normal range 11–13 s), aspartate aminotransferase concentration 1062 U/L (<37 U/L), alanine aminotransferase concentration 2012 U/L (<40 U/L), lactated hydrogenase concentration 2319 U/L (<49 U/L), alkaline phosphatase concentration 714 U/L (<49 U/L), total bilirubin concentration 187 μmol/L (<17 μmol/L), γ-glutamyl transferase concentration 2012 U/L (<40 U/L), lactate dehydrogenase concentration 2319 U/L (<460 U/L), and a direct bilirubin of 66 μmol/L. Serum copper, iron, ceruloplasmin, and α₁-antitrypsin concentrations were normal. Serology for hepatitis A, B, and C viruses and non-organ-specific autoantibodies (ANA, ASMA, and AMA) were negative.

A chest radiograph showed a moderate right-sided pleural effusion, which was transudate. Abdominal ultrasonography was normal. A trans-jugular liver biopsy (figure) showed diffuse liver cell necrosis in acinar zone 3, without inflammatory changes, and mild mixed steatosis and cholestasis; portal tracts were normal.

1 month after anastrozole withdrawal, when prothrombin time was normal and alanine aminotransferase concentrations had decreased to 117 U/L, the patient developed an acute abdomen with pneumoperitoneum. A laparotomy disclosed a perforated duodenal ulcer, and a Billroth II procedure was done, but the patient developed septic shock and died in the postoperative period.

In our patient, a complete diagnostic workup ruled out non-toxic causes of liver injury. Doxorubicin has seldom been incriminated in hepatic toxicity, and cyclophosphamide has mainly been associated with sinusoidal obstructive syndrome in patients with haematological malignancies. In fact, late-onset hepatotoxicity due to cyclophosphamide could not be ruled out, but we did not see clinical evidence of liver disease during the courses of combination chemotherapy in our patient. She had been treated for 2 years with valsartan, a drug with a low risk of hepatotoxicity.⁴

The temporal evidence seems to favour anastrozole as the most probable cause of liver injury in our patient. However, over the past 6 years, more than 30 000 patients with breast cancer have been treated with third-generation aromatase inhibitors with a good liver safety profile.¹ We found no similar cases in the WHO database. Nevertheless, selection of ideal participants and analysis of predetermined side-effects in preclinical studies partly explain the appearance of unexpected drug-related events in the post-approval phase. Most importantly, uncommon genetic-based metabolic variants, or drug-drug interactions at the level of microsomal drug metabolism, are the basis for cases of toxic hepatitis detected only through a careful post-marketing surveillance. In fact, a case of anastrozole-related hepatitis was reported after the submission of this one, although liver histology was not documented in this patient.³

In our patient, the absence of inflammatory changes in the hepatic biopsy and the location of necrosis at zone 3 of the liver acinus, paralleling the preferred location of most of the P450 isoenzymes involved in drug metabolism, were all compatible with a metabolically mediated hepatocellular injury. Anastrozole is extensively metabolised in the liver, by N-dealkylation, hydroxylation, and glucuronidation, but no data exist on the cytochromes involved in anastrozole hepatic detoxification. The drug, but not its metabolites, has been shown to inhibit the reactions catalysed by cytochromes P450 1A2, 2C8/9, and 3A4. However, pharmacological studies suggest that the risk of CYP-mediated drug-drug interactions is negligible in individuals treated with anastrozole or valsartan.⁴ For these reasons, although CYP2C9 has a minor role in valsartan metabolism, an interaction between both drugs seems unlikely in our patient.

Coadministration of tamoxifen and anastrozole significantly lowers the plasma concentrations of anastrozole, suggesting that a cytochrome-mediated drug-drug interaction might modify anastrozole concentrations in plasma. Thus, on theoretical grounds, if the drug is the toxic mediator and since CYP3A4 and CYP2C9 are the main phase I enzymes involved in N-dealkylation and hydroxylation of many other drugs, a genetic polymorphism of any of these cytochromes would predispose to anastrozole liver toxicity.

For the WHO database of drug information see http://www.who.int/druginformation/
Correspondence

in some patients. But the pathogenesis of this liver injury remains speculative, since the toxic potential of the three main pharmacologically inactive metabolites of anastrozole is unknown, and an immune-mediated mechanism cannot be ruled out. In conclusion, clinicians need to be aware of the possible toxic effects of anastrozole on the liver. Additional well-documented communication of suspicious cases is necessary to confirm this toxic effect, and to determine its prevalence and the underlying pathogenic mechanisms.

We declare that we have no conflict of interest.

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Your Editorial on violence against women and children3 is timely and thought-provoking. It is pleasing that the UN report4 you discuss coincides with implementation of a new law against domestic violence in India. The Protection of Women from Domestic Violence Act 20055 came into force on Oct 26, 2006. The array of cases reported nationwide within a week of its implementation underscores the long-felt need for such legislation.6 This stringent act clearly defines and recognises domestic violence for the first time and promises to provide comprehensive attention to actual abuse or the threat of abuse whether physical, sexual, verbal, emotional, or economical.7

At the same time, however, the success of this legislation depends on combating problems of illiteracy and ignorance among women as well as deep-rooted social stigmas about reporting domestic violence. Also, impediments such as slow bureaucratic and police processes, along with any possible misuse of the legislation in terms of acts of vengeance, need to be overcome. Non-governmental organisations and women’s rights groups need to usher in awareness programmes to educate the women about this new empowerment tool. Hence, a watchful expectancy is warranted before we can be assured of the convincing outcomes of this legislation to emancipate women.

This is a laudable step by a developing nation: more than two-thirds of countries worldwide either lack a well-defined law or have an ambiguous law on these disturbing acts of violence.2 Clearly, the commitment by a nation where such stigmas are deep-rooted provides a tangible precedent to other nations to follow suit, mobilising the much-needed international response.

We declare that we have no conflict of interest.

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It is fair to highlight the wide complicity of every actor—international, governmental, and private citizen—in allowing violence against women and children to continue. You rightly call for high-level commitment to ending this atrocity, in your Oct 21 Editorial.1 However, the deadly intersection between this violence and HIV/AIDS, which has important implications for bilateral and multilateral AIDS programmes, was left unmentioned.

Funders of AIDS interventions, especially such large ones as the US President’s Emergency Plan For AIDS Relief (PEPFAR) and the UK’s Department for International
Development (DFID), should be requiring contractors to address this problem in a substantive way. But an external evaluation of DFID’s programmes\(^1\) found that gender violence was “not strategically addressed in practice”. Likewise, PEPFAR’s lack of transparency makes it impossible to verify its claims of bold action in this area or to assess its effectiveness.\(^2\) The Global Fund could also do much more to encourage proposals that include a substantial anti-violence component.

We urgently need a multisectoral response to violence that can change entrenched social norms. The multi-billion dollar international effort to address HIV/AIDS is certain to fail unless programmes that respond to violence are both appropriately designed and dramatically scaled-up to meet the need.

I declare that I have no conflict of interest.

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**Cholesterol lowering in patients with CHD and metabolic syndrome**

The post-hoc analysis of the Treating to New Targets (TNT) study (Sept 9, p 919)\(^3\) provides important mortality implications regarding atorvastatin dose that beg further discussion.

Overall, there was no change in all-cause mortality over the 4.9-year trial of atorvastatin 10 mg versus 80 mg daily in patients with stable coronary heart disease.\(^4\) Patients randomly assigned high-dose atorvastatin had less cardiovascular mortality but more non-cardiovascular mortality than those assigned low-dose atorvastatin, resulting in unchanged all-cause mortality.

Post-hoc analysis revealed that patients with metabolic syndrome, representing about half the patients with stable coronary heart disease, had a decrease in all-cause mortality with high-dose atorvastatin. This finding implies that the other half had an increase in all-cause mortality with the high-dose regimen.

This finding might be statin-specific. Post-hoc analysis of the Scandinavian Simvastatin Survival Study showed a decrease in all-cause mortality in patients with or without metabolic syndrome.\(^3\) Interestingly, atorvastatin is more likely than simvastatin or pravastatin to increase macrophage density in atheromatous plaque.\(^4\)

Therefore, regarding atorvastatin dose in patients with stable coronary heart disease without metabolic syndrome, perhaps less is more.

I declare that I have no conflict of interest.

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Prakash Deedwania and colleagues\(^1\) found that, in patients with coronary heart disease and metabolic syndrome, intensive cholesterol lowering with high-dose atorvastatin reduced cardiovascular events without improving overall survival. We are concerned that this strategy might lessen the perceived importance of a healthy lifestyle.

Adherence to healthy lifestyle practices has been associated with an 83% reduction in the rate of coronary disease, a 91% reduction in diabetes in women, and a more than 50% lower rate of all-cause and cause-specific mortality in elderly individuals.\(^2\)

Effects of a healthy lifestyle have also been studied in randomised trials.\(^3\) In fact, lifestyle change alone has been shown to improve several angiographic variables and to lower cardiac events.\(^4\) Furthermore, in the Lyon Diet Heart Study,\(^1\) individuals with established coronary disease who followed the experimental Mediterranean-type diet showed a 70% reduction in all-cause mortality owing to a reduction in death from coronary heart disease; these effects were seen without a significant change in serum cholesterol, indicating that this clinical variable is only one of the many to be considered.

Why were the patients with major lifestyle problems in the study by Deedwania and colleagues, such as those with features of metabolic syndrome, only given drugs?

We declare that we have no conflict of interest.

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Prakash Deedwania and colleagues1 highlight the clear benefits of 80 mg/day versus 10 mg/day atorvastatin on the reduction of cardiovascular events in patients with clinically evident coronary heart disease and metabolic syndrome. As one of the major risk factors for myocardial infarction and stroke, current smoking was thoroughly investigated. However, Deedwania and colleagues did not address daily alcohol intake and how this factor could have affected the results.

Alcohol consumption is widespread in the dietary lifestyle of European and Anglo-Saxon countries. Moreover, several epidemiological studies have clearly documented a benefit of light to moderate daily alcohol intake (1–3 units of alcohol, where 1 unit is about 10 g alcohol) in decreasing the risk of death from coronary heart disease and of ischaemic stroke.2,3 An “aspirin-like” thrombolytic effect of alcohol, mainly due to a reduction in platelet activation and aggregation, seems to have a mechanistic role.4,5

We recommend a thorough investigation of dietary alcohol intake during this kind of trial. A moderate daily amount of alcohol might be a confounding factor in assessing the efficacy of drugs in preventing cardiovascular events.

We declare that we have no conflict of interest.

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Authors’ reply

In the full Treating to New Targets (TNT) study, the risk of death from any cause did not differ significantly between the two drug regimens (hazard ratio 1.01, 95% CI 0.85–1.19; p=0.92). There was a non-significant trend towards a reduction in cardiovascular mortality with atorvastatin 80 mg/day and a reverse non-significant trend for non-cardiovascular mortality. However, no single cause of death accounted for the reverse trend in non-cardiovascular mortality and, in the similarly designed Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study,1 atorvastatin 80 mg/day did not result in any increase in all-cause, cardiovascular, or non-cardiovascular mortality compared with simvastatin 20 mg/day. It is also of note that the mortality rates in both atorvastatin treatment groups in the TNT study (5.6% and 5.7%) were lower than in any other statin-treated patient cohort from previous secondary prevention trials (8.2–12.9%).2,3

In our subgroup analysis of patients with metabolic syndrome, there was no significant difference in all-cause mortality between the two doses of atorvastatin in patients with metabolic syndrome (hazard ratio 0.97, 0.79–1.20; p=0.80) or in those without metabolic syndrome (1.07, 0.82–1.40; p=0.60). It must be emphasised that the TNT study lacked the statistical power to provide definite answers to the total mortality question, whereas in the post-hoc analysis of patients with metabolic syndrome from the Scandinavian Simvastatin Survival Study (4S), the primary endpoint was all-cause mortality. Further, the benefit of simvastatin for all-cause mortality in patients with metabolic syndrome in 4S was achieved compared with placebo, and the incidence of mortality in the simvastatin treatment group (8.3%) was higher than in metabolic syndrome patients treated with either of the atorvastatin doses in the TNT study (4.8% and 5.1%).

Small and non-significant directional changes provide little useful information on whether high-dose atorvastatin would reduce (or increase) total mortality in an adequately powered study. Hence, there is no definitive reply one way or another to the issue raised by Mark Goldstein.

We accept the importance of adherence to healthy lifestyle practices, as discussed by Luca Mascitelli and Francesca Pezzetta. As such, the TNT study was designed to ensure all patients received dietary information at screening to obtain compliance with the National Cholesterol Education Program Step I, Step II, or other equivalent diet, and dietary counselling was continued throughout the study.

Fabio Caputo and Mauro Bernardi’s comments regarding the influence of alcohol are well taken. However, the influence of alcohol in the TNT study could not be assessed, because the study was not designed to actively monitor alcohol intake. However, we expect that the intake of alcohol would have been similar between the treatment groups in this large randomised trial. Nonetheless, further studies are needed to determine whether there is any effect...
of alcohol on the efficacy of statins in this patient population.

I have received grants, consultant’s fees, and speaker’s fees from Pfizer and Astra Zeneca.

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Further data from the Treating to New Targets (TNT) study support the evidence for high-dose statins after acute coronary syndromes, in patients with established coronary heart disease, and in mechanistic studies.

We felt it timely to publicise an audit of statin use after acute coronary syndromes in the UK, which highlights the effect of a growing trend towards low-dose statin therapy for fiscal reasons. We believe that such a strategy can increase the morbidity and mortality of patients with cardiovascular disease.

The Department of Cardiology in Stoke on Trent, UK, took a corporate decision to give high-dose statin therapy to patients after myocardial infarction or revascularisation. This involved the prescription of atorvastatin 80 mg or 40 mg.

However, owing to mounting cost pressures, a decision was subsequently taken jointly between the local Primary Care Trusts (the funders of health care) and the local National Health Service Trust (the provider of secondary and tertiary health care) to suspend the prescription of atorvastatin and institute a switch to generic simvastatin 20–40 mg. Despite clinical objections to this decision, the changeover occurred in September and October, 2005.

Our department decided to audit the effect of this change. We compared patients who presented to our institution with a discharge diagnosis of myocardial infarction or unstable angina over two time periods: December, 2004, to February, 2005 (high-dose atorvastatin period) and the same months 1 year later (low-dose simvastatin period). Both groups were observed from December to May. Data were recorded on the index acute coronary syndrome event, cardiac readmissions, non-cardiac readmissions, and death. The results are shown in the table.

Such an audit might be of limited use when compared with the results of randomised controlled trials such as TNT and PROVE-IT. However, it highlights a more pertinent point: that wholesale change from an effective treatment to one less efficacious might adversely affect patients’ morbidity and mortality. The cost of the additional cardiac readmissions will almost certainly offset the additional cost of the high-dose statin therapy.

Perhaps it is time to reconsider the financially motivated short-termism regarding high-dose statin therapy and promote a more overarching approach to the management of lipids in patients who have had a myocardial infarction and who do not have time to up-titrate lipid-lowering therapy. As a result of this audit, along with the large volume of evidence from randomised trials, Primary Care Trusts within the North Staffordshire area have started to review the role of high-dose statin therapy after myocardial infarction.

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RR has received honoraria from Astra Zeneca, Pfizer, and Sanofi-Aventis.

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-dose atorvastatin (n=100)</th>
<th>Low-dose simvastatin (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) age (years)</td>
<td>67 (56–74)</td>
<td>70 (61–76)</td>
</tr>
<tr>
<td>Number male</td>
<td>73 (73%)</td>
<td>83 (68%)</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>5 (5%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>Number with cardiac readmission</td>
<td>33</td>
<td>53</td>
</tr>
<tr>
<td>Number with non-cardiac readmission</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Median (IQR) infarct size (units?)</td>
<td>0.40 (0.17–0.19)</td>
<td>0.29 (0.11–0.63)</td>
</tr>
</tbody>
</table>

* Some patients were readmitted more than once.

Table: Characteristics and outcome of patients given high-dose atorvastatin or low-dose simvastatin after myocardial infarction or unstable angina.
Public assessment of priorities for research: a citizens’ jury

There has been an increasing call for users to be involved in research. One of the aims is to make research increasingly relevant and salient to users’ needs.1 The innovative method of eliciting public views via a Citizens’ Jury was conducted in Bristol, UK, to consider what should be the research priorities for Primary Health and Social Care.

After hearing the evidence from key witnesses and deliberating, the jury developed a vision of creating Bristol as a caring city with a high quality of life for all. Prevention, education, and equality were the general, cross-cutting research priorities, which provided the foundation for five interconnected and more specific priority themes.

The questions for research shown in the panel are examples of those that were agreed unanimously. These questions should be considered when planning research into primary health and social care for Bristol and regionally; some of the questions might be relevant to the country as a whole.

We declare that we have no conflict of interest.

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Panel: Citizens’ jury recommendations on priorities for health research in Bristol, UK

Prevention and education
- Are preventive measures provided through local primary health care effective?
- How can local preventive strategies be most effective with high-risk groups and deprived groups?

Equality
- How do we empower minority and deprived groups of service users to access the services available to them?
- How can resources and services best be provided for people who may be vulnerable or inarticulate and find it hard to access health and social care?

Older people
- What is the most effective way of enhancing the quality of life of older people living in the community?
- Do home services meet the care and lifestyle needs of individuals?

Younger people
- Would the introduction of school doctors and nurses for all ages of schoolchildren help identify early and alleviate social and health problems?
- What works best to prevent antisocial behaviour in Bristol?

Mental health
- What methods of intervention in mental health problems help avoid crisis and emergency treatment?
- How can we make sure that post-treatment care is provided in such a way that everyone involved is kept up to date and that the patient is properly supported?

Addictions
- What effect can recovering addicts have on young people’s behaviour?
- Is limited access to rehabilitation service clinics a problem in Bristol?

Service provision
- How can the quality of life for service users and patients be enhanced?
- What kind of health and social care services really make a difference to the quality of life of the community?

Japan’s aid commitment to health and Africa

Your World Report on Japan’s aid commitments (Nov 4, p 1561) did not illustrate the effect of Japan’s official development assistance (ODA) on health, which the Commitment to Development Index fails to measure. Admittedly, Japan’s ODA, like that of all other donor countries, is an integral part of foreign policy2 and has indeed been in decline since the bursting of the Asian economic bubble. Nevertheless, in 2005, Japan pledged to double aid to Africa by 2009, to help extend Japan’s “Village Living” concept to the beleaguered continent. With declining global interest in Africa after the Cold War, Japan convened the first Tokyo International Conference on African Development (TICAD) in 1993, subsequently extending more than US$12 billion in aid to Africa and holding regular TICAD conferences, the next being scheduled for 2008. Japan last year cancelled $4·9 billion of Africa debt and committed a similar amount to a new Health and Development Initiative.3 Japan has also decided to establish the Hideo Noguchi Prize, a $1 million award envisaged as the equivalent of a Nobel Prize for outstanding contributions to medicine in Africa, to be inaugurated at the 2008 TICAD.

Japan has an excellent recent history in originating global health initiatives, including the 1997 International Parasite Control Initiative (known as the Hashimoto Initiative), which proved to be the forerunner of the Global Fund to Fight AIDS, TB and Malaria, and the Okinawa Infectious Diseases Initiative. Furthermore, Japan’s funding pledges have always been fulfilled. The Infectious Diseases Initiative, for example, was planned to see expenditure of $3 billion over 5 years, yet some $4·1 billion was spent in 4 years. Countering past criticism, many of the funds from the Health and Development Initiative will be disbursed in the form of grants, not loans, including an additional $500 million for the Global Fund.

We declare that we have no conflict of interest.

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2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial

Iain Smith, Marion Procter, Richard D Gelber, Sébastien Guillaume, Andrea Feyeriseiova, Mitch Dowsett, Aron Golzhirsch, Michael Untch, Gabriella Mariani, Jose Baselga, Manfred Kaufmann, David Cameron, Richard Bell, Jonas Bergh, Robert Coleman, Andrew Wardley, Nadia Harbeck, Roberto I Lopez, Peter Mallmann, Karen Gelmon, Nicholas Wilcken, Erik Wist, Pedro Sánchez Rovira, Martine J Piccart-Gebhart, for the HERA study team

Summary

Background Trastuzumab—a humanised monoclonal antibody against HER2—has been shown to improve disease-free survival after chemotherapy in women with HER2-positive early breast cancer. We investigated the drug’s effect on overall survival after a median follow-up of 2 years in the Herceptin Adjuvant (HERA) study.

Methods HERA is an international multicentre randomised trial that compared 1 or 2 years of trastuzumab treatment with observation alone after standard neoadjuvant or adjuvant chemotherapy in women with HER2-positive node positive or high-risk node negative breast cancer. 5102 women participated in the trial; we analysed data from 1703 women who had been randomised for treatment with trastuzumab for 1 year and 1698 women from the control group, with median follow-up of 23·5 months (range 0–48 months). The primary endpoint of the trial was disease-free survival. Here, we assess overall survival, a secondary endpoint. Analyses were done on an intent-to-treat basis. This trial is registered with the European Clinical Trials Database, number 2005–002385–11.

Findings 97 (5·7%) patients randomised to observation alone and 58 (3·4%) patients randomised to 1 year of treatment with trastuzumab were lost to follow-up. 172 women stopped trastuzumab prematurely. 59 deaths were reported for trastuzumab and 90 in the control group. The unadjusted hazard ratio (HR) for the risk of death with trastuzumab compared with observation alone was 0·66 (95% CI 0·47–0·91; p=0·0115). 218 disease-free survival events were reported with trastuzumab compared with 321 in the control group. The unadjusted HR for the risk of an event with trastuzumab compared with observation alone was 0·64 (0·54–0·76; p<0·0001).

Interpretation Our results show that 1 year of treatment with trastuzumab after adjuvant chemotherapy has a significant overall survival benefit after a median follow-up of 2 years. The emergence of this benefit after only 2 years reinforces the importance of trastuzumab in the treatment of women with HER2-positive early breast cancer.

Introduction Trastuzumab (Herceptin; Roche, Basel, Switzerland) is a humanised monoclonal antibody that is targeted against the extracellular domain of the HER2 transmembrane growth factor receptor. Amplification of the HER2 gene and overexpression of the receptor occurs in around 15–25% of women with early breast cancer, and is associated with an aggressive disease course. Trastuzumab has been shown to be of overall survival benefit to women with HER2-positive metastatic breast cancer administered alone or in combination with chemotherapy. The Herceptin Adjuvant (HERA) trial (Breast International Group 0101) is one of several large trials designed to test the efficacy of trastuzumab in the adjuvant (ie, post surgery) treatment of women with HER2-positive early breast cancer. Results of a first planned interim analysis with a median 1-year follow-up showed that trastuzumab given every 3 weeks for 1 year after adjuvant or neoadjuvant (ie, presurgery) chemotherapy achieved a significant improvement in disease-free survival compared with women treated with adjuvant chemotherapy alone, with a hazard ratio (HR) of 0·54.

The combined analysis of two similar North American trials (North Central Cancer Treatment Group Trial N9831 and National Surgical Adjuvant Breast and Bowel Project B-31) has also shown a significant improvement in disease-free survival for trastuzumab given concurrently with four courses of paclitaxel either every week or every 3 weeks after a combination of doxorubicin and cyclophosphamide and continued for 1 year compared with the same chemotherapy schedule alone. A fourth adjuvant trastuzumab trial, known as BCIRG 006, has also shown much the same disease-free survival benefit when trastuzumab is given either with docetaxel after doxorubicin and cyclophosphamide or with docetaxel and carboplatin. Finally, a fifth, much smaller, trial has also shown an improvement in disease-free survival after only 9 weeks of trastuzumab given at the start of treatment concurrently with adjuvant chemotherapy.

The magnitude of the benefit, with a reduction in the early risk of recurrence of around 50% in all these trials, has led to the widespread use of trastuzumab as adjuvant therapy. However, this use has been criticised by some of the leading authorities on breast cancer.
because the findings arise from interim analyses, follow-up is short, and significant overall survival benefit has not been shown in any stand alone trial.3 Our aim is to report an analysis of overall survival, together with an updated assessment of disease-free survival, in the HERA trial with a median 2-year follow-up.

Methods

Patients

The study design, eligibility criteria, treatment schedules, monitoring, and statistical analysis plan have been described in detail elsewhere.6 Briefly, the HERA trial is an international intergroup open-label phase III randomised trial involving women with centrally confirmed HER2-positive (immunohistochemistry score 3 or fluorescence in-situ hybridisation positive) early stage invasive breast cancer who had completed local regional therapy and a minimum of four courses of predefined standard adjuvant or neoadjuvant chemo-

therapy. Eligibility criteria included node-positive disease or node-negative disease if the pathological tumour size was larger than 1 cm. Women with locally advanced disease including inflammatory breast cancers were excluded. Women with a left ventricular ejection fraction (LVEF) of less than 55% after completion of chemotherapy and radiotherapy, congestive cardiac failure, or other major cardiac problems8 were excluded.

The ethics review boards at all the participating institutions approved the study protocol and all patients gave written informed consent.

Procedures

After local regional therapy (surgery with or without radiotherapy), patients were randomly assigned to one of three groups: observation only, 8 mg/kg trastuzumab given intravenously by 90 minute infusion as a loading dose followed by 6 mg/kg every 3 weeks for 1 year, or the same schedule of trastuzumab for 2 years (not reported here). Randomisation was done within 7 weeks from day 1 of the last chemotherapy cycle or 6 weeks from the end of radiotherapy or definitive surgery, whichever was the last. A minimisation procedure was used with stratification according to region of the world, age, nodal status, title of chemotherapy, and hormone receptor status together with intention to use endocrine therapy.

When a significant disease-free survival in favour of 1 year’s treatment with trastuzumab over observation alone emerged with a median follow-up of 1 year,9 a protocol amendment was made after recruitment had been completed (except for the last five patients) to allow women in the observation group the option of switching to trastuzumab, irrespective of the interval since randomisation. Women who opted to switch were also given the further choice of a secondary randomisation to 1 year versus 2 years of treatment with trastuzumab.

The primary endpoint of the trial was disease-free survival (defined as time from randomisation to the first occurrence of any of the following events: recurrence of breast cancer at any site; the development of ipsilateral or contralateral breast cancer including ductal carcinoma in situ but not lobular carcinoma in situ; second non-breast malignant disease other than basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; or death from any cause without documentation of a cancer-related event), and the effect of trastuzumab on this endpoint has been described previously.9 Overall survival was a secondary endpoint; other secondary efficacy endpoints included time to recurrence, time to distant recurrence, and safety, including cardiac safety. Criteria for interrupting or stopping trastuzumab therapy on the basis of cardiotoxicity or other side-effects have been previously described.9

Severe congestive heart failure, which does not include death from cardiac causes, was defined as New York Heart Association grade III or IV functional class
confirmed by a cardiologist and a decrease in LVEF of at least 10% below baseline and to less than 50%. Symptomatic congestive heart failure was defined as symptomatic congestive heart failure confirmed by a cardiologist and LVEF less than 50% and a decrease in LVEF of at least 10% from baseline.

A significant LVEF drop was defined as a decrease in LVEF of 10 points or more from baseline to a level below 50 points. A confirmed significant LVEF drop was defined as an asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) significant drop in LVEF which is also confirmed on repeat LVEF assessment about 3 weeks after the first documented drop, or as identified by the cardiac advisory board review.

Statistical analysis
A target accrual of 4482 patients was planned to identify a 23% reduction in the risk of a disease-free survival event with 80% power with a two-sided level of significance of 2.5% for both of the pairwise comparisons: 2 years of treatment with trastuzumab versus observation alone and 1 year of treatment with trastuzumab versus observation alone. 951 endpoint events were required for the final analysis. One interim efficacy analysis was planned after 475 events, the results of which, reviewed by the independent data monitoring committee in April, 2005, resulted in the initial HERA trial publication.

The efficacy analyses were done on an intention-to-treat basis. χ² tests for categorical data and log-rank tests for time-to-event endpoints provided two-sided p values. Kaplan-Meier curves were calculated. Cox proportional hazards regression analysis was used to estimate hazard ratios and 95% CI. Statistical analyses were done with SAS version 8.

In addition to the main intent-to-treat analysis, an analysis that censored women at the time of switching to trastuzumab has also been done to compensate for a potential effect of delayed administration of trastuzumab.

The independent data monitoring committee continues to review data about deaths, compliance, and safety every 6 months. On the basis of a review in March, 2006, they recommended that overall survival results for observation alone versus treatment with trastuzumab for 1 year with a median follow-up of 2 years should be made public. Results for the group of patients treated with trastuzumab for 2 years remain blinded because the comparison with the group treated for 1 year continues to mature. This trial is registered with the European Clinical Trials Database, number 2005–002385–11.

Role of the funding source
The trial was sponsored and funded by Roche. The collection, analysis, and interpretation of the data were done entirely independently, under the auspices of the Breast International Group. The corresponding author led the writing of the paper with input from the HERA executive committee, which includes a Roche representative who was not allowed to influence the paper in any way other than as approved by the executive committee. All authors had access to all the data. The trials’ steering committee had final responsibility to submit the manuscript for publication.

Results
5102 women were recruited between December, 2001, and June, 2005, including 1698 in the observation group and 1703 assigned to receive 1 year of treatment with trastuzumab (figure 1). The baseline characteristics of patient tumours and treatment, updated from the

### Table 1: Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Observation group (n=1698)</th>
<th>1-year trastuzumab group (n=1703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>126 (7%)</td>
<td>127 (7%)</td>
</tr>
<tr>
<td>35–49</td>
<td>752 (44%)</td>
<td>756 (44%)</td>
</tr>
<tr>
<td>50–59</td>
<td>548 (32%)</td>
<td>548 (32%)</td>
</tr>
<tr>
<td>≥60</td>
<td>272 (16%)</td>
<td>272 (16%)</td>
</tr>
<tr>
<td>Prior (neo)adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anthracyclines</td>
<td>101 (6%)</td>
<td>101 (6%)</td>
</tr>
<tr>
<td>Anthracyclines, no taxanes</td>
<td>1156 (68%)</td>
<td>1154 (68%)</td>
</tr>
<tr>
<td>Anthracyclines and taxanes</td>
<td>441 (26%)</td>
<td>448 (26%)</td>
</tr>
<tr>
<td>Menopausal status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>234 (14%)</td>
<td>257 (15%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>692 (41%)</td>
<td>681 (40%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>770 (45%)</td>
<td>765 (45%)</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>843 (50%)</td>
<td>843 (50%)</td>
</tr>
<tr>
<td>Positive</td>
<td>855 (50%)</td>
<td>860 (50%)</td>
</tr>
<tr>
<td>Nodal status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not assessed (neoadjuvant chemotherapy)</td>
<td>178 (10%)</td>
<td>194 (11%)</td>
</tr>
<tr>
<td>Negative</td>
<td>555 (33%)</td>
<td>544 (32%)</td>
</tr>
<tr>
<td>1–3</td>
<td>490 (29%)</td>
<td>486 (29%)</td>
</tr>
<tr>
<td>≥4</td>
<td>474 (28%)</td>
<td>479 (28%)</td>
</tr>
</tbody>
</table>

Data are number (%). Percentages have been rounded. *Status at randomisation, in the observation group, one patient with unknown menopausal status at randomisation and one patient with missing menopausal status.
†One patient with missing nodal status in the observation group.

### Table 2: Site of first disease-free survival event (ITT analysis)

<table>
<thead>
<tr>
<th></th>
<th>Observation group (n=1698)</th>
<th>1-year trastuzumab group (n=1703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>321 (19%)</td>
<td>218 (13%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>90 (5%)</td>
<td>59 (3%)</td>
</tr>
<tr>
<td>Distant event</td>
<td>233 (14%)</td>
<td>152 (9%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>22 (1%)</td>
<td>26 (2%)</td>
</tr>
<tr>
<td>Locoregional event</td>
<td>68 (4%)</td>
<td>45 (3%)</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>9 (0.5%)</td>
<td>7 (0.4%)</td>
</tr>
<tr>
<td>Second non-breast malignant disease</td>
<td>8 (0.5%)</td>
<td>6 (0.4%)</td>
</tr>
</tbody>
</table>

Data are number of events (%). Percentages have been rounded.
original publication, are shown in table 1. 97 (5.7%) patients randomly assigned to observation alone and 58 (3.4%) patients randomly assigned to 1 year of treatment with trastuzumab were lost to follow-up.

As of May 15, 2006, 861 women in the observation group had switched to trastuzumab. In the February, 2006, analysis that censored patients at the time of moving to trastuzumab, the median time that had elapsed from the point of switching was 2.6 months. 705 patients originally randomly assigned to observation alone were censored for disease-free survival and overall survival at the date of switching treatment. Results from the censored analysis are much the same as those from the intention-to-treat analysis.

After a median follow-up of 23.5 months (range 0–48 months), 539 disease-free survival events had been recorded in the two groups. Table 2 shows data about the site of first disease-free survival events. The unadjusted HR for the risk of an event in the trastuzumab group compared with the observation group was 0.64 (95% CI 0.54–0.76; p<0.0001 by the log rank test), which corresponds to an absolute disease-free survival benefit of 6.3% (80.6% vs 74.3%) at 3 years (figure 2A). The HR for the disease-free survival benefit by censored analysis was 0.63 (0.53–0.75; p<0.0001).

149 deaths occurred in the two groups; more deaths occurred in the observation group than in the trastuzumab group (table 2). The unadjusted HR for the risk of death in the trastuzumab group compared with observation alone was 0.66 (0.47–0.91; p=0.0115 by the log rank test); which corresponds with an absolute overall survival benefit of 2.7% (92.4% vs 89.7%) at 3 years (figure 2B). The HR for overall survival by censored analysis was 0.63 (0.45–0.87; p=0.0051).

More distant metastases were reported in the observation group than in the group receiving trastuzumab (table 2); the HR for a distant recurrence in the trastuzumab group compared with the observation group was 0.60 (0.49–0.73; p=0.0001 by log rank test). These results correspond to an absolute time to distant recurrence event-free survival benefit of 6.3% at 3 years (85.7% vs 79.4%; p<0.0001).

There was no evidence of substantial heterogeneity in the relative treatment effect on disease-free survival between subgroups, and there was no evidence of any subgroup in which trastuzumab was seen to be less efficacious than observation alone (figure 3). All CIs overlap the overall result.

The annualised hazard rates for disease-free survival for both groups from the point of randomisation are shown in figure 4. An increase in risk during the first year for the observation group was seen, although this risk falls in the second year and beyond. Trastuzumab suppresses this increased early risk. Although the HR between the two groups decreases beyond the second year, there continues to be less chance of a disease-free survival event with trastuzumab compared with observation alone at all points up to 3 years.

There were more episodes of at least one grade 3 or grade 4 adverse event and of serious adverse events with trastuzumab than in the observation group (p<0.0001; table 3). The only grade 3 or grade 4 adverse event experienced by five or more patients in the observation group was hypertension (n=5). The grade 3 or grade 4 adverse events experienced by five or more patients in the trastuzumab group were hypertension (12), depression (8), diarrhoea (7), congestive cardiac failure (7), vomiting (6), arthralgia (6), cardiac failure (5), hot flush (5), headache (5), and back pain (5).

There was a higher incidence of fatal adverse events in the trastuzumab group than in the observation group.
(p=0·1601; table 3). However, the nature of the fatal adverse events did not seem to have any causal relation with trastuzumab. Of the 172 women who stopped trastuzumab prematurely, 115 (6·8%) stopped because of safety issues, 43 (2·5%) because of refusal, and 14 (0·8%) because of other reasons.

As described previously,13 there was one cardiac death in the observation group and none with trastuzumab. Severe congestive heart failure occurred in more women on trastuzumab than in the observation group (p<0·0001; table 4). Furthermore, a confirmed significant LVEF drop occurred in more women on trastuzumab than in those in the observation group (p<0·0001; table 4). 72 (4·3%) women discontinued trastuzumab because of cardiac problems. A more detailed account of cardiotoxicity in this trial is being prepared.

Discussion

Our results indicate that trastuzumab shows a significant overall survival benefit in early breast cancer over observation alone after chemotherapy. Such a survival benefit after only 2 years of follow-up is unusual in breast cancer trials. For example, adjuvant chemotherapy is of

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**Figure 3:** Exploratory disease-free survival subgroup analysis for 1 year of trastuzumab vs observation
major importance in the treatment of breast cancer and has achieved a long-term survival benefit of 38% for younger women, but the key early trial for such treatment had not begun to show a substantial survival difference after only 2 years of follow-up, nor have any subsequent chemotherapy trials. In the modern era, the same is true for the aromatase inhibitors, widely deemed to be a major development in adjuvant endocrine therapy.  Only tamoxifen—the most successful treatment ever developed for breast cancer—showed a similar survival benefit in such a short period. Thus, the early evidence of an overall survival benefit in the HERA trial after only 2 years of follow-up reinforces the importance of trastuzumab in the adjuvant treatment of women with HER2-positive early breast cancer.

That this survival difference will not be sustained with further follow-up is a possibility; however, there are few precedents for this in work already published on adjuvant therapies for early breast cancer. Furthermore, after the publication of disease-free survival results from HERA with a median follow-up of 12 months, we estimated that the chance of losing statistical significance with longer follow-up was less than 20%. This estimate was calculated on the basis of division of HRs for disease-free survival into a fixed component already observed and a random component, assuming that the risk for the observation group fell to the level seen in the trastuzumab group and follow-up was continued for a further 4 years. Because more events have occurred in the observation group than in the trastuzumab group during the subsequent 12 months, and the HR has fallen for both arms beyond 2 years, the chance of loss of significance remains below 20%. The same arguments pertain for overall survival. The one confounding issue is the recent cross-over of patients in the control group to trastuzumab; it could be that, with longer follow-up, a significant overall survival benefit might be maintained in the censored analysis, but not the intention-to-treat analysis because of this crossover.

The NSABP B-31 trial compared treatment with trastuzumab for 1 year starting concurrently with four courses of paclitaxel after a combination of doxorubicin and cyclophosphamide with the same chemotherapy schedule alone. When data from this trial were combined with results from two similar groups in the NCCTG 9831 trial, a significant overall survival benefit was noted after a median follow-up of 2 years and with an HR of 0.67 in favour of trastuzumab, which is much the same as that recorded here. The consistently high reductions in the risk of breast cancer recurrence of around 50% seen in these two trials, together with that noted in a fourth large adjuvant trastuzumab trial, BCIRG 006, suggest that these results will probably translate into stand-alone survival gains in the near future.

Our exploratory subgroup analysis suggests that all subgroups of women seem to benefit from trastuzumab. In particular, there is so far no significant difference in efficacy between women with node-positive and node-negative disease, nor between those receiving adjuvant compared with neoadjuvant chemotherapy. Whether different patterns of treatment effect emerge for some subgroups with further follow-up remains to be seen.

That the risk of cardiotoxicity remains low is encouraging, and the absence of any substantial evidence of an increase in cumulative cardiotoxicity beyond 1 year has also been shown in the B-31 trial. The overall risk of severe congestive heart failure reported here is lower than

<table>
<thead>
<tr>
<th>Table 3: Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation</strong> (n=1708)</td>
</tr>
<tr>
<td>Patients with one or more grade 3 or 4 adverse event</td>
</tr>
<tr>
<td>Patients with one or more serious adverse event</td>
</tr>
<tr>
<td>Fatal adverse event</td>
</tr>
<tr>
<td>Treatment withdrawals</td>
</tr>
</tbody>
</table>

Data are number of events (%). Percentages have been rounded. NA=not applicable. *271 patients with at least one adverse event after moving to trastuzumab are not included. †Treatment group vs observation group. ‡Cardiac failure, suicide, unknown cause of death. §Cerebral haemorrhage, cerebrovascular accident, sudden death, appendicitis, intestinal obstruction, unknown cause of death after a road accident, pulmonary carcinomatous lymphangitis, two unknown. The intestinal obstruction occurred after a second occurrence of non-breast malignant disease.

<table>
<thead>
<tr>
<th>Table 4: Cardiac safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation</strong> (n=12708)</td>
</tr>
<tr>
<td>Cardiac death</td>
</tr>
<tr>
<td>Severe congestive heart failure (NYHA III and IV)†</td>
</tr>
<tr>
<td>Symptomatic congestive heart failure‡</td>
</tr>
<tr>
<td>Confirmed significant LVEF drop§</td>
</tr>
<tr>
<td>Trastuzumab discontinued due to cardiac problems</td>
</tr>
</tbody>
</table>

Data are number of events (%). Percentages have been rounded. NA=not applicable. *Treatment group vs observation group. †Not including cardiac death. ‡Not including severe congestive heart failure but not including cardiac death. §Asymptomatic or mildly symptomatic.
that reported in the B-31 trial (0.6% vs 4.1%), as is the proportion of women who stopped treatment because of cardiac problems (4.3% and, of evaluable trastuzumab patients, 15.6%). These findings could be a result of the longer time interval between stopping chemotherapy with anthracyclines and starting trastuzumab in the HERA trial than in B-31, or the requirement of a postchemotherapy LVEF of 55% or more before enrolment in HERA, or both. In this context, one should note that the incidence of cardiotoxicity in the anthracycline followed by trastuzumab group of the BCIRG 006 trial was much the same as that in B-31, but substantially lower in the trastuzumab group that did not receive anthracycline. Thus far, the only data for cardiotoxicity associated with trastuzumab continued for more than a year is in metastatic breast cancer: in one recent study involving 218 patients with a median treatment duration of 21 months and a median follow-up of 32.6 months, 49 (28%) experienced a cardiac event and 19 (10.9%) grade 3 cardiotoxicity. However, most patients improved after withdrawal of trastuzumab and appropriate treatment, and there was only one cardiac death. One should note that these patients would often be less fit than those in HERA and other adjuvant trials because of their metastatic disease, and some would have received a greater cumulative dose of anthracycline chemotherapy.

Two major questions remain for adjuvant trastuzumab. The first is whether trastuzumab started concurrently with taxane chemotherapy (as in the USA trials) is better than trastuzumab starting sequentially after completion of chemotherapy (as here). The NCCTG N9831 trial addresses this issue—this trial includes a third group given sequential trastuzumab. Preliminary data suggest that sequential treatment might be less effective than concurrent treatment, but this was an unplanned comparison with low statistical power, and longer follow-up is needed for confirmation. In this context, one should note that the median time from diagnosis of breast cancer to starting trastuzumab in the HERA trial was 8.5 months, which could have affected efficacy or resulted in some patients with very high-risk disease relapsing before the opportunity arose to enter the trial.

The second issue concerns the duration of trastuzumab treatment. A third group in the HERA trial, in which patients are treated with trastuzumab for 2 years, addresses this issue. That trastuzumab suppresses the increased early hazard rate seen in the observation group during the first year, but has less effect thereafter, might be of relevance (figure 4). This finding supports our decision to compare 2 years of treatment with trastuzumab with 1 year of treatment. However, one should also note that a small Finnish trial involving 232 women has reported a disease-free survival benefit with 9 weeks of trastuzumab treatment given concurrently with chemotherapy at the start of treatment. The HR from this trial (0.42; 95% CI 0.21-0.83; p=0.01) is within the same range as those recorded in trials of trastuzumab treatment for 1 year, but the small number of women involved, together with the wide CI, require confirmatory data.

The data presented here confirm earlier reports that trastuzumab, a rationally designed biological therapy that is targeted against a specific amplified gene (HER2) and its over-expressed receptor protein, is of benefit to women with HER2-positive breast cancer when given after completion of adjuvant chemotherapy. The survival benefit that has emerged over such a short period emphasises the potential of this approach and underlines the importance of developing further specific targeted therapies in breast and other cancers.

Contributors
M Untch was a member of the executive committee and participated in the conduct of the trial and the preparation of the manuscript. M Kaufmann participated in the HERA study with the German GABG-Study Group, of which he is chairman and participated in the conduct of, and recruitment to, the HERA trial as a key investigator. R Bell participated in the concept, management, and conduct of the HERA trial as a member of the executive committee, steering committee, and as an investigator. R I Lopez participated in the conduct of, and recruitment to the HERA trial as a key investigator. M Procter was involved in the statistical analysis. P Mallmann participated in the conduct of, and recruitment to the HERA trial as a key investigator. K Gelmon participated as an investigator, as the representative of the National Cancer Institute of Canada–Clinical Trials Group (NCIC-CTG), and on the trial committee, and contributed to the final version of the manuscript. E Wist was principal investigator in Norway. J Bergh took part in the study planning, was a member of the steering committee, and made comments on a draft version of the manuscript. G Mariani was principal investigator for the Michelangelo group. M J Piccart-Gebhart participated in the design, conduct, and analysis of the trial as chief investigator and chairman of the steering committee. P Sánchez-Rovira took part in the conduct of recruitment to the HERA trial as a key investigator. I Smith took part in the planning and execution of the HERA trial, and wrote the first and final drafts of this manuscript. N Wiltken was a member of the steering committee and took part in the writing of the manuscript. A Goldhirsh took part in the study design, conduct, and interpretation of the results. R Coleman took part as an investigator, was leader of the participating FORTI collaborative group, and was a member of the HERA steering committee. A Wardley participated in the conduct of, and recruitment to the HERA trial as a key investigator and helped write the manuscript. S Guillaume was the intergroup and monitoring coordinator. N Harbeck was a member of the German HERA steering committee, and took part in the design, revision, and amendment of the study design. She was a local principal investigator, involved in patient recruitment. J Baselga took part in the design, conduct, patient accrual, and interpretation of the data as a member of the executive committee and as an investigator. M Dowsett was a member of the executive committee and co-chair of the translational research committee. D Cameron was an investigator in the HERA trial, and was a member of the steering and executive committees. As the executive committee member representative for all Breast International Group collaborative groups, he was involved in the day-to-day running of the trial. R D Gelber took part in the design, conduct, analysis, and reporting of the trial in his role as senior statistician. He directed statistical analyses and contributed to the writing of the manuscript. A Feyerislova was a coordinator and reviewed the published data. All authors saw and approved the final version of the manuscript.

Conflict of interest statement
M Untch has received speaker’s honoraria from Roche. R Bell has served as an adviser to Roche. In the past 2 years, K Gelmon has been on advisory boards and has received honoraria from Roche, sanofi aventis, Bristol-Myers Squibb, AstraZeneca, Novartis, Pfizer, Lilly, Amgen, Genetech, and GlaxoSmithKline. She has also received research grants from Roche. J Bergh’s research group has received research support from Roche, and J Bergh has taken part in advisory boards for Roche. M J Piccart-Gebhart has served on an advisory board on Aromasin, has received consulting fees from GlaxoSmithKline, and an unrestricted educational grant from Roche.
on behalf of the Breast International Group. I Smith has received honoraria from Roche for lectures and attendance at advisory boards. N Wäckèn has received honoraria from Roche for educational presentations. A Goldhirsch has received honoraria and travel expenses from Roche. A Wardley has received honoraria from Roche for speaking engagements including the use of adjuvant trastuzumab. He has also received travel grants from Roche and worked and done a small amount of advisory work for Roche. N Harbeck has received speaker's honoraria from Roche and received the investigators fee from the German Breast Group. J Baselga is a member of the Roche hercepthin advisory board. M Dowsett has received fees for attending advisory board meetings and giving ad-hoc lectures for Roche. D Cameron has received research funding from Roche (separate to that for the conduct of this trial), and has also received honoraria and consultancy fees from Roche. R D Gelber declares that Roche provided financial support for the Breast European Adjuvant Study Team (BreAST), which in turn provided him with partial salary support. A Feyerisen is an employee of Roche. R Coleman, M Kaufmann, S Guillaume, M Procter, P Mallmann, E Wist, G Martani, P Sanchez-Rovira, and R I Lopez declare that they have no conflict of interest.

Acknowledgements

We thank Donna Saffery for her invaluable skill and expertise in the preparation of this manuscript.

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13. HERA Study Team. Trastuzumab (H: Herceptin®) following adjuvant chemotherapy (CT) significantly improves disease-free survival (DFS) in early breast cancer (BC) with HER2 overexpression: the HERA Trial. 28th Annual San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 7–10, 2005. Abstract 11.
Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study

Bridget Wilcken, Marion Haas, Pamela Joy, Veronica Wiley, Meredith Chaplin, Carly Black, Janice Fletcher, Jim McGill, Avihu Boneh

Summary

Background Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the disorder thought most to justify neonatal screening by tandem-mass spectrometry because, without screening, there seems to be substantial morbidity and mortality. Our aim was to assess the overall effectiveness of neonatal screening for MCAD deficiency in Australia.

Methods We identified MCAD-deficient patients from a total population of 2495 000 Australian neonates (810 000 screened) born between April 1, 1994, and March 31, 2004. Those from a cohort of 1995 000 (460 000 screened) were followed up for at least 4 years, and we recorded number of deaths and severe episodes, medical and neuropsychological outcome, and hospital admissions within the screened and unscreened groups.

Findings In cohorts aged at least 4 years there were 35 MCAD-deficient patients in those not screened (2.28 per 100 000 total population) and 24 in the screened population (5.2 per 100 000). We estimated that patients with this disorder in the unscreened cohort remained undiagnosed. Before 4 years of age, three screened patients had an episode of severe decompensation (including one neonatal death) versus 23 unscreened patients (including five deaths). At the most conservative estimate, relative risk of an adverse event was 0.44 (95% CI 0.13–1.45). In the larger cohort the relative risk (screened vs unscreened) of an adverse event by age 2 years was 0.26 (95% CI 0.07–0.97), also a conservative estimate. 38 of 52 living patients had neuropsychological testing, with no suggestions of significant differences in general cognitive outcome between the groups.

Interpretation Screening is effective in patients with MCAD deficiency since early diagnosis reduces deaths and severe adverse events in children up to the age of 4 years.

Introduction Neonatal screening by tandem-mass spectrometry has burgeoned in the past decade. This type of screening is universal in Australia and widespread in many other countries, but despite preliminary studies, the overall effectiveness of this expanded screening has not been clearly shown.

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the disorder most frequently diagnosed by neonatal screening with tandem-mass spectrometry, together with phenylketonuria. The disorder results in decreased ability to withstand catabolic stress. Patients risk hypoketotic hypoglycaemia, which leads to coma or death during intercurrent illness. In reports of patients diagnosed clinically with the disorder, 20–25% died, usually during a first episode, and a further 20% sustained neurological damage. A retrospective neonatal-screening study of 100 000 stored samples reported one in eight patients had died and only one survivor had learning difficulties. Some individuals with MCAD deficiency could remain healthy, with no episodes of decompensation. After diagnosis, management plans to avoid catabolism during fasting or illness generally prevent adverse episodes. This success with intervention implies the probable advantage of newborn baby screening for MCAD deficiency, which is the disorder thought to most justify neonatal screening by tandem-mass spectrometry. However, there have been only very few reports of outcome after screening.

Data for patients’ outcome after screening for rare disorders are scarce and difficult to interpret because of small numbers, variable definitions and phenotypes of individual disorders, increased detection by screening, different mutation range in screened and unscreened patients, and often insufficient follow-up. We have therefore done a nationwide study in Australia of the overall effectiveness of neonatal screening by tandem-mass spectrometry.

Methods

Patients We obtained data from all five newborn baby screening laboratories, all six biochemical genetics laboratories, and all five genetic metabolic clinical services in Australia, to identify patients with MCAD deficiency born between April 1, 1994 and March 31, 2004. The institutional ethics committees of all six centres approved this study, and written informed consent was obtained from parents of the patients for data access and additional testing.

There were three main patient groups: clinically diagnosed historical patients born between April 1, 1994 and March 31, 1998; clinically diagnosed contemporaneous patients born between April 1, 1998 and March 31, 2002 in states not screening at the time; and babies born between April 1, 1998 and March 31, 2002 who were tested by neonatal screening. Additionally, we recorded deaths and severe episodes of metabolic decompensation.

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in all screened and unscreened babies with MCAD deficiency, born between April, 2002 and March, 2004.

**Procedures**

Neonatal screening by tandem-mass spectrometry was done with dried blood samples obtained between 48 and 72 h of age. MCAD deficiency was suspected in babies whose initial blood octanoylcarnitine (C8) concentration was greater than the concentration predetermined by individual laboratories, (≥1 μmol/L) and whose C8: decanoylcarnitine ratio was greater than one. These samples also had analysis of the common disease causing 985A→G mutation. Low free-carnitine concentrations triggered further investigation in all patients irrespective of C8 concentrations. MCAD deficiency was confirmed by an isolated increase in straight medium-chain acylcarnitines in plasma and increased urinary hexanoylglycine concentrations (both criteria were present in all living patients) or two copies of the common ACADM (acyl-coenzyme A dehydrogenase, C-4 to C-12 straight chain) gene mutation. In clinically diagnosed patients, diagnosis was principally by enzymatic analysis and increased urinary hexanoylglycine concentration.

Parents of babies diagnosed with MCAD deficiency were given a written management plan, which included maximum length of overnight fasts by age, a sick-day regimen for minor illness, and instructions to telephone the metabolic physician for advice during illness. All parents had a letter for emergency departments, to expedite treatment and administration of intravenous glucose. Carnitine treatment was not routine.

Hospital admissions, episodes of decompensation, other complications, and death were recorded from the medical case-notes and after discussion with physicians treating genetic metabolic disease. A questionnaire to families recorded admission to other centres. A severe episode was defined as an emergency admission, with need for intravenous therapy, and not a prophylactic admission. For young patients (born April, 2002–March, 2004) only severe episodes and death were recorded.

The Woodcock-Johnson III (WJ III) tests of cognitive abilities and achievement were used to assess cognitive abilities, and academic achievement, across a wide range of ages (2–90 years). Vineland adaptive behaviour scales (VABS) were used to measure the child’s adaptive functioning across communication, daily living, and socialisation domains.

**Statistical analysis**

To estimate effectiveness of screening on rates of death and severe episodes before 4 years of age, we assumed that the birth incidence in the unscreened cohorts would be the same as that seen in the screened group. The undiagnosed patients in the unscreened cohorts could have been never symptomatic, could have been as symptomatic as those diagnosed, or might have occupied some midpoint. We did not consider the extreme position that all undiagnosed patients might have died or had severe episodes. The relative risk of adverse events was analysed, with 95% CIs and an absolute risk of adverse events provided.

We used a bigger sample (from April, 1994, to March, 2004) to compare actual rates of death or a severe episode by 2 years of age, and the relative risk was analysed with 95% CIs. A series of independent samples t tests were done to compare neuropsychological outcome variables in the screened group with those in the unscreened group and fully tested with partly tested groups.

Because admissions data were not normally distributed, we used non-parametric tests (Mann-Whitney U tests) to compare admission rates and length of stay per admission in the screened and unscreened groups.

**Role of the funding source**

This study was supported by a grant from The National Health and Medical Research Council, Australia, which played no part in study design, collection, analysis or interpretation of data, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

**Results**

For those with at least 4 years follow-up, (1994–2002 cohorts) the median age at diagnosis was substantially later in the unscreened patients than in those who were screened (table 1). Five (14%) unscreened patients clinically

<table>
<thead>
<tr>
<th>Number of births</th>
<th>Clinical diagnoses</th>
<th>Family screening diagnoses</th>
<th>Diagnosis by age 4 years (total diagnoses at any age)</th>
<th>Total diagnoses per 100 000 population</th>
<th>Number of deaths by age 4 years (total at any age)</th>
<th>Number who had severe episode by age 4 years (total at any age)</th>
<th>Median age at diagnosis of proband (range) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unscreend 1994–98</td>
<td>1 002 000</td>
<td>13</td>
<td>6</td>
<td>10 (19)</td>
<td>1·9</td>
<td>2 (3)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Unscreened 1998–2002</td>
<td>533 000</td>
<td>12</td>
<td>4</td>
<td>16 (26)</td>
<td>3·0</td>
<td>3* (3)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>All unscreened</td>
<td>1 535 000</td>
<td>25</td>
<td>10</td>
<td>26 (35)</td>
<td>2·3</td>
<td>5 (6)</td>
<td>18 (20)</td>
</tr>
<tr>
<td>Screened 1998–2002</td>
<td>460 000</td>
<td>...</td>
<td>...</td>
<td>24 (24)</td>
<td>5·2</td>
<td>11 (2)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*2/3 neonatal deaths: †including neonatal deaths. ‡1/1 neonatal death.

Table 1: Medium-chain acyl-CoA dehydrogenase deficiency cases in screened and unscreened cohorts, age at diagnosis, and numbers of cases with severe adverse events by 4 years of age.
diagnosed and four (11%) siblings diagnosed by family screening were older than 4 years of age at diagnosis. The unscreened cohorts included three (9%) patients diagnosed after a younger sibling had been detected by newborn screening. The total diagnoses in the screened cohort was just over double that in unscreened babies; no false-negative screening results are known. The 1998–2002 overall false-positive rate was 0·01%, and the positive predictive value was 42%. Based on MCAD deficiency frequency in the screened population, the expected number of patients with the disorder in the unscreened group was 80 (95% CI 52–121). The results of analysis for the common 985A→G mutation in the 1998–2002 cohort study were available for 21 (88%) of 24 screened patients (12 homozygous for 985A→G, allele frequency 76%) and for 20 (80%) of the 25 unscreened patients (16 homozygous 985A→G, allele frequency 90%). Only one patient had no copy of the common mutation. (Data from one state, New South Wales, were reported in a study of genotype and biochemical phenotype correlations. This cohort included all 17 patients from New South Wales included in the main study). Two patients carried one copy of the mild mutation 199C→T, neither of whom had any hospital admissions or events attributable to MCAD deficiency.

In the unscreened 1994–2002 cohorts, there were six (17%) deaths, at age 3 days (two babies), and at 17, 19, 47, and 93 months, all apparently secondary to MCAD deficiency. In the 24 patients diagnosed by screening there was one death, at 3 days of age, after poor feeding, then irrecoverable coma. The newborn screening sample taken post mortem was diagnostic (octanoylcarnitine concentration 34 μmol/L) and the baby was homozygous for the common 985A→G mutation. A 6-year-old sibling, who had been admitted twice for prostration during intercurrent illness, was reported to be affected. In all deaths, the diagnosis was made post mortem, and only one child had had a previous admission.

In the unscreened 1994–2002 cohorts, 20 (57%) patients had a severe episode of decompensation that led to diagnosis, 18 (90%) of whom were less than 4 years of age. In the 24 patients diagnosed by screening there was one death, at 3 days of age, after poor feeding, then irrecoverable coma. The newborn screening sample taken post mortem was diagnostic (octanoylcarnitine concentration 34 μmol/L) and the baby was homozygous for the common 985A→G mutation. A 6-year-old sibling, who had been admitted twice for prostration during intercurrent illness, was reported to be affected. In all deaths, the diagnosis was made post mortem, and only one child had had a previous admission.

Patients who died or were known to have had a severe decomposition in unscreened cohorts were 1·5×10⁻⁵ of the population, versus 0·65×10⁻⁵ in the screened cohorts (relative risk [RR] 0·44; 95% CI 0·13–1·45). This result is the most conservative estimate of the true picture, and assumes that all patients never diagnosed were completely asymptomatic. A liberal estimate (same rate of severe adverse episodes in undiagnosed as diagnosed patients, including siblings diagnosed by family screening) and a midpoint estimate between these two extremes would both show significantly fewer severe adverse events in the screened population than in the unscreened—three versus 53 events (0·19; 0·06–0·60) for the liberal estimate, and three versus 38 events (0·26; 0·08–0·85) for the midpoint estimate.

We identified 17 further MCAD-deficient patients by screening 350 000 patients between April, 2002, and March, 2004 (more states in Australia were by then screening) and these patients were all healthy between 2 and 4 years of age (figure). In the same 2 years, five patients were identified among 150 000 patients, one of whom died aged 2 days, and three others had severe events. Table 2 shows the total number of patients studied to 2 years of age (born from April, 1994 to March, 2004), and number of deaths of less severe adverse events. The relative risk of death or a severe event by 2 years of age in screened patients (the most conservative estimate) was 0·26 (95% CI 0·07–0·97). The absolute risk of death or a severe event by 2 years of age was 5% (two of 41) for screened patients, and 55% (22 of 40) for unscreened patients diagnosed clinically or by family testing.

Of the 24 children diagnosed by screening between 1998, and 2002, ten (42%) were admitted in their first 4 years, generating 43 admissions, compared with 22 (63%) of the 35 unscreened children, who generated 74 admissions (table 3). Overall, the rate of admission for the screened group was 1·8 per child and for the unscreened group 2·1 per child. On a population basis the total admissions were, however, significantly higher for the screened cohort (p=0·038), and all but one of these were prophylactic admissions during intercurrent illness.  

![Figure: Birth cohorts from April, 1994 to March, 2004, unscreened and screened, and the number of babies diagnosed with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in each cohort](./image.png)
illness or poor feeding. The length of admission was shorter for screened patients (mean 2.35 vs 2.95 days) but this was not significant (U=1456, p=0.44).

We tested 38 (73%) of 52 living patients for neuropsychological outcomes. Of these, 25 (13 screened) had full testing and a further 13 (six screened) were tested only by VABS. 14 could not be tested—four patients were geographically distant, four refused, and six were not able to be contacted for this part of the study. Mean general intellectual ability scores by the WJ III testing were 103.6 (SD 11.7) for screened and 104.9 (14.8) for unscreened patients (p=0.809). Only two of 25 patients (one screened) had a score greater than one SD below the mean. Adaptive behaviour composite scores were also similar—19 screened patients had a mean score of 101.6 (17.8), versus 98.4 (14.6) for 19 unscreened patients (p=0.547). Patients without cognitive testing had similar adaptive behaviour scores to those tested (data not shown).

The detailed results of neuropsychological testing will be presented elsewhere.

**Discussion**

We have identified all patients diagnosed with MCAD deficiency in Australia, who are now at least 2 years of age. From a population of almost 2.5 million newborn babies, 32% were screened for the disorder. One patient in the screened cohort died on day 3 (before screening), and all remaining patients are well. No cases are known to have been missed by screening. More patients in the unscreened cohort died or had a severe adverse event by 2 years of age than in the screened cohort, but we detected no difference in cognitive outcome in surviving screened or unscreened children in the older cohorts.

There are several distinct advantages to our study. First, we are confident about complete ascertainment of our patient population, because all laboratories that provide neonatal screening and biochemical genetic services, and all genetic metabolic clinical services in Australia collaborated in this study. Second, there was an agreed definition for MCAD deficiency, on the basis of our findings in clinically diagnosed cases over the past 20 years, and published reports. In some other reports there have not been clear definitions of what was included as MCAD deficiency, which could in part be responsible for the lower birth rate we noted compared with the rate others have reported. Additionally, our study adds in that we report outcomes in patients up to 4 years of age in a screened cohort. Previous studies reported results for children of mixed ages, many of whom had shorter follow-up. No other study has documented numbers of hospital admissions, nor have outcomes been reported with use of a validated measure of cognitive ability.

There were two main factors that complicated the interpretation of our results. First, the higher frequency of MCAD deficiency recorded by screening, as we previously reported, makes comparison between the clinical phenotype of screened and unscreened patients somewhat difficult. For the analysis we modelled different clinical situations for the missing patients in the unscreened groups—ie, those who were never diagnosed with the disorder. The first model assumes that all were asymptomatic, which is a very conservative and unlikely

<table>
<thead>
<tr>
<th>Screened (n=24)</th>
<th>Unscreened (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children ever admitted *</td>
<td>Number of admissions (range per child)</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>&lt;1 year 5 (21%)</td>
<td>18 (1-8)</td>
</tr>
<tr>
<td>1 to &lt;2 years 6 (25%)</td>
<td>17 (1-9)</td>
</tr>
<tr>
<td>2 to &lt;3 years 3 (13%)</td>
<td>3 (1-1)</td>
</tr>
<tr>
<td>3 to &lt;4 years 2 (8%)</td>
<td>5 (1-4)</td>
</tr>
<tr>
<td>Total 10 (42%)</td>
<td>43</td>
</tr>
</tbody>
</table>

*The proportion of children alive at the beginning of a period who were admitted to hospital.

Table 2: Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency diagnosed by the age of 2 years in babies born in Australia from April, 1994 to March, 2004

Table 3: Number of hospital admissions and length of stay for cohorts born April, 1994 to March, 2002
estimate. In this case there was no statistically significant
difference in the occurrence of death or a severe
decompensation in screened and unscreened patients to
the age of 4 years. In reality, we are certain that some
unscreened patients experienced severe events, but
remained undiagnosed. This notion was proven in one of
the three older siblings, who had been very symptomatic,
but was diagnosed only because of a neonatal screening
diagnosis in a younger brother. There could also have been
patients with MCAD deficiency who died undiagnosed.
Although pathologists were alerted to the implications of
hepatic steatosis, appropriate further investigations are
only now becoming routine.

The second model assumes the rate of adverse events to
be similar to those in the unscreened cohorts diagnosed
clinically or by family study, and those never diagnosed.
The third model assumes a midpoint between these two
models. In both of these two models there were significant
differences seen, which favour newborn screening. When
we analysed the larger cohort, which included infants with
MCAD deficiency aged 2–4 years, there were substantially
more patients who had died or had a severe adverse event
in the unscreened than the screened group.

A second complication was a consideration of how
comparable were patients diagnosed clinically or by
screening in terms of genotype and biochemical phenotype.
Patients diagnosed by neonatal screening had a different
profile of mutations in the ACADM gene, which could
have included a group with milder disease. Before neonatal
screening, around 80% of patients with symptoms were
homozygous for the common mutation 985A→G and a
further 18% were heterozygous for this mutation and
another. In our screened patients the allele frequency for
this mutation was only 76%, although all but one screened
patients diagnosed with MCAD deficiency carried at least
one copy.

A different mutation profile has also been documented
in other neonatal screening programmes in the USA and
Germany. All our patients had altered biochemistry, which
indicates changed function, and biochemical hall-
marks of pronounced enzyme deficiency. Our definition of
the disorder for diagnosis by neonatal screening is based
on our findings in symptomatic, clinically diagnosed
patients. However, there is no doubt that MCAD deficient
patients diagnosed by newborn baby screening do include
some patients with more marginal biochemical changes.
With further screening programmes worldwide the
diagnosis of MCAD deficiency could be better refined.

Population demographics are probably an important
factor that contributes to the varying rate of deficiency
reported from screening centres and the lower rate we
recorded. In some 10% of births in our study, both parents
were from east Asia, where the disorder is believed to be rare.
Only one patient in our study had a parent from east
Asia (Indonesia); he was a compound heterozygote for
uncommon mutations, which Waddell and colleagues have
reported.

Previous studies of neonatal screening outcome have
not taken into account the probable missing patients,
who were never diagnosed, in unscreened cohorts or
have used a retrospectively screened group from
another country as a control group, although this study
did confine the comparison to patients homozygous for
the common 985A→G mutation. Otherwise there has
been no clear diagnosis of MCAD deficiency, and
management protocols might have differed from ours,
so we are unclear how comparable other studies are. In
the Bavarian study there were two non-neonatal deaths,
both at 10 months, in the screened cohort. One of these
patients also had congenital adrenal hyperplasia, which
could have contributed to outcome. Non-neonatal
deaths have also been reported in two patients diagnosed
by screening in Pennsylvania, USA whereas previously
deaths after diagnosis were assumed to be very rare. Our
patients and their primary-care physicians were
given a written management plan, and encouraged to
telephone a metabolic physician for advice at any time,
which could have helped to avoid severe events.
However, four of our 81 patients (5%) died in the first
72 h. Such deaths cannot be avoided by neonatal
screening, since the process includes an overnight
assay at a central laboratory, with samples not valid in
Australia unless taken after 24 h.

Previously, we and others reported that around 20% of
patients who survived had some neuropsychological
impairment, although a major review on this topic
suggested fewer than this proportion. By contrast, in
our study both unscreened and screened patients were
progressing well. Since fully tested children were as young
as 4 years of age, some could later develop subtle
problems such as specific learning difficulties, although
emergency care is now more readily available and
treatment more timely and skilled than previously.

In summary, we have shown that screening for
MCAD deficiency provides a benefit, with reduction
in mortality and morbidity in screened patients up to
4 years of age, compared with unscreened patients, but
no differences in neuropsychological functioning in
survivors.

Contributors
B Wilcken conceived the study, participated in data collection, analysis
and interpretation, wrote the first draft of the report, and approved the
final version. M Haas, P Joy, and V Wiley participated in designing the
study, and in data collection, analysis and interpretation, in writing the
report, and approved the final version. M Chaplin, C Black, J McGill,
J Fletcher, and A Boneh participated in data collection, analysis and
interpretation, and approved the final version of the report. A Boneh also
participated in writing the report.

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

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References
Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study

Mary Jane Platt, Christine Cans, Ann Johnson, Geraldine Surman, Monica Topp, Maria Giulia Torrioli, Inge Krageloh-Mann

Summary

Background The risk of cerebral palsy, the commonest physical disability of children in western Europe, is higher in infants of very low birthweight (VLBW)—those born weighing less than 1500 g—and those from multiple pregnancies than in infants of normal birthweight. An increasing proportion of infants from both of these groups survive into childhood. This paper describes changes in the frequency and distribution of cerebral palsy by sex and neurological subtype in infants with a birthweight below 1000 g and 1000–1499 g in the period 1980–96.

Methods A group of 16 European centres, Surveillance of Cerebral Palsy in Europe, agreed a standard definition of cerebral palsy and inclusion and exclusion criteria. Data for children with cerebral palsy born in the years 1980–96 were pooled. The data were analysed to describe the distribution and prevalence of cerebral palsy in VLBW infants. Prevalence trends were expressed as both per 1000 livebirths and per 1000 neonatal survivors.

Findings There were 1575 VLBW infants born with cerebral palsy; 414 (26%) were of birthweight less than 1000 g and 317 (20%) were from multiple pregnancies. 1426 (94%) had spastic cerebral palsy, which was unilateral (hemiplegic) in 336 (24%). The birth prevalence fell from 60·6 [99%CI 37·8–91·4] per 1000 liveborn VLBW infants in 1980 to 39·5 (28·6–53·0) per 1000 VLBW infants in 1996. This decline was related to a reduction in the frequency of bilateral spastic cerebral palsy among infants of birthweight 1000–1499 g. The frequency of cerebral palsy was higher in male than female babies in the group of birthweight 1000–1499 g (61·0 [53·8–68·2] vs 49·5 [42·8–56·2] per 1000 livebirths; p=0·0025) but not in the group of birthweight below 1000 g.

Interpretation These data from a large population base provide evidence that the prevalence of cerebral palsy in children of birthweight less than 1500 g has fallen, which has important implications for parents, health services, and society.

Introduction Cerebral palsy is the commonest disability of children in western Europe, with a birth prevalence of about two cases per 1000 livebirths. Studies of the patterns of cerebral palsy in relation to birthweight show that infants of very low birthweight (VLBW)—ie, less than 1500 g—are between 20 and 80 times more likely to have cerebral palsy than infants of birthweight more than 2500 g. Data from Sweden, Australia, and the UK suggest that the prevalence of cerebral palsy among VLBW infants increased during the 1980s, and data from the northeast of England and the USA, seem to show a rise in severity of cerebral palsy in this group of infants. Studies from Denmark, Oxford, UK, Sweden, and Liverpool, UK suggest that the prevalence of cerebral palsy in VLBW infants has begun to fall, although studies from other centres in Australia, and Atlanta, GA, USA, have not shown a fall. Decreased neonatal mortality of VLBW infants is related to improved care of premature infants and has also changed perceptions of viability of these infants. There has also been an increase in multiple births over this period. These changes have resulted in a rise in the absolute number of VLBW infants at risk of cerebral palsy.

Previous studies describing the distribution, determinants, and clinical picture of cerebral palsy in VLBW infants included small numbers of infants, which reduced the precision of results and did not allow detailed investigation of the various subtypes of cerebral palsy. Even less information is available about the subset of infants who weighed less than 1000 g at birth (whose survival also improved substantially since the 1980s). Thus, little is known about the distribution of cerebral palsy by sex, severity, or neurological subtype in such small infants. Birthweight-specific differences might reflect different origins; very immature infants could be more vulnerable to white-matter damage of different extent and topography than more mature infants and could also be less susceptible to primary cortical damage.

A collaborative network of cerebral palsy registers and surveys, Surveillance of Cerebral Palsy in Europe (SCPE), was established in 1998. The 16 European centres in this network have developed a standard definition of cerebral palsy (with inclusion and exclusion criteria), and have agreed definitions and descriptions of affected children. On the basis of these definitions, the prevalence of cerebral palsy among VLBW infants was calculated as 72·6 per 1000 neonatal survivors (children who survived for longer than 1 month after birth), compared with a prevalence of 1·2 per 1000 among infants of birthweight more than 2500 g. The 16 centres provide a large study population, which gives an opportunity to examine the distribution, determinants, and clinical patterns of cerebral palsy among VLBW children.
This collaboration showed a non-significant downward trend in the overall prevalence of cerebral palsy at the end of the 1980s,1 and with reports from individual centres suggesting a reduction in prevalence and severity of cerebral palsy among VLBW infants,4,6 the hypothesis that the birthweight-specific prevalence of cerebral palsy among VLBW infants will have remained stable or fallen further during the 1990s, is reasonable. This paper aims: to describe the epidemiology of cerebral palsy in VLBW infants in detail, looking at those of birthweight less than 1000 g separately from infants of birthweight 1000–1499 g, where possible; to examine changes in the prevalence of cerebral palsy in these two groups over the period 1980–96; and to identify whether the two birthweight groups differ in terms of sex, severity, or neurological subtype.

**Methods**

The collaboration of centres with data from population-based studies on the prevalence of cerebral palsy in nine European countries has previously been described.1 Case definitions and inclusion and exclusion criteria were agreed in these centres, and data for children with cerebral palsy from 16 European surveys and registers were pooled in a common SCPE dataset. Cerebral palsy was defined as a permanent, but not unchanging, disorder of movement or posture, or both, and of motor function, caused by a non-progressive interference, lesion, or abnormality in the brain. Children with hypotonia but no other neurological signs were excluded.1 Since motor disorders in young children generally change over time, some children with severe cerebral palsy have the diagnosis confirmed within the first year of life, but others, especially those less severely affected, might not have the diagnosis confirmed until later in childhood.

Most population-based cerebral palsy surveys and registers do not include children until they are at least 3 years old to ensure full ascertainment. This approach also means that the clinical picture of each child with cerebral palsy can be described accurately (eg, whether the child can walk, the degree of intellectual and other associated impairment). Affected children were at least 4 years old at the time of inclusion in the SCPE database. This analysis included children who were born with cerebral palsy between 1980 and 1996, whose birthweight was known, and whose mothers lived in an area covered by the survey or register at the time of birth or registration of birth. Children with cerebral palsy linked to a specific event or episode that happened after 28 days of age (postneonatal origin) were excluded. Population data for livebirths and neonatal deaths, by birthweight and by gestational-age were requested from each centre, for the years it contributed data to the SCPE database.

This study looked at demographic characteristics of mother (age and parity), child (sex, weight, and gestational age at birth) and whether the child was from a multiple pregnancy; the neurological subtype of cerebral palsy (spastic [unilateral or bilateral], dyskinetic, or ataxic), and measurements of each child’s function (ability to walk, intelligence quotient [IQ], vision, and hearing). Severe cerebral palsy was defined as inability to walk, even with aids, and with an IQ of less than 50 (measured or clinician’s impression). Severe visual impairment was defined as a clinical diagnosis of blind or near blind. Hearing loss was defined as more than 70 dB in the best ear.

**Statistical methods**

Exact CI were calculated with Stata (version 8.0). Time trends were examined by individual years if data allowed, or in 4 or 5-year cohorts (1980–83, 1984–87, 1988–91, and 1992–96).1 When data for livebirths and neonatal deaths stratified by birthweight or gestational age were available, prevalence of cerebral palsy was calculated to allow the rates to be expressed per 1000 neonatal survivors as well as per 1000 livebirths. Stratification by birthweight and sex was also possible for some centres. A threshold of \( p<0.005 \) was used for significance (to allow for multiple hypothesis testing) and in view of the large numbers in the dataset, to guard against identification of statistically significant findings that were not clinically significant, 99% CI were calculated. For data from individual centres, 95% CI were calculated. Centre 10 (Tübingen, Germany) provided data only for children with bilateral spastic cerebral palsy, and these data were included only in the analysis of this particular subgroup.

A Z score was derived for each child, by use of the north of England birthweight standard,18 a widely used standard calculated from more than 118 000 singleton, non-malformed births (antepartum stillbirths were excluded) from the 1980–96 period. Children with cerebral palsy from singleton births were compared with this standard separately by sex.

In models used to test trends over time, prevalence was the outcome variable, and the models were adjusted for birth year and centre as potential confounders. The data were tested for any centre effect and for interactions between birth year and centre. If a centre effect was present, year effect was tested after adjustment by centre in a multivariate model. If interaction was present, the birth year effect on this prevalence (ie, overall trend over time) was tested and is given here adjusted by the centre effect, if the latter was significant.

**Role of the funding source**

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the 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**

16 centres contributed data for children with cerebral palsy to the SCPE database, which covered births in years
1980–96, although not all centres were actively collecting data in all birth years. There were 7884 children with cerebral palsy born between 1980 and 1996 (after exclusion of those with cerebral palsy of post neonatal origin), whose mothers were resident in an area covered by the register at the time of birth or birth registration. Of these children, 2103 (26·6%) were of birthweight less than 1500 g or of gestational age less than 32 weeks at the time of birth, and formed the study population for subsequent analyses (table 1).

There were significant differences by sex, Z score, and the proportion with unilateral spastic cerebral palsy between the birthweight groups (table 2).

Between 1980 and 1996, in VLBW infants, the mean birthweight of affected children fell from 1169 g to 1094 g (75 g fall, p=0·0004). Children from both Northern Ireland and east Ireland had significantly lower birth weight than those from other centres, after exclusion of centre 10 (49 children), and controlling for year effect. There was a similar, significant difference in mean gestational age.

### Table 1: Description of SCPE data on children with cerebral palsy included in the study

<table>
<thead>
<tr>
<th>Location of centre</th>
<th>Centre</th>
<th>Data available</th>
<th>Number of cases &lt;1000 g</th>
<th>Number of cases 1000-1499 g</th>
<th>Number of cases ≥1500 g and &lt;32 weeks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isère, France</td>
<td>C 01</td>
<td>1980–96</td>
<td>9</td>
<td>57</td>
<td>24</td>
<td>90</td>
</tr>
<tr>
<td>Haute Garonne, France</td>
<td>C 02</td>
<td>1981–93</td>
<td>0</td>
<td>20</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>Scotland, UK</td>
<td>C 03</td>
<td>1984–90</td>
<td>38</td>
<td>117</td>
<td>54</td>
<td>209</td>
</tr>
<tr>
<td>Cork and Kerry, Ireland</td>
<td>C 04</td>
<td>1981–95</td>
<td>11</td>
<td>27</td>
<td>16</td>
<td>54</td>
</tr>
<tr>
<td>Northern Ireland, UK</td>
<td>C 05</td>
<td>1981–96</td>
<td>74</td>
<td>130</td>
<td>60</td>
<td>264</td>
</tr>
<tr>
<td>Göteborg, Sweden</td>
<td>C 06</td>
<td>1980–96</td>
<td>34</td>
<td>101</td>
<td>50</td>
<td>185</td>
</tr>
<tr>
<td>East Ireland, Ireland</td>
<td>C 07</td>
<td>1980–93</td>
<td>31</td>
<td>53</td>
<td>39</td>
<td>123</td>
</tr>
<tr>
<td>Northern Region, UK</td>
<td>C 08</td>
<td>1980–96</td>
<td>55</td>
<td>98</td>
<td>42</td>
<td>195</td>
</tr>
<tr>
<td>Oxford, UK</td>
<td>C 09</td>
<td>1984–96</td>
<td>58</td>
<td>141</td>
<td>55</td>
<td>254</td>
</tr>
<tr>
<td>Tübingen, Germany†</td>
<td>C 10</td>
<td>1980–86</td>
<td>14</td>
<td>28</td>
<td>7</td>
<td>49</td>
</tr>
<tr>
<td>Mersey Region, UK</td>
<td>C 11</td>
<td>1980–89</td>
<td>36</td>
<td>123</td>
<td>38</td>
<td>197</td>
</tr>
<tr>
<td>East Denmark, Denmark</td>
<td>C 12</td>
<td>1980–96</td>
<td>49</td>
<td>201</td>
<td>105</td>
<td>355</td>
</tr>
<tr>
<td>Viterbo province, Italy</td>
<td>C 13</td>
<td>1981–95</td>
<td>9</td>
<td>19</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Gelderland, Netherlands</td>
<td>C 14</td>
<td>1981–89</td>
<td>3</td>
<td>14</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>Tonsberg, Norway</td>
<td>C 15</td>
<td>1991–96</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Bologna, Italy</td>
<td>C 16</td>
<td>1991–96</td>
<td>6</td>
<td>14</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>428</td>
<td>1147</td>
<td>528</td>
<td>2103</td>
</tr>
</tbody>
</table>

*Centre 10 provided data only on cases with bilateral spastic CP.

### Table 2: Summary of characteristics of cerebral palsy among children of birthweight less than 1000 g, of 1000–1499 g and of those of birthweight 1500 g but gestational age less than 32 weeks

<table>
<thead>
<tr>
<th>Birthweight &lt;1000g (n=414)</th>
<th>Birthweight 1000-1499 g (n=1119)</th>
<th>Birthweight ≥1500 g, &lt;32/40 (n=521)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of male children</td>
<td>203 (49%)</td>
<td>619 (55%)</td>
<td>326 (63%)</td>
</tr>
<tr>
<td>Mean (SD) birthweight, g</td>
<td>840 (114)</td>
<td>1249 (143)</td>
<td>1721 (228)</td>
</tr>
<tr>
<td>Mean (SD) gestational age, weeks</td>
<td>26.7 (2.1)</td>
<td>29.3 (2.1)</td>
<td>30.0 (1.1)</td>
</tr>
<tr>
<td>Mean maternal age in years (SD)</td>
<td>27.9 (5.7)</td>
<td>27.4 (5.7)</td>
<td>28.1 (5.8)</td>
</tr>
<tr>
<td>Primigravida</td>
<td>206 (70%)</td>
<td>632 (69%)</td>
<td>269 (64%)</td>
</tr>
<tr>
<td>Mean (SD) Z score</td>
<td>-0.56 (1.15)</td>
<td>-0.23 (1.08)</td>
<td>1.0 (1.29)</td>
</tr>
<tr>
<td>Number of children known to have died</td>
<td>9 (2%)</td>
<td>16 (1%)</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Number of multiple births</td>
<td>85 (21%)</td>
<td>232 (21%)</td>
<td>80 (15%)</td>
</tr>
<tr>
<td>Number with spastic cerebral palsy</td>
<td>380 (93%)</td>
<td>1046 (94%)</td>
<td>488 (95%)</td>
</tr>
<tr>
<td>Number with unilateral spastic cerebral palsy</td>
<td>111 (29%)</td>
<td>225 (21%)</td>
<td>88 (18%)</td>
</tr>
<tr>
<td>Number with severe cerebral palsy</td>
<td>53 (13%)</td>
<td>146 (13%)</td>
<td>64 (12%)</td>
</tr>
<tr>
<td>Number with severe visual impairment</td>
<td>57 (15%)</td>
<td>119 (11%)</td>
<td>47 (10%)</td>
</tr>
<tr>
<td>Number who have seizures</td>
<td>40 (12%)</td>
<td>98 (11%)</td>
<td>43 (10%)</td>
</tr>
<tr>
<td>Number with hearing loss</td>
<td>42 (11%)</td>
<td>81 (8%)</td>
<td>24 (5%)</td>
</tr>
</tbody>
</table>

*Centre 10 provided data only on cases with bilateral spastic cerebral palsy (49 children) and are excluded from this table.
(30-0 weeks vs 29-5 weeks; p<0.0001). Both trends remained significant after adjustment for centre. However, there was no significant change in Z score over this time.

In children of VLBW, there was no significant change with time in the proportion of male children with cerebral palsy, in the proportion of children with spastic cerebral palsy, or in the proportion of children with unilateral spastic cerebral palsy. The proportion of children with severe cerebral palsy did not change over the duration of the study. The proportion of VLBW children from multiple births with cerebral palsy increased significantly over the study period, from 17% (40/230) in the period 1980–83 to 24% (87/324) (χ² test for linear trend; p=0.004).

In all centres, the proportion of VLBW births among livebirths has increased since 1980. This increase was highest in UK centres and in Sweden, from 0-5% (109/1946) in 1980 to almost 1% (133/19009) in 1996. The proportion of VLBW infants increased significantly (p<0.0001) over time, after we had taken into account centre differences and excluded the Danish centre (C12) where there was a significant decrease among singleton VLBW births (p=0.003) although the overall proportion of VLBW infants remained steady.

The neonatal mortality rate has fallen since 1980. A significant decrease in the VLBW-specific neonatal mortality rate was seen in most of the eight centres that provided data for this variable. Among infants with a birthweight of less than 1000 g the neonatal mortality rate fell from 50% to 35% (p<0.0001), and among those with a birthweight of 1000–1499 g it fell from 20% to 5% (p<0.0001) (figure 1). The decline in neonatal mortality rate in babies of birthweight less than 1000 g was smaller in Denmark.

The overall prevalence of cerebral palsy in VLBW children during the study period (1314 children, with centre 10 excluded) was 50.6 per 1000 livebirths (99% CI 47.2–54.2). In the group of children with birthweight less than 1000 g (353 children), the prevalence of children with cerebral palsy was 40.0 per 1000 livebirths (34.8–45.7) and in the group of birthweight 1000–1499 g (961 children) the prevalence was 56.1 per 1000 livebirths (51.6–60.8; figure 2). This difference in prevalence remained significant after adjustment for centre (p<0.0001). Prevalence also differed by sex; in 450 boys of birthweight 1000–1499 g, the prevalence was 61.0 per 1000 livebirths (53.8–68.2) compared with 49.5 per 1000 livebirths (42.8–56.2) in 344 girls (p=0.0025). There was no difference in prevalence by sex among children of birthweight less than 1000 g; the prevalence was 39.5 per 1000 livebirths (31.1–49.0) for 140 boys and 37.1 per 1000 livebirths (29.1–45.1) for 137 girls of the same birthweight (p=0.59).

There was a significant fall in the prevalence of cerebral palsy among VLBW infants over the study period from 60.6 per 1000 livebirths (37.8–91.4) in 1980 to 39.5 (28.6–53.0) in 1996 (p<0.0004), which remained significant after adjustment for centre. The significant decline in prevalence was restricted to the group of children with birthweight 1000–1499 g. Figure 3 shows that this decline varied over time, with a steep fall in the prevalence in the first 5 years (1980–85), then a plateau phase (1986–89), before another fall in the later years (1990–96). The decline is mainly explained by a reduction in the prevalence of bilateral spastic cerebral palsy among children of birthweight 1000–1499 g (717 children); the
prevalence was 64.2 per 1000 livebirths (38.5–99.2) in 1980, and fell to 29.4 (17.6–45.5) in 1996 (figure 4). In children of birthweight less than 1000 g (240 children), there was no significant change in prevalence over the 17-year period (figure 3). Rates of unilateral spastic cerebral palsy were similar in both birthweight groups (9.2 of <1000 g and 11.0 of 1000–1499 g), and these rates remained steady during the study period.

In children of birthweight 1000–1499 g, there was a significant decline in the rate of cerebral palsy with inability to walk (p=0.001), which matches the reduction in overall cerebral palsy rate. The proportion of children with cerebral palsy who were unable to walk does not seem to have changed over time in either birthweight group. Although most of the fall in cerebral palsy prevalence can be attributed to a reduction in the frequency of bilateral spastic cerebral palsy, the clinical profile of children with this form was constant for the duration of the study period, with 35% (32–39) of affected children unable to walk and 24% (99%CI 20–27) with an IQ of less than 50.

To take into account the changes in neonatal mortality over the period and their effect on the prevalence of cerebral palsy, particularly among children of birthweight less than 1000 g, cerebral palsy rate per 1000 neonatal survivors was calculated for centres able to provide birthweight-specific population data on neonatal death (centres 3, 6, 8, 9, 11, 12, and 15). For VLBW infants (996 children), the overall rate was 64.8 per 1000 neonatal survivors (59.8–70.1); it fell from 90.4 per 1000 (55.3–136.4) in 1980 to 44.1 per 1000 (27.7–66.1) in 1996. Neonatal survivors in the group of birthweight less than 1000 g (258 children) had a cerebral palsy rate of 74.3 per 1000 children (63.3–86.5), compared with 62.1 (56.5–68.0) in the group of birthweight 1000–1499 g (738 children). The pattern of cerebral palsy prevalence per 1000 neonatal survivors in the higher birthweight group is similar to that seen in the prevalence per 1000 livebirths (p<0.0001), (figure 3). By contrast, the pattern per 1000 neonatal survivors in the group of birthweight less than 1000 g differed from that seen in livebirth prevalence, showing a non-significant decrease over the study period,
with most of the fall in prevalence among infants of birthweight less than 1000 g who were born after 1990 (p=0·039, figure 3).

Population data stratified by gestational age were available for fewer centres than population data by birthweight. In 868 children from six centres, the prevalence of cerebral palsy for those born before 32 weeks of gestation was 58·0 per 1000 livebirths (53·1–63·1). Among 203 children born before 28 weeks’ gestation, the prevalence of cerebral palsy was 48·6 per 1000 livebirths (40·5–57·8); this rate was significantly lower (p=0·002) than that of infants born at 28–31 weeks’ gestation (66·5 children), who had a prevalence of 61·1 per 1000 livebirths (55·8–67·8). This difference remained significant after adjustment for year and centre of birth. Among infants born before 28 weeks’ gestational age, there was no significant trend over time, but among those born at 28–31 weeks’ gestation, there was a significant fall in prevalence (p<0·0001) between 1981 and 1995 (figure 5).

Discussion
Our findings are unlikely to be subject to selection bias associated with hospital-based studies because the data come from population-based centres. This study shows that the survival of infants of birthweight less than 1500 g continues to improve and that this continued improvement is not accompanied by increased morbidity. Although other studies have reported no change in the cerebral palsy rate over time among VLBW survivors to 1 year born between 1975 and 1991,11 the data presented here for a similar period show a decline in the rate of cerebral palsy among such infants, especially of bilateral spastic cerebral palsy. Rates of other subtypes remained steady. This decline was seen initially only in infants of birthweight 1000–1499 g, but in the most recent period, the decline was also apparent in infants of birthweight less than 1000 g. Although ascertainment could have varied between centres, children with bilateral spastic cerebral palsy are generally the most severely affected.
and their ascertainment is unlikely to vary. The rigorous harmonisation procedures undertaken before data pooling26 should ensure that the results represent true findings rather than methodological errors.

The changes in the rate of cerebral palsy by gestational age follow those of birthweight, with a significant fall over the period for children born at 28–31 weeks’ gestation. The absence of a significant trend in infants of less than 28 weeks’ gestation, adds to the evidence that a shift in the proportion of small-for-gestational-age infants is not an explanation for the fall in prevalence of cerebral palsy. We cannot explore in more detail the relation between birthweight and maturity, because we do not have denominator information in gestational-age bands stratified by birthweight.

Among children with cerebral palsy of birthweight less than 1500 g, the mean birthweight and gestational age has fallen slightly over the 17-year period, and the mean Z score remained the same, which suggests that infants who develop cerebral palsy are born slightly earlier in pregnancy and are light for that reason. The change in prevalence of cerebral palsy is not related to a change in the frequency of VLBW infants who are born small for their gestational age.

What is less clear is whether these findings suggest a reduction in the risk of cerebral palsy in infants of slightly greater maturity at delivery or reflect a change in clinical practice resulting in the earlier delivery of infants already at risk of cerebral palsy—for example, showing antenatal signs of distress. Clarke and colleagues29 have argued that an increase in survival of infants with cerebral palsy is unlikely to have resulted from the more active management of intrapartum asphyxia, since the increase in the number of caesarean sections done because of fetal distress would be too small to have a detectable effect on the cerebral palsy rate.29

Over the period of this study, there have been many changes in the care and management of VLBW infants; these changes happened at different times in the different centres in this collaboration. Thus, the trends reported here cannot be associated with the introduction or withdrawal of specific perinatal management strategies—eg, antenatal steroids and surfactant therapy. Clinical trials and hospital-based follow-up studies are needed to assess the effects of perinatal interventions.29,33,35 This paper provides an overview of the effect of neonatal intensive care over 17 years. Evidence suggests that part of the reduction seen in the prevalence of cerebral palsy is a result of greater maturity at delivery and that this difference by sex is not significant in children with cerebral palsy of birthweight less than 1000 g. The difference between the rate per 1000 neonatal survivors and the prevalence among all livebirths was 50%, which decreased to 20% by 1996.

Additionally, there was large and probably random variation in the rate per 1000 neonatal survivors in the lowest birthweight group resulting from the small number of infants with cerebral palsy, which probably affected the precision of estimates of rates in the early years of the study. Later, when a greater number of infants in this birthweight group survived, this variation became less influential, as shown by the non-significant downward trend in the rate of cerebral palsy per 1000 neonatal survivors in infants of birthweight less than 1000 g in the most recent years studied. Fewer centres were able to provide birthweight-specific data for neonatal survivors than were able to provide birthweight-specific data for livebirths, and centres able to provide gestational-age-specific denominators were fewer still. This factor affects the precision of the estimated rates of cerebral palsy per 1000 neonatal survivors and prevalence of cerebral palsy by gestational age. However, although the relation between the provision or otherwise of these denominators and quality of prenatal care is uncertain, there is no evidence to suggest a significant source of bias that would affect the trends reported here.

The denominator data also showed an increasing rate of VLBW per 1000 livebirths, which might be a result of changes in recording of births around viability, with decreasing numbers of stillbirths in all countries contributing data to this study.22 Aggressive resuscitation of premature infants and an increase in the proportion of VLBW infants from multiple births, related to both demographic changes in maternal age and to the increasing use of fertility treatments might also contribute to this trend. The pattern observed in centre 12 (Denmark), of no trend in the rate of cerebral palsy in VLBW infants, and a small fall in neonatal mortality among the VLBW infants, might relate to Denmark having the highest rate of multiple births.23 Concern has been expressed that the increased rate of multiple births could increase the proportion of children at risk of cerebral palsy.24 However, the higher proportion of infants with cerebral palsy coming from multiple pregnancies simply parallels the overall rise in the proportion of VLBW infants coming from multiple pregnancies.25

This study also showed that among VLBW infants, the male excess in children with cerebral palsy reported previously is seen only in children of birthweight 1000–1499 g, and that this difference by sex is not significant in children with cerebral palsy of birthweight less than 1000 g. Although the absence of a sex difference among the smaller infants might be due to chance, it could suggest a greater survival advantage of female infants in the higher birthweight group, which might not be evident in the group with lowest birthweight and highest mortality. Some
researchers have reported a sex difference in the prevalence of cerebral palsy among infants with birthweight less than 1000 g, but others have reported no difference by sex in adverse neurological outcomes or cerebral palsy in such infants.

The significant reduction in the prevalence of cerebral palsy per 1000 livebirths is mostly due to a reduction in bilateral spastic cerebral palsy among infants of birthweight 1000–1499 g. Prevalence of unilateral spastic cerebral palsy has not changed significantly over the study period. Spastic cerebral palsy in children of birthweight less than 1500 g is predominantly caused by periventricular leukomalacia and cerebral palsy. The prevalence data here suggest a decline in unilateral motor-tract damage and unilateral spastic lesions. Periventricular leukomalacia damages both motor tracts in many cases, thus causing bilateral spastic cerebral palsy, and periventricular haemorrhage mainly causes unilateral motor-tract damage and unilateral spastic cerebral palsy. The prevalence data here suggest a decline in unilateral periventricular leukomalacia in children of birthweight less than 1500 g, as reported by Hamrick and colleagues.

In conclusion, this paper presents evidence that infants of birthweight less than 1500 g and in particular those of birthweight less than 1000 g now have a better chance of survival than previously, and more importantly, a better chance of survival without severe neurological impairment, which demonstrates that improvement in neonatal care has not resulted in increased survival at the cost of substantial morbidity.

Contributors
Mary Jane Platt, Christine Cans, Ann Johnson, and Inge Krageloh-Mann participated in the conception and design of the study. Mary Jane Platt and Christine Cans analysed the data and Mary Jane Platt drafted the manuscript. All authors participated in data acquisition, revision, and critical review, and all have seen and approved the final version.

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We declare that we have no conflict of interest.

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References
Dental caries
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Dental caries, otherwise known as tooth decay, is one of the most prevalent chronic diseases of people worldwide; individuals are susceptible to this disease throughout their lifetime. Dental caries forms through a complex interaction over time between acid-producing bacteria and fermentable carbohydrate, and many host factors including teeth and saliva. The disease develops in both the crowns and roots of teeth, and it can arise in early childhood as an aggressive tooth decay that affects the primary teeth of infants and toddlers. Risk for caries includes physical, biological, environmental, behavioural, and lifestyle-related factors such as high numbers of cariogenic bacteria, inadequate salivary flow, insufficient fluoride exposure, poor oral hygiene, inappropriate methods of feeding infants, and poverty. The approach to primary prevention should be based on common risk factors. Secondary prevention and treatment should focus on management of the caries process over time for individual patients, with a minimally invasive, tissue-preserving approach.

Dental caries is one of the most common preventable childhood diseases; people are susceptible to the disease throughout their lifetime. It is the primary cause of oral pain and tooth loss. It can be arrested and potentially reversed in its early stages, but is often not self-limiting and without proper care, caries can progress until the tooth is destroyed. Therefore, physicians and other health-care providers should be familiar with dental caries and its causes. The aim of this Seminar is to enhance physicians’ knowledge of the dental caries process and its management; to encourage physicians to incorporate relevant aspects of caries prevention and control into their daily practice, and to educate physicians about when to refer patients to a dentist.

Definition
Dental caries is the localised destruction of susceptible dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates. The signs of the carious demineralisation are seen on the hard dental tissues, but the disease process is initiated within the bacterial biofilm (dental plaque) that covers a tooth surface. Moreover, the very early changes in the enamel are not detected with traditional clinical and radiographic methods. Dental caries is a multifactorial disease that starts with microbiological shifts within the complex biofilm and is affected by salivary flow and composition, exposure to fluoride, consumption of dietary sugars, and by preventive behaviours (cleaning teeth). The disease is initially reversible and can be halted at any stage, even when some dentine or enamel is destroyed (cavitation), provided that enough biofilm can be removed. Dental caries is a chronic disease that progresses slowly in most people. The disease can be seen in both the crown (coronal caries) and root (root caries) portions of primary and permanent teeth, and on smooth as well as pitted and fissured surfaces. It can affect enamel, the outer covering of the crown; cementum, the outermost layer of the root; and dentine, the tissue beneath both enamel and cementum. Caries in primary teeth of preschool children is commonly referred to as early childhood caries.

The terms dental caries or caries can be used to identify both the caries process and the carious lesion (cavitated or non-cavitated) that is formed as a result of that process. In daily practice, dental practitioners, other health-care providers, and patients often refer to an established caries lesion as a cavity in the tooth. The cavity, or decayed surface, is the sequela of the disease process and is a sign of fairly advanced disease. Dental caries is a continuum of disease states of increasing severity and tooth destruction that ranges from sub-clinical sub-surface changes at the molecular level to lesions with dentinal involvement, either with an intact surface or obvious cavitation (figure 1). Assessment of the presence or absence of dental caries is dependent on the diagnostic cutoff points selected; this decision greatly affects practitioners’ treatment decisions. Carious lesions are the outcome of events that progress over time.

Search strategy and inclusion criteria
Sources of information for this Seminar were: (1) systematic reviews of dental caries (cariology), including the Cochrane Library, Centre for Reviews and Dissemination, University of York (restoration longevity), and the NIH Consensus Development Conference on Diagnosis and Management of Dental Caries Throughout Life; (2) formally constructed and peer-reviewed consensus development papers and statements published in the Proceedings from the International Consensus Workshop on Caries Clinical Trials; (3) summaries of peer-reviewed reviews, such as proceedings of the 50th Anniversary Congress of the European Organisation for Caries Research, Cariology in the 21st Century and a specialist review on caries diagnostic literature; (4) MEDLINE database through PubMed to identify papers containing the term dental caries and associated definitions, epidemiological considerations, aetiological agents, pathogenic factors, and risk factors; and (5) as additional sources, comprehensive textbooks on dental caries.
Pathogenesis

Dental caries results from interactions over time between bacteria that produce acid, a substrate that the bacteria can metabolise, and many host factors that include teeth and saliva. Dental caries results from an ecological imbalance in the physiological equilibrium between tooth minerals and oral microbial biofilms. Bacteria live on teeth in microcolonies that are encapsulated in an organic matrix of polysaccharides, proteins, and DNA secreted by the cells, which provides protection from desiccation, host defences and predators and provides enhanced resistance to antimicrobial agents. Teeth offer non-shedding surfaces for microbial colonisation and large numbers of bacteria and their by-products accumulate in a biofilm on tooth surfaces in health and disease.

The mechanisms of the caries process are similar for all types of caries. Endogenous bacteria (largely mutans streptococci [Streptococcus mutans and Streptococcus sobrinus] and Lactobacillus spp) in the biofilm produce weak organic acids as a by-product of metabolism of fermentable carbohydrates. This acid causes local pH values to fall below a critical value resulting in demineralisation of tooth tissues. If the diffusion of calcium, phosphate, and carbonate out of the tooth is allowed to continue, cavitation will eventually take place. Demineralisation can be reversed in its early stages through uptake of calcium, phosphate, and fluoride. Fluoride acts as a catalyst for the diffusion of calcium and phosphate into the tooth, which remineralises the crystalline structures in the lesion. The rebuilt crystalline surfaces, composed of fluoridated hydroxyapatite and fluorapatite, are much more resistant to acid attack than is the original structure. Bacterial enzymes can also be involved in the development of caries.

Whether dental caries progresses, stops, or reverses is dependent on a balance between demineralisation and remineralisation. The process of demineralisation and remineralisation takes place frequently during the day in most people. Over time this process will lead to either cavitation within the tooth or repair and reversal of the lesion, or maintenance of the status quo. Remineralisation is frequent, especially when the biofilm pH is restored by saliva, which acts as a buffer. The remineralised areas have a higher concentration of fluoride and less microporous enamel structure than the original tooth structure because of the acquisition of calcium and phosphates from saliva (figure 2).

Caries lesions develop where oral biofilms are allowed to mature and remain on teeth for long periods. If a cavity is allowed to develop, the site provides an ecological niche in which plaque organisms gradually adapt to a reduced pH. Formation of a cavitated lesion protects the biofilm, and unless the patient is able to cleanse this area, the carious process will continue (figure 2). Dental caries in enamel is typically first seen as white spot lesions, which are small areas of subsurface demineralisation beneath the dental plaque. Root-surface caries is similar to enamel caries, but unlike enamel caries, the surface can become softened, and bacteria penetrate further into the tissue at an earlier stage of lesion development. Recession of the gingival margin, resulting from poor oral hygiene and loss of periodontal attachment with age, leads to exposure of the juncture of the crown with the
root surface. This area retains dental plaque and is prone to developing carious lesions.4

Early childhood caries is an aggressive presentation of dental caries that affects the primary teeth of infants and toddlers, and typically develops in anterior tooth surfaces and can also affect maxillary or mandibular primary molars. It begins with white spot lesions in upper primary incisors along the margin of the gingiva. If the disease continues, caries can progress and lead to complete destruction of the crown. In the moderate stage, cavitation takes place, and caries begins to spread to the upper molars. In severe cases, the caries process destroys the upper teeth and spreads to the lower molars.5,18

Risk factors
A person’s risk of caries can vary with time since many risk factors are changeable. Physical and biological risk factors for enamel or root caries include inadequate salivary flow and composition, high numbers of cariogenic bacteria, insufficient fluoride exposure, gingival recession, immunological components, need for special health care, and genetic factors.4,19–23 Caries is related to one’s lifestyle, and behavioural factors under a person’s control are clearly implicated. These factors include poor oral hygiene; poor dietary habits—ie, frequent consumption of refined carbohydrates; frequent use of oral medications that contain sugar; and inappropriate methods of feeding infants.4,19,20,24,25 Other factors related to caries risk include poverty, deprivation, or social status; number of years in education; dental insurance coverage; use of dental sealants; use of orthodontic appliances; and poorly designed or ill-fitting partial dentures.18,20–26 Also, children with a history or evidence of caries or whose primary caregiver or siblings have severe caries should be regarded as at increased risk for the disease.27 Although evidence of a link between low birthweight and dental caries is inconclusive, clinicians are advised to regard such children as at risk for dental caries.27

Colonisation by mutans streptococci, and other cariogenic bacteria at a young age could be a key risk factor for caries development.16,28 However, the role of mutans streptococci as the main cause of caries has not been proven. Because of the complexity of the oral microflora, which contains several hundred species of bacteria and millions of cells growing on a single tooth surface, no single bacterial species can predict caries development in a particular person. Moreover, the present knowledge of this complex disease does not allow for accurate prediction of caries activity in any one person or tooth.29 However, evidence that consideration of risk factors such as the presence of mutans streptococci or lactobacilli; low socioeconomic status; previous caries experience; amount of fluoride exposure and salivary flow; and the dentist’s judgment can lead to beneficial outcomes. The major reservoir from which infants acquire mutans streptococci, a widely studied cariogenic bacterial species, is the primary care giver, usually the mother.4,28 Evidence suggests that mutans streptococci can colonise the mouth of pre-dentate infants and are acquired by both vertical and horizontal transmission from human reservoirs.28 The report of the 2001 US National Institutes of Health Consensus Development Conference on Diagnosis and Management of Dental Caries Throughout Life contains additional information on caries risk.30 Figure 3 summarises the factors implicated in the caries process.31

Epidemiology
Comparisons of the global frequency and distribution of dental caries are complicated by diagnostic criteria that differ from study to study,4,28,31,32 but a fall in the prevalence and severity of caries in permanent teeth has been seen in many developed countries over recent decades.18,33 Also, the rate of progression of the disease slows down with increased age.29 The disease is mainly found in specific teeth and tooth types in both primary and permanent teeth.29,31 The caries decline in permanent teeth has been greater on interproximal and smooth surfaces than on fissured or occlusal surfaces.29 Coronal caries in children’s permanent teeth is predominately a disease of the pits and fissures.29,31 In early childhood caries lesions develop in smooth surfaces, which are usually at low risk of caries.29 In some population groups,
caries prevalence and severity in primary teeth might have stabilised or increased slightly.3,4,14

Despite the widespread decline in caries prevalence and severity in permanent teeth in high-income countries over the past few decades, disparities remain and many children and adults still develop caries.18,20,42,43 In the USA, caries is the most common chronic disease of childhood, and is five times more common than asthma.1 Dental caries is increasing in frequency among elderly people in the USA and elsewhere as more people are retaining more teeth throughout their lifespan.19 Older adults might have similar or higher levels of new caries formation than have children.44,45 Studies show that nursing home residents are more likely to have root caries than do elderly people who live in their own homes.7 Other population groups at high risk for dental caries include people living in poverty; people with poor education or low socioeconomic status; ethnic minority groups; individuals with developmental disabilities; recent immigrants; individuals with HIV or AIDS; elderly people who are frail; and people with several risky lifestyle factors.3,20,42,43,46–49

The effect of dental caries on the overall quality of health and wellbeing has not been well studied. This disease and its sequelae can cause significant pain and are expensive to treat. The burden of dental caries lasts a lifetime because once the tooth structure is destroyed it will usually need restoration and additional maintenance throughout life. In developing countries, where the prevalence of dental caries is low and the disease clusters on occlusal surfaces of a few teeth, the costs of treatment are higher than can be met by the funds available for

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of posterior teeth is also a challenge, and the inadequacy of clinical visual and tactile methods is the reason that use of ionising radiation for bitewing radiographs is still sanctioned. However, the same systematic review of high quality studies showed that, for approximal surfaces, radiographs had an overall sensitivity of 50% and a specificity of 87%. Thus, using conventional clinical and radiographic methods, the dentist will detect only about half the lesions present and, could misclassify sizeable numbers of sound surfaces as decayed. Radiographs are not very helpful for anything but advanced dentinal lesions on occlusal surfaces (sensitivity 39%, specificity 91%).

The consequence of diagnostic errors depends on the treatment strategy used.

The international trend in caries management is to move away from the surgical model (to excise and replace diseased tooth tissue) towards a preventive approach aiming to control the initiation and progression of the disease process over a person’s lifetime. Therefore, a major challenge for the clinician is to detect lesions at an early stage, before surgical intervention is needed. The epidemiological examiner has to capture information about need of preventive treatment rather than just the number of fillings required; and the clinical researcher has to assess the effectiveness of products and strategies aiming to control the caries process and prevent disease progression to advanced stage disease that needs restoration. Another major challenge is to detect caries activity at the lesion stage. Unfortunately, despite claims that some new clinical criteria systems are reliable, we contend that additional studies are needed before clinicians in general practice can reliably assess caries activity. In view of the range of dental caries and the various stages of caries that can be detected and differentiated from one another (figure 1), clarity is needed in discussion and reporting of these stages of decay to ensure that patient care, dental-care policies and evidence-based practices are in agreement. Some controversy exists as to the effect of the different diagnostic cutoff points and to the feasibility of epidemiological data collection that includes lesions in the enamel, although results of studies and practices in some countries show that both are desirable. Seemingly trivial changes in diagnostic criteria can produce sizeable differences in the amount of disease recorded. Figure 4 shows the caries process as recorded by classic epidemiology and the inappropriateness of using the term caries free when reporting the results of surveys that only record dentine lesions seen clinically, in view of the proportion judged caries free who could have undetected disease. Rather than claim such groups are free of disease, many authorities are now using terms such as no obvious decay.

Treatment

Over a long period from the turn of the 20th century dentists have thought of tooth restoration as a cure for dental caries. The focus on restoration and retention of teeth was an advance on the previous treatment method
of tooth extraction, and became widely used at a time when there was little knowledge of caries prevention. Caries formed quickly, and progression rates were high, but there were few dental practitioners.

In clinical practice, caries management by restorative treatment, despite its constraints and tendency to promote repeated restorations,64 is still the favoured method in many countries. However, in some regions such as Scandinavia, more preventive approaches to care have been in place for many years.6 The main flaws of restoration without a prevention approach are the short durability of restorations65 and the propensity of new caries to form at the margins of restorations if the causes of the disease are not removed.66

Over the past three decades there has been a transition in many countries towards a largely preventive and preservative approach to caries management. Although caries rates vary greatly between individuals, groups, and countries and the dental workforce is sizeable, prevention and preservation of tooth tissue is desirable as the normal treatment for caries, since we know that caries progresses slowly in most people, that prevention is effective, and that excessive and premature tooth cutting can cause harm.11,12,14,16,70 Prevention of early carious lesions by meticulous removal of the biofilm, as well as application of fluoride, or placement of sealants, is successful in preserving tooth structure. When restorative intervention is needed, the use of modern micro-restorative techniques that use new adhesive materials can also preserve tooth structure.

Prevention

Discussions about improved methods for caries detection, assessment, and diagnosis for effective caries prevention should not be seen as an alternative to public health and health promotion strategies to reduce the burden of disease before a patient arrives at a dental practice with obvious disease. New clinical developments should work in conjunction with such public health approaches.

In dentistry, the promotion of evidence-based care and the production of clinical guidelines to support appropriate care for individual patients is now possible. In dental caries management, the focus has been around preventive caries management for children,46 but caries is a disease process that needs to be managed over a person’s lifetime.12,65 The evidence is leading to an international trend in clinical practice, to move away from operative intervention towards prevention of caries.1 The theory is that the caries process should be managed over time for individual patients and that the least invasive preservative dentistry should be provided.67 This approach relies on accurate diagnosis of disease and lesions, disease prevention, just-in-time restoration, minimally invasive operative procedures, and prevention of recurrence.

It should be noted that there has been some controversy about the increased use of a high-risk individual approach for identification of people in need of caries prevention.70 However, the distribution of caries is very skewed and although risk groups are increasingly targeted for prevention, appropriate and prudent surveillance and care should be provided for all patients since caries can occur and can progress in all risk groups. Risk classifications, are dynamic and vary from person to person, so should be periodically reviewed and updated.68

For self-administered care, fluoride toothpaste is the most powerful intervention for caries prevention because it has high clinical effectiveness and social acceptability.71 A Cochrane review71 of randomised or quasi-randomised controlled trials with blind outcome assessment, comparing fluoride toothpaste with placebo in children aged 16 years or more for at least 1 year, concluded that fluoride toothpastes are clearly effective in prevention of caries. This conclusion is supported by more than 50 years of research. Studies of other oral hygiene interventions alone are not as clear cut because many are confounded by the concurrent use of fluoride toothpaste. However, consensus supports the use of tooth brushing in combination with fluoride toothpaste, especially for occlusal surfaces at the time of tooth eruption.

Another Cochrane review72 looked at the effectiveness of fluoride gels administered by professionals. Randomised or quasi-randomised controlled trials with blind outcome assessment compared fluoride gel with placebo or no treatment in children aged 16 years or younger for at least 1 year, and the reviewers concluded that fluoride gel showed clear evidence of a caries-inhibiting effect. However, little information exists about effects on primary teeth, adverse effects, or acceptability of treatment. Pit-and-fissure sealants were the subject of another Cochrane review73 of randomised or quasi-randomised controlled trials of sealants used for caries prevention in children and adolescents aged less than 20 years. The reviewers recommended sealing of the occlusal surfaces with resin based sealants to prevent
treatment guidelines. In an additional review fluoride varnishes gave promising results. The reviewers suggested a substantial effect of caries inhibition of fluoride varnish in both permanent and deciduous teeth.

Effective caries prevention programmes can use a range of interventions including community fluoridation of water or salt, school water fluoridation, school mouth-rinse programmes, provision of fluoride tablets at school, and school dental sealant programmes.

Additional interventions include those that focus on saliva. Lack of saliva results in catastrophic dental consequences with rapidly progressive caries that attack many sites. Saliva production can be reduced as a result of head and neck irradiation or as a consequence of other diseases (eg, Sjögrens syndrome) or medications. New theories are emerging aimed at the reduction of transmission of cariogenic organisms from caretaker to child to prevent early-childhood caries.

Prevention and control of dental caries can be promoted by clinicians other than dentists, if such clinicians are appropriately trained. Children can be examined by their primary care provider or paediatrician for signs of early carious demineralisation, which show as white areas around the gingival margin or brown-stained pits and fissures. Patients undergoing radiotherapy of the head and neck or who are on medication that lowers their salivary flow should also have regular dental examinations before and after such treatment. The detection of early signs of dental caries should complement preventive programmes in which biofilm on the affected tooth surfaces is frequently removed with a toothbrush, fluoride-toothpaste, and dental floss. Professional topical fluoride applications could be provided in medical offices, especially for infants and toddlers from high-risk population groups. Advice to restrict the consumption of sugary snacks and drinks should also be given to all patients as part of general dietary counselling. The detection of gross cavitated lesions and referral to an appropriate dental care professional for treatment should be thought of as a secondary preventive measure.

**Future research directions**

Prevention or control of dental caries cannot be achieved by reliance only on current methods and models of dental care. We need to consider the integrated roles of dental, medical, and other health-care providers and assess effective public health interventions and the introduction of oral health promotion activity linked to general health promotion. Most importantly, caregivers of children could play a major part in keeping children free of obvious dental caries.

Initiatives recently announced in Scotland, and widely practised in Scandinavia, and some parts of the USA seek to improve oral health by use of a broad range of people from community and education settings, a mix of health-care professionals from visiting nurses to dental hygienists, in addition to dentists. Such interventions need to be carefully assessed to establish the health improvement that can be achieved. Primary care clinicians should be familiar with effective interventions for the youngest children before they need dental services. Additionally, dentists need to establish the best ways to provide preventive and clinically effective care. Medical providers can detect early signs of carious lesions and provide preventive care in their clinics and can also counsel their patients to restrict their consumption of sugary snacks and drinks.

A key concern is the implementation of high quality clinical research focused on useful topics that primary care clinicians regard as generalisable. In several countries, efforts are being mounted to try to support the ability of researchers and practitioners to conduct such studies. Future research should focus on better understanding of the determinants of caries activity—ie, how to tell if a caries lesion shows progression or regression, or has stopped. Knowledge of restorative care will continue to progress, but such an approach to care will not adequately resolve the worldwide caries problem. In the future, when practitioners discover that their patients’ risk of dental caries development has increased, new biomaterials that release remineralising fluorides or probiotic agents could be used for caries management and control. Dental practitioners will need to progress from the notion of surgical removal of tooth structure to a strategy that avoids operative intervention if possible, but relies on micro-removal of hard tissues or minimally invasive restorative care if needed.

Physicians and other health-care providers will not concentrate on restorative dentistry in their practices. Rather, early detection of caries, by use of visual or other instruments that use advanced optics or other techniques, will be feasible in the future. In the USA, paediatric primary care providers who were given 2 h of training in infant oral health were equally able to detect cavitated lesions with similar accuracy to paediatric dentists. Detection of early carious lesions, which is done by a few physicians in the USA, is difficult, but is possible on the anterior maxillary teeth of infants and toddlers. We need to know more about how best to educate health-care providers to detect early signs of dental caries and how effective they could be in promotion of remineralisation of early carious lesions.

Additionally, physicians and other health-care providers can play a part in advising patients about sound nutritional and dietary habits that could reduce the risk of developing dental caries. Frequent drinking or sipping of sugary drinks provides an abundant food supply for the caries-causing bacteria on tooth surfaces. Other
disease prevention approaches, which should be researched, include provision of instruction in sound oral hygiene practices; application of fluoride varnishes to teeth; and introduction of so-called good bacteria to replace the bad-causing bacteria in a child with high caries activity.

Increased understanding of the complex biofilm that exists on tooth surfaces might hold the key to more effective control of dental caries. Another possibility the future could bring is genetic modification of the salivary glands to increase flow or secretion of protective proteins, which could change the ecology in the oral cavity and increase defensive mechanisms in the mouth.

Scientific advances should blur the demarcation between dental and medical practices—dental caries is a health problem that can be managed by a team of health-care providers including dentists and physicians. For now, physicians should concentrate on use of existing methods to detect signs of early and advanced caries, and should provide advice on how to prevent and control the caries in their patients.

Conflict of interest statement
N Pitts is a director and consultant for Innovative Detection & Monitoring Systems plc. He is a co-founder of Innovative Detection & Monitoring Systems with the University of Dundee and owns equity in the company.

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References
Many children younger than 5 years in developing countries are exposed to multiple risks, including poverty, malnutrition, poor health, and unstimulating home environments, which detrimentally affect their cognitive, motor, and social-emotional development. There are few national statistics on the development of young children in developing countries. We therefore identified two factors with available worldwide data—the prevalence of early childhood stunting and the number of people living in absolute poverty—to use as indicators of poor development. We show that both indicators are closely associated with poor cognitive and educational performance in children and use them to estimate that over 200 million children under 5 years are not fulfilling their developmental potential. Most of these children live in south Asia and sub-Saharan Africa. These disadvantaged children are likely to do poorly in school and subsequently have low incomes, high fertility, and provide poor care for their children, thus contributing to the intergenerational transmission of poverty.

Introduction

A previous *Lancet* series focused attention on the more than 6 million preventable child deaths every year in developing countries. Unfortunately, death is the tip of the iceberg. We have made a conservative estimate that more than 200 million children under 5 years fail to reach their potential in cognitive development because of poverty, poor health and nutrition, and deficient care. Children's development consists of several interdependent domains, including sensory-motor, cognitive, and social-emotional, all of which are likely to be affected. However, we focus on cognitive development because of the paucity of data from developing countries on other domains of young children's development. The discrepancy between their current developmental levels and what they would have achieved in a more nurturing environment with adequate stimulation and nutrition indicates the degree of loss of potential. In later childhood these children will subsequently have poor levels of cognition and education, both of which are linked to later earnings. Furthermore, improved parental education, particularly of mothers, is related to reduced fertility, and improved child survival, health, nutrition, cognition, and education. Thus the failure of children to fulfill their developmental potential and achieve satisfactory educational levels plays an important part in the intergenerational transmission of poverty. In countries with a large proportion of such children, national development is likely to be affected.

The first UN Millennium Development Goal is to eradicate extreme poverty and hunger, and the second is to ensure that all children complete primary schooling. Improving early child development is clearly an important step to reaching these goals. Although policymakers recognize that poverty and malnutrition are related to poor health and increased mortality, there is less recognition of their effect on children’s development or of the value of early intervention. This paper is the first of a three part series reviewing the problem of loss of developmental potential in young children in developing countries. The first paper describes the size of the issue, the second paper discusses the proximal causes of the loss, and the final paper reviews existing interventions. Here, we first examine why early child development is important and then develop a method to estimate the numbers of children who fail to fulfill their developmental potential. We then estimate the loss of income attributed to poor child development.

Why early child development is important

Children’s development is affected by psychosocial and biological factors and by genetic inheritance. Poverty and its attendant problems are major risk factors. The first few years of life are particularly important because vital developmental occurs in all domains. The brain develops rapidly through neurogenesis, axonal and dendritic growth, synaptogenesis, cell death, synaptic pruning, myelination, and gliogenesis. These ontogenetic events happen at different times (figure 1) and build on each other, such
that small perturbations in these processes can have long-term effects on the brain's structural and functional capacity.

Brain development is modified by the quality of the environment. Animal research shows that early undernutrition, iron-deficiency, environmental toxins, stress, and poor stimulation and social interaction can affect brain structure and function, and have lasting cognitive and emotional effects.18–24

In humans and animals, variations in the quality of maternal care can produce lasting changes in stress reactivity,25 anxiety, and memory function in the offspring, Despite the vulnerability of the brain to early insults, remarkable recovery is often possible with interventions,18,26,27 and generally the earlier the interventions the greater the benefit.28

Early cognitive development predicts schooling

Early cognitive and social-emotional development are strong determinants of school progress in developed countries.29–31 A search of databases for longitudinal studies in developing countries that linked early child development and later educational progress identified two studies. In Guatemala, preschool cognitive ability predicted children's enrolment in secondary school32 and achievement scores in adolescence.33 In South Africa, cognitive ability and achievement at the end of grade one predicted later school progress.34 Three further studies had appropriate data that we analysed (from the Philippines35,36 and Jamaica37) or requested the investigators to analyse (from Brazil38,39). In each case, multiple regression of educational outcome (or logistic regression for dichotomous variables), controlling for a wealth index,40 maternal education, and child's sex and age, showed that early cognitive development predicted later school outcomes. Table 1 shows that each SD increase in early intelligence or developmental quotient was associated with substantially improved school outcomes. Further evidence of the importance of early childhood is that interventions at this age37,41 can have sustained cognitive and school achievement benefits (table 135–39).

Problem of poor development

National statistics on young children's cognitive or social-emotional development are not available for most developing countries, and this gap contributes to the invisibility of the problem of poor development. Failure to complete primary education (Millennium Development Goal 2) gives some indication of the extent of the issue, **Table 1**: Change in later school outcomes per SD increase in intelligence quotient (IQ) or developmental quotient (DQ) in early life

<table>
<thead>
<tr>
<th>N</th>
<th>Independent variable</th>
<th>Outcome variable</th>
<th>Measure of effect</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamaica†</td>
<td>IQ on the Stanford Binet test (42) at 7 years</td>
<td>Dropped out before grade 11</td>
<td>Odds ratio</td>
<td>0.53†</td>
<td>0.32–0.87</td>
</tr>
<tr>
<td>Philippines</td>
<td>Cognitive Score at 8 years</td>
<td>Reading and arithmetic score at 17</td>
<td>Mean difference in SD</td>
<td>0.655</td>
<td>0.53–0.78</td>
</tr>
<tr>
<td>Brazil**</td>
<td>DQ on Griffiths test (43) at 4.5 years</td>
<td>Always repeat a grade by age 14 years</td>
<td>Odds ratio</td>
<td>0.60†</td>
<td>0.49–0.75</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, mother’s education, and wealth quintile. **Sample consisted of stunted (<–2 SD) children participating in an intervention trial and a non-stunted (>–1 SD) comparison group. Intervention and stunting status were also adjusted for: Sp=0.0117; HOSMER–LEIESHOW goodness-of-fit test p=0.5704. Sp=0.0001, R²=54.4%, sp=0.0001, Hosmer–Lemeshow goodness-of-fit test p=0.5375. /boys only. **p=0.0002; R²=51.9%.

Figure 1: Human brain development

although school and family characteristics also play a part. In developing countries, an estimated 99 million children of primary-school age are not enrolled, and of those enrolled, only 78% complete primary school. Most children who fail to complete are from sub-Saharan Africa and south Asia. Only around half of the children enrol in secondary schools. Furthermore, children in some developing countries have much lower achievement levels than children in developed countries in the same grade. In 12 African countries, surveys of grade 6 (end of primary school) children showed that on average 57% had not achieved minimum reading levels (webtable).

### Indicators of poor development

In the following section we estimate the numbers of children who fail to reach their developmental potential. We first identify early childhood growth retardation (length-for-age less than –2 SD according to the National Center for Health Statistics growth reference) and absolute poverty as possible indicators for poor development. We then show that they are good predictors of poor school achievement and cognition. Finally, we use these indicators to estimate the number of children involved. We identified stunting and poverty for indicators because they represent multiple biological and psychosocial risks, respectively, stunting and to a lesser extent poverty are consistently defined across countries, both are relevant to most developing countries, and worldwide data are available. We omit other risk factors that could affect children’s development because they fail to fit all the above criteria and there is marked overlap between them and with stunting and poverty. However, by using only two risk factors we recognise that our estimate is conservative.

### Assessment of stunting, poverty, and child development

Growth potential in preschool children is similar across countries, and stunting in early childhood is caused by poor nutrition and infection rather than by genetic differences. Patterns of growth retardation are also similar across countries. Faltering begins in utero or soon after birth, is pronounced in the first 12–18 months, and could continue to around 40 months, after which it levels off. Some catch-up might take place, but most stunted children remain stunted through to adulthood.

There are multiple approaches to measuring poverty. One assessment used measures of deprivation of basic needs, availability of services, and infrastructure, and surveys in 45 developing countries reported that 37% of children lived in absolute poverty, more so in rural areas. We use the percentage of people having an income of less than US$1 per day, adjusted for purchasing power parity by country because this information is available for the largest number of countries. This indicator is considered the best available despite excluding important components of poverty, and is more conservative than measures based on deprivation since it identifies only the very poorest families.

Poverty is associated with inadequate food, and poor sanitation and hygiene that lead to increased infections and stunting in children. Poverty is also associated with poor maternal education, increased maternal stress and depression, and inadequate stimulation in the home. All these factors detrimentally affect child development (figure 2). Poor development on enrolment leads to poor school achievement, which is further exacerbated by inadequate schools and poor family support (due to economic stress, and little knowledge and appreciation of the benefits of education).

Risk factors related to poverty frequently occur together, and the developmental deficit increases with the number of risk factors. Deficits in development are often seen in infancy and increase with age. For example, a cross-sectional study in Ecuador reported that the language deficit in poor children increased from 36 to 72 months of age compared with wealthier children (figure 3). As a first step to examining the use of poverty and stunting as indicators, we did regression analyses of the relation between the percentage of children completing primary school and poverty and stunting, with data from

![Figure 2: Hypothesised relations between poverty, stunting, child development, and school achievement](image-url)

![Figure 3: Vocabulary scores of Ecuadorian children aged 36 to 72 months by wealth quartiles](image-url)
developing countries (defined as the non-industrialised countries in UNICEF classification). Stunting prevalence was based on the WHO Global Database on Child Growth and Malnutrition, and absolute poverty prevalence came from UNICEF. In 79 countries with information on stunting and education, the average prevalence of stunting was 26·0%. For every 10% increase in stunting (less than –2 SD), the proportion of children reaching the final grade of primary school dropped by 7·9% (b=–0·79, 95% CI –1·03 to –0·55, R²=36·2%, p<0·0001). In 64 countries with information on absolute poverty, the average prevalence was 20%; for every 10% increase in the prevalence of poverty there was a decrease of 6·4% (b=–0·64, 95% CI=–0·81 to –0·46, R²=46·3%, p<0·0001) of children entering the final grade of primary school.

To establish whether stunting and absolute poverty were useful predictors of poor child development in individual studies, we searched the published papers and identified all observational studies that related stunting and poverty in early childhood to concurrent or later child development or educational outcomes. We also identified all studies that related stunting at school age to cognition or education, based on the assumption that stunting developed in early childhood. We selectively reviewed studies of older children that linked economic status to education, based on the assumption that stunting during early childhood predicted age of walking. Excluding studies of infants and toddlers, all studies included were useful predictors of poor child development in late adolescence,114 to cognition, literacy, numeracy, and general knowledge in late adolescence,114 and stunting at 72 months was related to cognition between 25–42 years. In Indonesia,116 weight-for-age at 1-year of age did not predict scores on a cognitive test at 7 years, whereas growth in weight between 1 and 7 years did.

To assess the size of the deficit in later function associated with a loss of 1 SD in height in early childhood, we reanalysed the data from Philippines,6 Jamaica,7 Peru,10 Indonesia,16 and Vietnam,4,7 and Chile). Only three studies46-48 reported no significant relation between stunting and poor school progress. In the Philippines, associations were recorded with weight-for-height,49 and in Ghana49 stunted children enrolled in school late but taller children left school early to earn money or help with family farming.

There are fewer studies with younger children. In Guatemala,49 Jamaica,101 Chile,102 and Kenya103 associations between height and child development measures were reported. Age of walking was related to height-for-age in Zanzibarian41 and Nepalese children,45 but height was not related to motor development in Kenyans at 6 months of age.46 Weight-for-age, which indicates a combination of weight-for-height and height-for-age, has often been used instead of stunting to measure nutrition in young children. Weight-for-age was associated with child development in India,6 Ethiopia,108 and Bangladesh.50,100

### Longitudinal studies

In Pakistan111 and Guatemala,102 growth retardation in infancy predicted age of walking. Excluding studies of children hospitalised for severe malnutrition, four published longitudinal studies showed that early stunting predicted later cognition, school progress, or both. Stunting at 24 months was related to cognition at 9 years in Peru110 and, in the Philippines to intelligent quotient (IQ) at 8 and 11 years, age at enrolment in school, grade repetition, and dropout from school.35,36 In Jamaica, stunting before 24 months was related to cognition and school achievement at 17–18 years and dropout from school.6 In Guatemala, height at 36 months was related to cognition, literacy, numeracy, and general knowledge in late adolescence,114 and stunting at 72 months was related to cognition between 25–42 years. In Indonesia,116 weight-for-age at 1 year of age did not predict scores on a cognitive test at 7 years, whereas growth in weight between 1 and 7 years did.

To assess the size of the deficit in later function associated with a loss of 1 SD in height in early childhood, we reanalysed the data from Philippines,6 Jamaica,7 Peru,10 Indonesia,16 (Guatemala had too few well-nourished children to be included). We added two other longitudinal studies, from Brazil117 and South Africa,118 that had not previously analysed the effect of stunting (table 2). In these studies, stunting between 12 and 36 months was
Table 3: Descriptive summary of follow-up studies showing association between wealth quintiles in early childhood, and later cognitive and school outcomes

<table>
<thead>
<tr>
<th>Series</th>
<th>Philippines</th>
<th>Indonesia</th>
<th>South Africa</th>
<th>Brazil</th>
<th>Guatemala*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive score</td>
<td>Reasoning and arithmetic</td>
<td>Ravens progressive matrices</td>
<td>Attained grades</td>
<td>Reading and vocabulary</td>
<td></td>
</tr>
<tr>
<td>(5 years of age at assessment, n=2485)</td>
<td>(9 years of age at assessment, n=771)</td>
<td>(7 years of age at assessment, n=1143)</td>
<td>(18 years of age at assessment, n=2222)</td>
<td>(25–41 years of age at assessment)</td>
<td></td>
</tr>
<tr>
<td>Boys (n=683)</td>
<td>Girls (n=786)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fifth quintile (wealthiest)</td>
<td>56·9</td>
<td>12·1</td>
<td>0·47</td>
<td>9·3</td>
<td>50·9</td>
</tr>
<tr>
<td>Fourth quintile</td>
<td>52·5 (–0·35)</td>
<td>11·0 (–0·31)</td>
<td>0·13 (–0·34)</td>
<td>8·2 (–0·48)</td>
<td>43·3 (–0·45)</td>
</tr>
<tr>
<td>Third quintile</td>
<td>51·6 (–0·42)</td>
<td>11·0 (–0·31)</td>
<td>0·16 (–0·63)</td>
<td>7·4 (–0·84)</td>
<td>43·6 (–0·01)</td>
</tr>
<tr>
<td>Second quintile</td>
<td>49·4 (–0·60)</td>
<td>9·5 (–0·74)</td>
<td>0·20 (–0·67)</td>
<td>6·8 (–1·11)</td>
<td></td>
</tr>
<tr>
<td>First quintile (poorest)</td>
<td>46·4 (–0·84)</td>
<td>8·4 (–1·06)</td>
<td>0·23 (–0·70)</td>
<td>6·5 (–1·24)</td>
<td>41·0 (–0·53)</td>
</tr>
<tr>
<td></td>
<td>43·6 (–0·45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (effect size as unadjusted difference from the richest quintile in z scores). *Tertiles. †SD scores.

Table 3: Descriptive summary of follow-up studies showing association between wealth quintiles in early childhood, and later cognitive and school outcomes

Related to later measures of cognition\(^{17}\) or grade attainment.\(^{18}\) Being moderately or severely stunted compared with not stunted (height-for-age greater than –1 SD) was associated with scores for cognition in every study, and the effect size varied from 0·4 to 1·05 SD. Stunting was also associated with attained grades. The consistent relation between early childhood stunting and poor child development, with moderate to large effects, justifies its use as an indicator of poor development.

**Poverty and poor development**

### Cross-sectional studies

Nationally representative studies from many countries have seen relations between household wealth and school enrolment, early dropout, grades attained, and achievement.\(^{46–50,61,121–125}\) Gaps in mean attained grades between the richest and poorest children were particularly large in western and central Africa and south Asia, reaching as high as ten grades in India.\(^{125}\) In Zambia, poor children were four times more likely to start school late than the richest children, and in Uganda the difference was ten times. Representative surveys in 16 Latin American countries\(^{122}\) also reported that family income predicted the probability of completing secondary schooling. Rural children were worse off in most studies.\(^{121}\)

There are fewer studies on wealth and development in preschool children. In 3668 Indian children under 6 years, paternal occupation was associated with developmental milestones.\(^{107}\) In Ecuador, wealth was related to vocabulary scores of children from 3 to 6 years of age.\(^{108}\) In Jamaica, 71·4% of 3887 children from more affluent families entering fee-paying preparatory schools had mastery of all four school-readiness subjects tested, compared with 42·7% of 22 241 children entering free government primary schools.\(^{125}\) An association between poverty and child development was recorded at as early as 6 months of age in Egypt,\(^{126}\) 12 months in Brazil,\(^{127}\) 10 months in India,\(^{128,129}\) and 18 months in Bangladesh.\(^{130}\) In another Brazilian study, preschool children’s language scores were associated with maternal working but not income.\(^{131}\)

**Longitudinal studies**

Several longitudinal studies have assessed the association between wealth at birth and later educational and cognitive attainment. Socioeconomic status in infancy was associated with children’s cognition at 5 years of age in Kenya.\(^{130}\) In Brazil, parental income at birth was associated with poor performance on a developmental screening test at 12 months in 1400 infants, and with school grades attained at 18 years in 2222 men on army enlistment.\(^{131}\) In Guatemala,\(^{132}\) socioeconomic status at birth was associated with school attainment and cognition in 1469 adults. We analysed data from three other longitudinal studies (table 3). Wealth quintiles at birth were related to IQ at 8 years in the Philippines;\(^{133}\) and to cognitive scores at 7 years in South Africa\(^{134}\) and 9 years in Indonesia.\(^{135}\) The effect size in all these studies was substantial, ranging from 0·70 to 1·24 SD scores between the top and bottom quintiles in children from varied socioeconomic backgrounds, and from 0·45 to 0·53 SD scores in Guatemala where all study children were poor. We had to use wealth quintiles rather than the cutoff of US$1 per day because of limitations in the data. Poor children consistently had considerable developmental deficits compared with more affluent children. Thus poverty can be used as an indicator of poor development.

**Estimate of number of children who are stunted or living in poverty**

We estimated the prevalence of children under 5 years who are stunted or living in absolute poverty in developing countries. Data for the number of children in 2004 and percent living in poverty were obtained from UNICEF\(^{136}\) and data for stunting obtained from WHO.\(^{137}\) Of the 156 countries analysed, 126 have a known stunting prevalence and 88 have a known proportion living in absolute poverty (table 4). We replaced missing country values of stunting and poverty with the average prevalence of the region for the purpose of estimating the proportion and number of disadvantaged children. Sensitivity analysis based on imputing stunting by poverty and imputing poverty by stunting through regression analysis gave similar results to using the regional average.
The most recent poverty data we obtained was up to year 2003, with median 2000 and inter-quartile range of 4 years. The most recent stunting data were up to year 2004, with median 2000 and inter-quartile range of 4 years. We extrapolated all the stunting and poverty data from 13 Multiple Indicator Cluster Surveys in developing countries with data for both stunting and a wealth index. A meta-analysis of the datasets showed that 43% of children below the poverty line were stunted. Based on this estimate, the total number of disadvantaged children is 227 million. Although the estimate of 219 million is inevitably crude, it is more conservative than the alternative estimate of 227 million; we use the lower estimate in the rest of the paper.

Figure 4 shows the numbers of disadvantaged children in millions by region. Most disadvantaged children (89 million) are in south Asia. The top ten countries with the largest number of disadvantaged children (in millions) are: India 65, Nigeria 16, China 15, Bangladesh 10, Ethiopia 8, Indonesia 8, Pakistan 8, Democratic Republic of the Congo 6, Uganda 5, and Tanzania 4. These ten countries account for 145 (66%) of the 219 million disadvantaged children in the developing world.

Figure 5 shows the prevalence by country. Sub-Saharan Africa has the highest prevalence of disadvantaged children under 5 years, 61% (table 4), followed by south Asia with 52%.
Limitations of the estimate of numbers of disadvantaged children

More than 200 million disadvantaged children is an exceedingly large amount. However, limitations in the data suggest that the estimate is conservative. We assumed that the percentage of people in absolute poverty was equal to the percentage of children in absolute poverty. This assumption probably underestimates the number of children because poverty is associated with higher fertility levels and larger household size. Furthermore, less than US$1 per day is an extreme measure of poverty, and children in slightly better off households are probably also at risk. Also, we did not take into account many other risk factors for poor development, such as maternal illiteracy, unstimulating homes, and micronutrient deficiencies.

WHO recently produced new growth standards, and the −2 SD curves for length and height-for-age are slightly higher than the −2SD curves of the previous standards in certain age ranges under 60 months. Therefore, if we used the new growth standards our estimate of prevalence of stunting and disadvantaged children would be slightly higher.

The precision of the estimate of disadvantaged children would be improved with internationally comparable data for maternal education and stimulation in the home. We also need data to establish which cutoff for income and poverty is best for identifying children at high risk. Internationally comparable and feasible measures of child development would produce the best estimate of disadvantaged children, and there is an urgent need to develop such measures both to more accurately assess the problem and to assess interventions.

Some of the disadvantaged children would have IQs of less than −2 SD, the level used to diagnose mild mental retardation (IQ 50–69). However, a deficit in adaptive behaviour is usually needed to make the diagnosis and these data are not available, although most would have learning problems in school and restricted employment opportunities. We are concerned in this series about the loss of potential across the whole range of cognitive ability.

Economic implications of poor child development

Disadvantaged children in developing countries who do not reach their developmental potential are less likely to be productive adults. Two pathways reduce their productivity: fewer years of schooling, and less learning per year in school. What is the economic cost of one less year of schooling? Studies from 51 countries show that, on average, each year of schooling increases wages by 9.7%. Although some of the studies had methodological weaknesses, this average matches another more rigorous study, which reported that each year of schooling in Indonesia increased wages by 7–11%.

Both stunting and poverty are associated with reduced years of schooling. Table 5 presents data for school grades attained in 18-year-old Brazilian men, by income quintile and stunting status in early childhood. We estimate from these data that the deficit attributed to being stunted (height-for-age less than −2 z scores compared with non-stunted greater than −1 z scores), stratified for income quintiles, was 0.91 grades, and the deficit from living in poverty (first vs third quintile of income) stratified for stunting status was 0.71 grades. Furthermore, the deficit from being both stunted and in poverty (first income quintile) compared with being non-stunted and in the third income quintile was 2.15 grades.

Stunted children also learn less per year in school. Data from the Philippines has shown that, controlling for years of schooling and income, the combined reading and math test score of stunted children was 0.91 SD below that of non-stunted children. This reduction was equivalent to 2.0 fewer years of schooling. Regression analysis with Jamaican data corroborate this finding; controlling for wealth and grade level, stunted children’s combined math and reading test score was 0.78 SD below those of non-stunted children. Controlling for stunting, poor children almost certainly learn less per year in school, but we know of no studies that convincingly estimate the deficit.

<table>
<thead>
<tr>
<th>Income quintile</th>
<th>Poorest 20%</th>
<th>2nd quintile</th>
<th>3rd quintile</th>
<th>4th quintile</th>
<th>Wealthiest 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAZ ≥ −1</td>
<td>6.96 (2.11)</td>
<td>7.10 (2.17)</td>
<td>7.69 (2.05)</td>
<td>8.43 (1.89)</td>
<td>9.40 (1.83)</td>
</tr>
<tr>
<td>n</td>
<td>141</td>
<td>213</td>
<td>274</td>
<td>325</td>
<td>336</td>
</tr>
<tr>
<td>HAZ −1 to −2</td>
<td>6.67 (2.05)</td>
<td>6.44 (2.08)</td>
<td>7.06 (1.92)</td>
<td>7.74 (1.91)</td>
<td>9.27 (2.03)</td>
</tr>
<tr>
<td>n</td>
<td>116</td>
<td>123</td>
<td>127</td>
<td>111</td>
<td>59</td>
</tr>
<tr>
<td>HAZ &lt; −2</td>
<td>5.54 (2.17)</td>
<td>6.56 (1.98)</td>
<td>7.03 (2.05)</td>
<td>6.65 (2.42)</td>
<td>8.69 (2.29)</td>
</tr>
<tr>
<td>n</td>
<td>71</td>
<td>78</td>
<td>38</td>
<td>17</td>
<td>13</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated. HAZ=height-for-age z score. *Data provided by the Pelotas Birth Cohort Study, Brazil.
Assuming that every year of schooling increases adult yearly income by 9%,137,138 we estimate that the loss in adult income from being stunted but not in poverty is 22-2%, the loss from living in poverty but not being stunted is 5-9% and from being both stunted and in poverty is 30-1% (table 6). Taking into account the number of children who are stunted, living in poverty, or both (table 6), we calculate the average deficit in adult yearly income for all 219 million disadvantaged children to be 19-8%. This estimate is limited by the scarcity of data for the loss of learning ability of children in poverty, and almost certainly underestimates the true loss.

Clearly, disadvantaged children are destined not only to be less educated and have poorer cognitive function than their peers but also to be less productive. In consideration of the total cost to society of poor early child development, we need to take into account that the next generation will be affected, sustaining existing inequities in society with their attendant problems.67 Where large numbers of children are affected, national development will also be substantially affected. These costs have to be weighed against those of interventions.

Conclusion

Many children in developing countries are exposed to multiple risks for poor development including poverty and poor health and nutrition. There are few national data for children's development but our conservative estimate is that more than 200 million children under 5 years of age in developing countries are not developing to their full potential. Sub-Saharan African countries have the highest percentage of disadvantaged children but the largest number live in south Asia. The children will subsequently do poorly in school and are likely to transfer poverty to the next generation. We estimate that this loss of human potential is associated with more than a 20% deficit in adult income and will have implications for national development. The proximal causes of poor child development are analysed in the second paper in this series.

The problem of poor child development will remain unless a substantial effort is made to mount appropriate integrated programmes. There is increasing evidence that early interventions can help prevent the loss of potential in affected children and improvements can happen rapidly (see third paper in this series). In view of the high cost of poor child development, both economically and in terms of equity and individual well-being, and the availability of effective interventions, we can no longer justify inactivity.

Conflict of interest statement

We declare that we have no conflict of interest.

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International Child Development Steering Group—

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### Table 6: Deficit associated with stunting, poverty (first vs third quintile of wealth), and both, in schooling and percentage loss in yearly income in developing countries

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Deficit in school grades attained (compounded)</th>
<th>Deficit in learning ability per grade in grade equivalents</th>
<th>Total deficit in grade equivalents</th>
<th>Percentage loss of adult yearly income per grade</th>
<th>Total percentage loss of adult yearly income (compounded)</th>
<th>Number (%) of children younger than 5 years in developing countries</th>
<th>Average percentage loss of adult yearly income per disadvantaged child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil19</td>
<td>0·911</td>
<td>2·0</td>
<td>2·91</td>
<td>8·3%</td>
<td>22·2%</td>
<td>92·9 (16·6%)</td>
<td>19·8%</td>
</tr>
<tr>
<td>Poor only</td>
<td>0·715</td>
<td>≥0 ¶</td>
<td>0·71 ¶</td>
<td>8·3%</td>
<td>5·9%</td>
<td>62·8 (11·2%)</td>
<td></td>
</tr>
<tr>
<td>Poor only</td>
<td>2·15†</td>
<td>≥2·0 ¶</td>
<td>4·15 ¶</td>
<td>8·3%</td>
<td>30·1%</td>
<td>62·8 (11·2%)</td>
<td></td>
</tr>
<tr>
<td>Poor only</td>
<td>Sum of columns 1 and 2</td>
<td></td>
<td></td>
<td>30·1%</td>
<td>30·1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil19</td>
<td>Sum of columns 1 and 2</td>
<td></td>
<td></td>
<td>30·1%</td>
<td>30·1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*An increase of one grade of schooling is assumed to increase income by 9%.137,138 Implies that a reduction of 1 year of schooling will reduce income by 8·3% (1/1·09–1 = 0·083); that is, a person with an income of 91·7 due to a loss of 1 year of schooling would have had an income of 100 (91·7×0·99) had that person not lost that year of schooling: (1/1·092.91)–1=–0·222; (1/1·090·71)–1=–0·059; (1/1·094·15)–1=–0·301. (Deficit associated with stunting, controlling for wealth quintiles. (The estimate is a weighted average of the differences between stunted [≥2·0] and non-stunted [<2·0] children in the five wealth quintiles, with the weights inversely proportional to the square of the SE of the quintile-specific difference). §Deficit associated with poverty, controlling for stunting (similar method to ‡). ¶Indicates that the figure is the lower bound and under-estimates true figure because the effect of poverty on learning per year of schooling is unknown. |(Difference between non-stunted and third quintile vs stunted and first quintile in Brazil (table 5).)


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Drug treatments for obesity: orlistat, sibutramine, and rimonabant

Raj S Padwal, Sumit R Majumdar

Antiobesity treatment is recommended for selected patients in whom lifestyle modification is unsuccessful. Two antiobesity drugs are currently licensed for long-term use. Orlistat, a gastrointestinal lipase inhibitor, reduces weight by around 3 kg on average and decreases progression to diabetes in high-risk patients; adverse gastrointestinal effects are common. Sibutramine, a monoamine-reuptake inhibitor, results in mean weight losses of 4–5 kg, but is associated with increases in blood pressure and pulse rate. Rimonabant, the first of the endocannabinoid receptor antagonists, reduces weight by 4–5 kg on average and improves waist circumference and concentrations of HDL cholesterol and triglyceride; however, an increased incidence of mood-related disorders has been reported. To date, all antiobesity drug trials have been limited by their high attrition rates and lack of long-term morbidity and mortality data. Other promising antiobesity drugs, including those acting within the central melanocortin pathway, are in development, but are years away from clinical use. In light of the lack of successful weight-loss treatments and the public-health implications of the obesity pandemic, the development of safe and effective drugs should be a priority. However, as new drugs are developed we suggest that the assessment processes should include both surrogate endpoints (ie, weight loss) and clinical outcomes (ie, major obesity-related morbidity and mortality). Only then can patients and their physicians be confident that the putative benefits of such drugs outweigh their risks and costs.

“The devil has put a penalty on all things we enjoy in life. Either we suffer in health or we suffer in soul or we get fat.”

Albert Einstein, 1879–1955

Driven by the need to survive, and influenced by complex genetic, emotional, and sociocultural factors, the desire to eat is one of the strongest of human instincts. In food deprivation, powerful orexigenic (appetite-stimulatory) responses are elicited.1 After weight loss, compensatory metabolic alterations resist further reductions in weight.2 However, there are no equally potent or effective counter-regulatory mechanisms for decreasing food intake or increasing physical activity after chronic weight gain. Thus, in modern times, the obesity pandemic represents the inevitable consequence of placing a population preselected for efficient fat storage into a sedentary environment of caloric overabundance. In such a setting, unless volitional control of energy intake and expenditure is consciously and persistently exercised, weight will gradually increase despite remarkably little net excess caloric intake.3

Over the past three decades, the consequences of this tendency to gain weight have become increasingly apparent. The International Obesity Task Force estimates that more than 300 million individuals worldwide are obese and an additional 800 million are overweight.4 For the first time, the number of overweight individuals in the world is equivalent to the number underweight.5 Unless current trends are reversed, the health-related and economic consequences will be enormous. Successful maintenance of the lifestyle changes needed for optimum bodyweight, although possible in some individuals,6 is uncommon7 and the current methods for lifestyle modification (alone) as a treatment for obesity are widely regarded as ineffective.

Antiobesity pharmacotherapy is a potentially important adjunctive treatment to lifestyle modification. The ideal antiobesity drug has three important characteristics. First, it should cause sustained clinically significant reductions in bodyweight and reduce obesity-related morbidity and mortality. Second, the benefit–risk ratio of the drug must be favourable. The track record for safety of antiobesity drugs has been particularly poor,8 whereas their potential for abuse by non-obese individuals striving to lose weight is high.9 Third, future affordability and availability are important considerations because obesity is a condition that disproportionately affects minorities and those of low socioeconomic status.7

With these factors in mind, who might benefit from antiobesity treatment? Patients with a body-mass index (BMI) of 30 kg/m² or greater or a BMI of 27·0–29·9 kg/m² with a major obesity-related comorbidity (eg, hypertension, diabetes, obstructive sleep apnoea) are currently deemed eligible for antiobesity drug treatment.10 Weight loss of between 5–10% of initial bodyweight is associated with improvements in cardiovascular risk profiles and reduced incidence of type 2 diabetes.11,12 Therefore, as a general guideline for weight reduction, the National Institutes of Health (NIH) has recommended a 10% weight-loss
threshold. For antiobesity drugs in particular, the European Agency for the Evaluation of Medicinal Products (EMEA) has suggested minimum target thresholds for placebo-subtracted weight loss of 10% for new drugs. This degree of weight loss has not been a requirement for approval and none of the marketed antiobesity drugs produces average placebo-subtracted weight losses of 10% or more. However, combined with the weight losses achieved through lifestyle modification, 5–10% weight-loss thresholds are achievable by most patients.

Here we review the three major drug options for the long-term treatment of obesity. We discuss orlistat and sibutramine, the two drugs currently available, as well as rimonabant, the first of a new class of antiobesity drugs known as the endocannabinoid receptor antagonists. For more comprehensive reviews of additional older drugs or early-phase investigational agents, the reader is referred elsewhere.11,14–20

Long-term antiobesity drug treatments

Orlistat

Orlistat, first approved in 1998, is a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by around 30%. The compound is a partly hydrated derivative of an endogenous lipstatin produced by *Streptomyces toxytricini*. Typically, 120 mg three times daily is prescribed with meals; half-strength orlistat is currently being assessed by the Food and Drug Administration (FDA) for over-the-counter use in the USA. Because of low systemic absorption and first-pass metabolism, the bioavailability of orlistat is less than 1%. Most of the drug is excreted unchanged in faeces (table 1).21,22

Efficacy

In a 4-year double-blind placebo-controlled randomised study of 3305 Swedish obese patients, orlistat reduced weight by 2.7 kg on average and decreased the incidence of type 2 diabetes from 9.0% to 6.2% (hazard ratio 0.63; 95% CI 0.46–0.86). Only 43% of patients completed this study and the beneficial effects were almost all in patients with impaired glucose tolerance at baseline. In a meta-analysis of 11 placebo-controlled trials of 1 year in 6021 overweight or obese patients, orlistat reduced weight by 2.9% (95% CI 2.3–3.4%).15,16 The number of patients reaching 5% and 10% placebo-subtracted weight-loss thresholds was 21% (19–24%) and 12% (8–16%) greater with orlistat than with placebo. Orlistat also reduced blood pressure by 1.8 mm Hg systolic (95% CI 0.9–2.6 mm Hg) and 1.6 mm Hg diastolic (0.7–2.4 mm Hg), LDL cholesterol by 0.27 mmol/L (0.22–0.31 mmol/L), and fasting glucose in patients with diabetes by 0.8 mmol/L (0.3–1.3 mmol/L). No clinically significant effects on triglycerides or HDL cholesterol were seen. Attrition rates were high, averaging 33%. Other than diabetes incidence, there are no long-term outcome data showing that orlistat reduces major obesity-related morbidity and mortality, and we were unable to find references to orlistat-related mortality trials underway.

Adverse effects

The major adverse effects with orlistat are gastrointestinal. Fatty and oily stool, faecal urgency, and oily spotting occurred in 15–30% of orlistat-treated patients (2–7% with placebo). Faecal incontinence was observed in 7% of orlistat-treated patients compared with 1% of those on placebo. To prevent possible deficiencies of fat-soluble vitamins, coprescription of a daily multivitamin is recommended. Orlistat can reduce the absorption of amiodarone and ciclosporin and can potentiate the effect of warfarin. Systemic adverse effects are minimal because of the lack of systemic absorption. Initial concerns of an increased risk of breast cancer in orlistat-treated patients were assuaged after an independent review showed that most cases had the cancer before the drug was started.24

Sibutramine

Pharmacology

Originally developed as an antidepressant, sibutramine is a centrally acting monamine-reuptake inhibitor that mainly acts to increase satiety. Sibutramine also stimulates thermogenesis; however, this secondary action plays a minor part in weight reduction. The drug was approved in the USA in 1997 and in the European Union in 1999. Sibutramine undergoes extensive first-pass metabolism, mainly by hepatic cytochrome P450 3A4 enzymes, to active primary (M1) and secondary (M2) amine metabolites, which are more potent than the parent compound. Most of the drug and its active metabolites are renally excreted (table 1).

Efficacy

In three randomised double-blind, placebo-controlled weight-loss trials of 1 year, in 929 overweight or obese patients, sibutramine reduced weight by 4.6% (95% CI 3.8–5.4%). Attrition rates in these three trials averaged 48%. The number of patients reaching 5% and 10% placebo-subtracted weight-loss thresholds was 34% (28–40%) and 15% (4–27%) greater with sibutramine than with placebo. In long-term studies, sibutramine has had little effect on concentrations of LDL cholesterol and on glycaemic control, and has had conflicting effects (no change to mild improvement) on concentrations of triglyceride and HDL cholesterol.19,21,22

The efficacy of sibutramine is greatly enhanced when used with intensive lifestyle modification and regular frequent follow-up visits. In a 1 year randomised trial, 224 obese adults received sibutramine alone, sibutramine plus brief individualised lifestyle modification (8–10 visits of 10–15 min each), group lifestyle modification alone (30 sessions), or sibutramine plus 30 sessions of group lifestyle modification.23 Those in
the lifestyle modification plus sibutramine group lost
the most weight, an average 12.1 kg compared with
5.0 kg with sibutramine alone (mean difference 7.1 kg,
estimated 95% CI 3.9−10.2 kg).

As with orlistat, long-term data on the effect of
sibutramine on major obesity-related morbidity and
mortality are lacking. However, the ongoing Sibutramine
Cardiovascular Outcomes (SCOUT) trial is assessing the
efficacy of sibutramine in reducing myocardial infarction,
stroke, and cardiovascular mortality in 9000 obese and
overweight patients. This study should finish in 2008.35

Adverse effects
Common side-effects include insomnia, nausea, dry
mouth, and constipation. By contrast with fenfluramine
and dexfenfluramine, sibutramine does not increase
release of serotonin and has not been associated with
valvular heart disease or pulmonary hypertension.36−38
Concomitant treatment with monamine-oxidase inhib-
itors or serotoninergic drugs is also not recommended
because of the potential risk of serotonin syndrome.38

Furthermore, sibutramine has been associated with
small increases in blood pressure and pulse rate, leading
to concerns about potential cardiovascular toxic effects.
In 2002, sales of sibutramine in Italy were temporarily
suspended after reports of adverse cardiovascular events
(mainly tachycardia, hypertension, and arrhythmias)
including two deaths.39 The evidence linking sibutramine
to these events was not deemed definitive; an independent
review by EMEA concluded that sibutramine had a
favourable risk–benefit ratio and the drug was reinstated.40
However, the drug is not recommended in patients with
uncontrolled hypertension, pre-existing cardiovascular
disease, or tachycardia.38,40

Rimonabant
Pharmacology
The mood-altering effects of Cannabis sativa are well
recognised and the plant has been used therapeutically
and recreationally for centuries for various medical
conditions.41 The ability of recreational marijuana to
reliably stimulate appetite (the munchies) generated
interest in the use of endogenous cannabinoid agonists and
antagonists for weight-related disorders.

The endocannabinoid system includes two major
receptors, the CB1 and CB2 receptors, and two major
ligands, anandamide (derived from the Sanskrit
ananda or bliss) and 2-arachidonoyl-glycerol (2-AG).42,43
Endocannabinoids are polyunsaturated phospholipid-derived
eicosanoids produced on demand44 from arachidonic
acid that elicit many biological responses, including
counteracting stressful stimuli such as food deprivation,
aversive memories, and pain.45 In the brain, endo-
cannabinoids act in a retrograde manner (moving from
postsynaptic neurons to presynaptic CB1 receptors) and are
rapidly cleared.45−47 The CB1 receptor is a G-protein-
coupled receptor that is extensively expressed in the
CNS, including in areas vital to the control of food
intake.46 Endocannabinoids interact with several
anorexigenic and orexigenic pathways within the CNS,
including the central melanocortin and mesolimbic
pathways, increasing motivation to eat and stimulating
food intake.45−48 Rimonabant, the first CB1-receptor blocker,49
was initially intended as an antiobesity and smoking-cessation
dual-purpose drug; however, the latter development
programme has been discontinued. Rimonabant is
currently under consideration for approval at the FDA
and has been approved by EMEA.

Rimonabant is a potent CB1-selective ligand, with
1000-fold greater affinity for the CB1 receptor than the
CB2 receptor (table 1).50 The drug is hepatically metabolised
and excreted in bile. Because of a larger peripheral
volume of distribution, obese individuals have a drug
half-life that is twice as long (16 days) as non-obese people
(table 1).51 Rimonabant produces a dose-dependent
reduction in food intake in various rodent models,52,53
effects that seem to be both centrally and peripherally
mediated (figure). Potential peripheral mechanisms
include enhanced thermogenesis via increased oxygen
consumption in skeletal muscle,54 diminished hepatic55
and adipocyte lipogenesis,56 augmentation of adiponectin

The mood-altering effects of
Pharmacology

<table>
<thead>
<tr>
<th>Sibutramine</th>
<th>Orlistat</th>
<th>Rimonabant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Monoamine-reuptake inhibitor (primarily norepinephrine and serotonin)</td>
<td>Gastrointestinal lipase inhibitor</td>
</tr>
<tr>
<td>Typical dose</td>
<td>10−15 mg once daily</td>
<td>120 mg twice daily with meals</td>
</tr>
<tr>
<td>Absorption</td>
<td>77%</td>
<td>Minimal</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>94%</td>
<td>99%</td>
</tr>
<tr>
<td>Time to peak concentration</td>
<td>1.2 h (2.5−3.6 h for metabolites)</td>
<td>8 h</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Primarily via hepatic cytochrome 3A4 enzymes to active M1 and NO metabolites</td>
<td>Some metabolism within gastrointestinal wall to inactive metabolites</td>
</tr>
<tr>
<td>Elimination</td>
<td>Primarily urine (77%)</td>
<td>Faeces (over 96% of total drug ingested, 83% unchanged)</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>1.1 h (M1 metabolite, 14 h; M2 metabolite, 16 h)</td>
<td>14−19 h</td>
</tr>
</tbody>
</table>

Table 1: Pharmacological properties of sibutramine, orlistat, and rimonabant
Table 2: Results of Rimonabant In Obesity (RIO) programme at 1 year

<table>
<thead>
<tr>
<th>Population</th>
<th>Follow-up rate</th>
<th>Comparison (n)</th>
<th>Placebo-subtracted improvement in outcome with rimonabant 20 mg daily* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIO-Europe64</td>
<td>63%</td>
<td>Rimonabant 20 mg daily (599) vs rimonabant 5 mg daily (603) vs placebo (305)</td>
<td>Weight (kg) 4·8 (3·9–5·7) vs 4·1 (3·1–5·1) vs 9 (6–12)</td>
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<td></td>
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<td></td>
<td>Waist circumference (cm) 4·1 (3·1–5·1) vs 4·1 (3·1–5·1) vs 9 (6–12)</td>
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<td>HDL cholesterol (%) 3·9 (3·2–4·6) vs 3·3 (2·4–4·1) vs 8 (6–11)</td>
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<td></td>
<td>Triglyceride (%) 5·4 (4·6–6·2) vs 4·7 (3·7–5·7) vs 8 (5–11)</td>
</tr>
<tr>
<td>RIO-Lipids62</td>
<td>62%</td>
<td>Rimonabant 20 mg daily (345) vs rimonabant 5 mg daily (345) vs placebo (342)</td>
<td>Weight (kg) 5·4 (4·6–5·2) vs 4·7 (3·7–5·7) vs 8 (5–11)</td>
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<td></td>
<td>Waist circumference (cm) 4·7 (3·7–5·7) vs 8 (5–11) vs 12 (6–19)</td>
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<td></td>
<td>HDL cholesterol (%) 3·9 (3·2–4·6) vs 3·3 (2·4–4·1) vs 8 (6–11)</td>
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<td></td>
<td>Triglyceride (%) 5·4 (4·6–6·2) vs 4·7 (3·7–5·7) vs 8 (5–11)</td>
</tr>
<tr>
<td>RIO-North America63</td>
<td>61%</td>
<td>Rimonabant 20 mg daily (1222) vs rimonabant 5 mg daily (1216) vs placebo (607)</td>
<td>Weight (kg) 4·7 (4·1–5·4) vs 3·6 (2·9–4·3) vs 7 (6–9)</td>
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<td>Waist circumference (cm) 3·6 (2·9–4·3) vs 7 (6–9) vs 13 (9–18)</td>
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<td></td>
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<td></td>
<td>HDL cholesterol (%) 3·9 (3·2–4·6) vs 3·3 (2·4–4·1) vs 8 (6–11)</td>
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<td></td>
<td>Triglyceride (%) 4·7 (4·1–5·4) vs 3·6 (2·9–4·3) vs 7 (6–9)</td>
</tr>
<tr>
<td>RIO-Diabetes64</td>
<td>66%</td>
<td>Rimonabant 20 mg daily (339) vs rimonabant 5 mg daily (358) vs placebo (348)</td>
<td>Weight (kg) 3·9 (3·2–4·6) vs 3·3 (2·4–4·1) vs 8 (6–11)</td>
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<td>Waist circumference (cm) 3·3 (2·4–4·1) vs 8 (6–11) vs 16 (10–23)</td>
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*Intention-to-treat last-observation-carried-forward, means shown. When necessary, 95% CIs were calculated from data reported.
Adverse effects
The most frequent adverse events are nausea, dizziness, diarrhoea, and insomnia, each occurring 1–9% more frequently than with placebo. Side-effects leading to drug discontinuation occurred in 13–16% of patients taking the 20 mg dose. In RIO-Europe, RIO-North America, and RIO-Lipids, drug discontinuation due to psychiatric disorders (mainly depression) occurred in 6–7% of rimonabant-treated individuals, an absolute increase of 2–5% over placebo. Because patients with significant mental illness were excluded from the RIO programme, these estimates of the potential psychiatric side-effects of this drug are conservative.

Clinical applications of the available evidence
There are no definitive data showing benefit of one antiobesity drug over another and all three drugs are limited by modest efficacy and low rates of persistence with treatment. Therefore, if drug treatment is to be started, the initial choice is largely based on patients’ preference, associated cardiovascular risk factors, and adverse effect profiles. Individual drug-plan coverage and local formulary costs are also important. Without definitive head-to-head trials, we suggest the following approach to initial pharmacotherapy on the basis of our review of the evidence and clinical experience. Orlistat reduces LDL concentrations and diabetes incidence, is associated with slight reductions of blood pressure, and is not associated with major systemic toxic effects. Thus this drug might be especially useful in patients at high risk for developing type 2 diabetes, with high LDL cholesterol concentrations, or with pre-existing cardiovascular disease. Orlistat should be avoided in patients with chronic diarrhoea. Sibutramine, because of its satiety-enhancing effects, might be beneficial in cases where a lack of satiety or frequent snacking is a major barrier to weight reduction. Until further efficacy and safety data are available, sibutramine should be avoided in patients with poorly controlled hypertension, pre-existing cardiovascular disease, or tachycardia. Rimonabant may be considered in patients with dyslipidaemia associated with the metabolic syndrome (low HDL cholesterol and high triglyceride concentrations) and in patients who are concurrently attempting to stop smoking. The drug should be used with caution in patients with pre-existing psychiatric illness, particularly depression or anxiety, and in those with liver impairment.

Irrespective of which drug is initially selected, treatment should be discontinued if clinically significant weight loss (ie, at least 5–10% of initial bodyweight or improvement in major obesity-related comorbidity) does not occur within the first 3–6 months. Combination treatment has not been well researched and the existing evidence does not suggest significantly greater weight loss than with single-drug treatment. Furthermore, the optimum duration of treatment is unclear. The longest duration of treatment in clinical trials is 4 years for orlistat and 2 years for sibutramine and rimonabant. Because drug discontinuation invariably leads to weight regain, if clinically significant weight loss is achieved, longer courses of treatment are reasonable to consider after the benefits and risks are re-reviewed with the patient and the lack of long-term data is acknowledged.

Conclusion
Orlistat and sibutramine produce average placebo-subtracted weight losses of less than 5%. Orlistat improves cardiovascular risk factors and reduces diabetes incidence in high-risk individuals. The risk–benefit of sibutramine, which can increase blood pressure, is being assessed in a large study of cardiovascular outcomes. Rimonabant is the first of the endocannabinoid receptor antagonists. The weight loss induced by rimonabant appears similar to that of sibutramine, and improvements in HDL cholesterol and triglyceride concentrations have been reported. An increase in the incidence of psychiatric disorders was observed in rimonabant-treated patients. Studies of all antiobesity drugs are notable for their high attrition rates and lack of data on major obesity-related morbidity and mortality.

The lack of cardiovascular morbidity and mortality endpoints in obesity drug trials represents a major gap in knowledge. Other endpoints, such as osteoarthritis, gastro-oesophageal reflux disease, sleep apnoea, and quality of life, have also been neglected. We think that antiobesity drug trials powered to show clinically important reductions in major obesity-related morbidity and mortality should be required either before these drugs are approved for widespread use or as a condition of ongoing approval. Why? First, drugs that improve surrogate endpoints such as weight loss might not necessarily improve endpoints judged to be more clinically relevant. Second, drugs can be toxic and these toxic effects are often not apparent on initial release. As a theoretical example, one might consider very preliminary data suggesting that endocannabinoids prevent stroke, limit myocardial infarction size, and inhibit cancer-cell proliferation and speculate that endocannabinoid antagonism could counteract such benefits, despite inducing weight loss. Third, new drugs are invariably expensive and, for obesity drugs, the enormous potential market amplifies projected costs. Justification of these costs when outcome data for antiobesity drugs are based only on improvements in surrogate endpoints is difficult, especially when studies show compromised internal validity due to high attrition rates.

Despite the limitations of current drugs, and their declining use in some jurisdictions, antiobesity drugs still accounted for sales of nearly a half billion US dollars in the seven largest global markets during 2000. With overall sales of antiobesity drugs projected to at least triple by 2010, development of effective drugs has become a research priority and an area of intense clinical interest. In addition to the endocannabinoid receptor antagonists, many other novel potential antiobesity drugs and targets.
have been identified, including those acting on the central melanocortin pathway, a group of neurons centred in the arcuate nucleus and hypothalamus that control appetite and energy expenditure. Examples include ciliary neurotrophic factor and other melanocortin-4 receptor agonists, ghrelin, neuropeptide Y antagonists, melanin-concentrating hormone antagonists, and peptide YY.

Detailed discussions of these drugs and targets are beyond the scope of this article and the reader is referred to [Results](#). Although newer drugs are years away from clinical use, the hope for research investments made to date is translation into safe and effective antiobesity drugs in the future. The neurobiology of obesity is extremely complex, however, with many overlapping and redundant pathways. This complexity decreases the probability that targeting any single pathway will result in dramatic weight loss and suggests that multiple drugs with different mechanisms will be needed to produce significant and persistent weight loss.

Other than bariatric surgery, which is neither a feasible nor a desirable population-based treatment for obesity, no intervention has produced consistent effective long-term weight loss. Treatments targeted at the individual are important, but equally essential is the need to elicit societal changes that address all aspects of the environment thought to be obesogenic. To be successful, such initiatives should involve the concerted efforts of all stakeholders, from policymakers to the food and drug industries, and from educators to patients and physicians. Even if lifestyle and population-based strategies are creatively and successfully implemented, the large burden of prevalent obesity dictates that many will remain at risk for obesity-related comorbidity and premature death. The search for novel drug treatments for obesity is, therefore, both legitimate and necessary. However, in our efforts to fill the therapeutic void that characterises contemporary obesity management, the benefits of obesity pharmacotherapy must outweigh the risks and costs.

**Contributors**

RSP did the literature search and wrote the initial draft of this manuscript. Both authors reviewed and interpreted the published data, identified additional studies, and co-wrote subsequent iterations of the manuscript, including the final draft.

**Conflict of interest statement**

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**References**


Lethal ECG changes hidden by therapeutic hypothermia

Hanno L Tan, Paola G Meregalli

At 0500 h one morning in September, 2005, a 42-year-old white man had a cardiac arrest while asleep. His wife, woken by his distressed breathing, provided basic life support. His medical history was unremarkable, and he used no medications. The first ECG, done by paramedics, showed ventricular fibrillation (VF), and, after defibrillation, sinus rhythm (83 beats per min) with widespread ST segment elevations, suggesting acute myocardial infarction (figure). However, on admission to hospital, primary coronary angiography and serial cardiac enzyme measurements were normal. Serum electrolytes, echocardiography, and cardiac MRI were also normal, and the cause of his VF, therefore, remained unknown. Moreover, ST elevations disappeared when he was cooled in the intensive care unit to preserve cerebral function after cardiac arrest (figure).

ST elevations reappeared as he was re-warmed 1 day later after an uneventful course—they had a triangular shape with a high take-off point and descended smoothly into a negative T wave. They occurred in lead V1 and in leads overlying the right ventricular outflow tract (ie, cranial to V1 over the third intercostal space [not shown]). This characteristic ST segment shape (coved-type') in right precordial ECG leads, their strong temperature sensitivity, and the classic clinical presentation (unexplained nocturnal VF in an otherwise healthy 40-year-old man with no structural heart disease), all fit the diagnosis of Brugada syndrome. ST elevations further increased during phlebitis-induced hyperthermia, and returned to normal at discharge (figure). The SCN5A gene, which encodes the cardiac sodium channel and is the only gene with generally accepted involvement in Brugada syndrome,2 was analysed, but no mutations were found. However, this autosomal dominant inherited disease was proven when, on family screening, the mother and two of four siblings showed the typical ST segment elevations (>2 mm in at least two contiguous leads) during drug challenge. Our patient received an implantable cardioverter/defibrillator (ICD), and had made a full recovery without recurrence of VF when seen at the last follow-up in August, 2006.

Brugada syndrome is a primary arrhythmia.2 In agreement with its functional basis, the ECG is highly variable, thereby confounding the diagnostic process. The signature ST elevations—harbingers of sudden death from VF—can increase during vagal stimulation1 and hyperthermia.4 In our patient, additional ECG changes occurred, which were previously reported to be associated with hypothermia, including sinus bradycardia, T-wave changes, and QT prolongation. Reported Brugada-syndrome-associated SCN5A mutations consistently result in reduced sodium current.2 Sodium-channel blockers (ajmaline and flecainide acetate), used in drug challenge, increase or reveal these ST elevations when they are not present at baseline. The prevalence of Brugada syndrome is unknown. In some southeast Asian regions it is endemic and a common killer among young men, second only to accidents.2 In Europe it is an important cause of previously unexplained sudden death in young individuals.3 Timely diagnosis (eg, by drug challenge) after unexplained syncope and screening of relatives of Brugada syndrome patients allows for preventive measures to avert sudden death (our patient underwent comprehensive cardiological examination, but no drug challenge; after recurrent syncopal episodes 3 years earlier). Preventive measures include the avoidance of drugs that block the cardiac sodium channel5 and the use of antipyretics during fever. In high-risk patients, prophylactic ICD implantation is recommended.7

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References
4 Smith J, Hannah A, Birnie DH. Effect of temperature on the Brugada ECG. Heart 2003; 89: 272.

Figure: ECG changes from initial cardiac arrest to discharge

Timing of ECG

<table>
<thead>
<tr>
<th>Temperature</th>
<th>After defibrillation</th>
<th>Cooling</th>
<th>Re-warming</th>
<th>Phlebitis</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>Not recorded</td>
<td>32.0°C</td>
<td>37.8°C</td>
<td>38.6°C</td>
<td>37.1°C</td>
</tr>
<tr>
<td>ST elevation in V1</td>
<td>Not recorded</td>
<td>0-0mm</td>
<td>4-0mm</td>
<td>5.5mm</td>
<td>0-0mm</td>
</tr>
</tbody>
</table>

V1
V2
V3
V4
V5
V6

Figure: ECG changes from initial cardiac arrest to discharge