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Governance questions at the Gates Foundation

The dedicated staff of the Bill & Melinda Gates Foundation do an excellent job of distributing grants to promote health and welfare for the world’s most vulnerable peoples. Indeed, funding in many crucially important areas, such as child survival, vaccines, and malaria, might well be neglected were it not for the generosity and vision of Bill and Melinda Gates. But are the US$32 billion that underpin the Foundation’s philanthropy invested in a manner that contradicts the Foundation’s ideals?

This question was raised by two articles that appeared in the Los Angeles Times on Jan 7 and 8 this year. The articles maintain that the Gates Foundation’s endowment is often invested in companies whose practices hurt the same people the Foundation’s donations seek to help. These businesses include major polluters in the developing world and pharmaceutical companies who have sought to restrict access to much-needed drugs. This is an important debate of strong public interest and with no easy answers.

In a statement responding to the LA Times articles, the Foundation’s Chief Operating Officer, Cheryl Scott, said the Foundation does not invest “if a company’s profit model is centrally tied to corporate activity that we find egregious”, which is why the Foundation does not own tobacco stocks. The Foundation would also avoid investments that represented a conflict of interest for the Gates family. “The Foundation is a passive investor because we want to stay focused on our core issues”, she writes. A more activist investment policy would be a major undertaking, she argues, which would distract the staff from the Foundation’s core work.

Alternatively, there are those who would contend that with $19 invested for every $1 given in grants, the investments provide an enormous opportunity to further the Foundation’s aims. For example, reported stakes of over $100 million each in Abbott Laboratories, Schering Plough Corporation, and Merck & Co, could influence those companies to improve access to medicines for less privileged populations; similarly sized holdings in BP and Exxon Mobil could be used to press for more environmentally sound practices. Moreover, shareholder activism may increase the value of holdings in the long-term and further the Foundation’s aims.

Traditionally, philanthropies have been judged by the purposes to which they apply their grants, not the provenance of their fortunes. But increasingly foundations are realising that as owners of stock, they have a responsibility to participate in environmental, social, and governance issues. The UN’s Principles for Responsible Investment, launched less than 1 year ago, is already supported by investors representing $4000 billion and provides a framework for ethical investing that emphasises the use of proxy voting rights to secure sustainable long-term outcomes that benefit investors, employees, and communities.

Many charitable foundations already embrace responsible governance. For instance, at the UK’s Wellcome Trust a synergistic approach between grant-giving and investment is part of the constitution. Not only does the £12 billion Trust seek ethical and socially responsible investments, but it also pursues a policy of active shareholder involvement and was the first institutional investor in the UK to commission a specialist shareholder activist firm to work on its behalf.

The Gates Foundation has begun well, by responding promptly to the LA Times allegations, and announcing a review of investment practices. In addition to consulting other foundations that have adopted socially responsible investment policies, Foundation officers should also consult grant recipients who translate the Foundation’s ideals into action, and members of the communities—in Africa, the Americas, Asia, and elsewhere—that the Foundation seeks to serve. If grant holders or their beneficiaries believe that the goals of the Foundation are compromised by the choice and management of investments, then the Gates’ good work could indeed risk being tarnished.

However, to limit analysis to the Gates Foundation misses a larger truth. All shareholders, regardless of amount invested, are responsible as investor-owners for the behaviour of their companies. While it is naive to assume that the action of a single investor, even one as large as the Gates Foundation, can effect substantial change, the actions of many investors—be they individuals, pension funds, or large foundations—can do a great deal to improve the practices and policies of companies that may now focus only on the financial bottom line. The LA Times articles should prompt wider debate on the social costs of investment, so that they are not borne by those who can least afford to do so.

The Lancet
Ready-to-use therapeutic foods for malnutrition

Médecins Sans Frontières has just released its ninth annual list, for 2006, of the top ten under-reported humanitarian stories. Eight of the ten arose from conflict situations, but two are of more direct clinical relevance: malnutrition and tuberculosis. The three-part Lancet series on child development in developing countries, which ends today, has much to say about malnutrition, and its sister evil, poverty.

The scale of the problem is huge. In a report last September in Food and Nutrition Bulletin, Steve Collins and colleagues estimated that, annually, 1.7 million children die because of severe acute malnutrition and 3.6 million die because of moderate acute malnutrition. The latest thinking to combat malnutrition is to move into community therapeutic feeding, which can cover larger populations than hospital-based programmes, does not tie up sometimes sparse hospital resources, and involves local communities directly.

The Collins report is an overview of more than 23,000 individuals with severe acute malnutrition treated in the community in Malawi, Ethiopia, and Sudan in 2000–05. This community-based therapeutic care provides outpatient visits for acute malnutrition, and admission to hospital first if the individual has serious complications. The feeding element involves use of ready-to-use therapeutic foods (RUTF), which are lipid-based pastes that are energy dense, resist bacterial contamination, and need no cooking. They usually contain milk powder, sugar, vegetable oil, peanut butter, vitamins, and minerals. In the three countries studied, coverage rates were 73% and almost 80% of individuals recovered. 73% of the severely malnourished children were treated solely in the community. The cost per year of life gained was US$12–132.

Community-based programmes with RUTF seem to be the way forward. But milk powder often has to be imported, and peanuts can be contaminated with aflatoxin. So alternative recipes that use locally available grains and legumes are being field tested. Local production will reduce the costs of RUTF, and provide an income for the local manufacturer and farmers.

Chimera research should be lightly regulated, not banned

There is nothing the UK tabloid newspapers like more than a good pun. So when the Human Fertilisation and Embryology Authority (HFEA) was asked to decide whether to allow researchers to create hybrid embryos, in which human DNA is inserted into a hollowed-out unfertilised animal egg, The Sun’s editors simply could not help themselves. “Mootants” ran the headline. “BOFFINS want to fuse human stem cells with COW eggs—to try to find a cure for Parkinson’s.” The Daily Star’s staff had just as much fun: “Frankenbunny: hide those carrots—British scientists are on the brink of creating a bunny monster.”

With such media onslaught, the HFEA did well not to succumb to pressure from the tabloids when, on Jan 11, it decided to defer its judgment until it has “built up a proper body of evidence”. This means that the applications from the two UK research groups to use human-animal hybrid embryos to create a plentiful supply of human embryonic stem cells will be reconsidered in the autumn. This delay is probably wise in the long run, especially since the UK government recently published a review of the Human Fertilisation and Embryology Act with a view to updating it in parliament in 2008.

However, while it is entirely justifiable to be cautious when regulating new biotechnology, the research community must continue to remind the UK government not to over-regulate scientists’ activities. The UK is leading the way in stem-cell research, largely because of strict regulation in the USA and the fraud scandal that set back South Korean scientists in 2005. That advantage could quickly be lost, however.

Most members of the UK public are likely to see the benefit of creating human-animal chimera embryos for purely research purposes once the arguments for the research are fully explained. However, there is a danger that the consultation process will be dominated by those who believe that embryonic research is morally wrong. It is essential that scientists educate the public themselves and insist that the consultation process uses scientifically valid sampling techniques. If they do not, they should not be surprised if the mootants and frankenbunnies make a dramatic reappearance.
Achieving the goal for global measles mortality

The effect of measles in young children barely enters the consciousness of most mothers in developed countries. However, the disease remains a real concern for parents in many parts of Africa, Asia, and particularly the Indian subcontinent, where it accounted for 4% of deaths in children younger than 5 years in 2000–03. About 85% of the 875,000 deaths from measles in 1999 were in Africa (59%) and southeast Asia (25%). Measles vaccine had only a small effect in these areas until the establishment of the Expanded Programme of Immunisation in 1974, and coverage was further increased with the launch of the Global Alliance on Vaccination and Immunization (GAVI). WHO estimates that 77% of children worldwide now receive a first dose of a measles-containing vaccine by their second birthday. Most countries also offer a second opportunity for measles immunisation, either as part of the routine schedule or as a mass campaign.

In 2001, WHO and UNICEF drew up a plan to halve measles mortality (based on 1999 figures) by 2005. In today’s Lancet, Lara Wolfson and colleagues describe the progress made to eliminate measles in developing countries during the past 6 years and the achievement of WHO’s ambitious goal. They estimated that only 345,000 deaths occurred in 2005—a reduction of 60%. Although concerns existed about the validity of the natural history model used by the researchers, an expert group convened in 2005 to advise WHO concluded that, in the absence of any better method, this approach was the most appropriate to monitor trends. Much uncertainty exists about some of the assumptions, including attack rates in non-immunised individuals, case-fatality rates, and the variable effect of supplementary immunisation activities, depending on the background immunisation rates. The researchers have taken every effort to account for these findings, but their wide uncertainty bounds indicate the remaining degree of doubt. Ideally, accurate monitoring of actual causes of death would be used, but because they are least likely to be available in the very countries where measles is a major problem, modelling will have to suffice.

As with smallpox in the 20th century, whether measles can be eradicated is debatable. The lack of an animal reservoir, the rarity of chronic infections, a single antigenically stable serotype, and a safe and effective vaccine make eradication feasible. The main barriers include the high infectivity of the virus (thus high vaccine coverage is needed) and appropriate strategies and resources to reach most vulnerable groups. By contrast, the prospects for poliomyelitis eradication in the near future are promising. The original WHO target of elimination by 2005 might even have been achieved but for events in Nigeria in 2003. In 2001, 15 countries reported 483 cases of poliomyelitis; in 2005, this number increased to 1979 cases. Recent reports suggest that in 2006, poliomyelitis remained endemic in Pakistan, India, Nigeria, and Afghanistan, with one or more cases in a further 12 countries, to give a global total of 1874 on Jan 2, 2007.

For the greatest effect on children’s health, immunisation should be delivered as part of a strategy of Integrated Management of Childhood Illness (IMCI). “IMCI is a broad strategy designed to reduce childhood mortality, morbidity and disability in developing countries, and to contribute to improved growth and development of children under five years of age. It encompasses improving: case management skills of health providers, the health system, and family and community practices.”

Contact with a health-care professional, even for an acute illness, provides an opportunity to inquire...
about and advise on issues such as nutrition and immunisation, as well as malaria prevention with mosquito nets and vitamin A supplementation when appropriate. This more holistic approach helps to address the five conditions that make up 70% of deaths in children younger than 5 years—ie, respiratory infections, diarrhoea, measles, malaria, and malnutrition. This strategy is the approach most likely to achieve Millennium Development Goal 4—a reduced mortality of two-thirds in this age group (compared with 1990) by 2015. This reduction will need not only a concerted effort from the developing countries themselves, but also a continuing input of money and expertise from developed countries. This goal is not only a moral imperative, but also in everybody’s best long-term interests.

*David Elliman, Helen Bedford
Children’s Population Health Unit, Great Ormond Street Hospital for Children, London WC1N 3JH, UK (DE); and Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London, UK (HB)
EllimD@gosh.nhs.uk
DE and HB have previously received funding from vaccine manufacturers to attend symposiums, speak at meetings, and undertake research.

Is dietary intake of folate too low?

In today’s Lancet, Jane Durga and colleagues1 report a favourable effect of folic acid supplementation on cognitive decline in adults aged 50–70 years. By design, the trial was focused on people whose folate status was inadequate, as shown by a raised homocysteine concentration in the absence of other disorders or diseases that could account for the raised concentration (eg, vitamin B12 deficiency, renal disease). The trial was well designed and unique in its approach of targeting individuals who might benefit from folate supplementation. But how well do the folate intakes of these highly selected trial participants correspond to intakes in more representative samples of the population? And, why might folate intake be so low in human populations?

Dietary intakes of folate in the trial participants were far lower than the US recommended dietary allowance (RDA) of 400 μg a day,1 and also lower than the RDA for the Netherlands (300 μg a day), but are in line with the recommended amount of 200 μg a day in Japan and Australia. Even though the participants had low dietary intakes of folate, most did not have subnormal serum folate or erythrocyte concentrations. This fact implies that the participants were not even in the first stage of negative nutrient balance,3 although current criteria for determining inadequate folate status are crude.4 Raised baseline concentrations of homocysteine, together with substantial improvement in biochemical measures of folate and homocysteine and in cognitive function after folic acid treatment, suggest that previous dietary intakes might have been inadequate.

The RDA defines an intake that is sufficient to meet daily nutrient requirements of most individuals (97.5%) of the same age group. These levels are approximate, especially for folate, because 150 different forms of folate exist, and chemical analysis of their composition in food has variable

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accuracy. Additionally, folate is highly susceptible to oxidative destruction. 50–95% of folate content in food is estimated to be lost in storage, preparation, or manufacturing processes.5

Taking into consideration the many problems with accurate measurement of folate intake, population comparisons suggest that intakes vary greatly according to differences in dietary behaviours across different regions, ethnic groups, age, and socioeconomic circumstances. The richest natural food sources of folate include yeast, organ meats (eg, liver, kidney, tongue), green leafy vegetables (eg, spinach, collard greens), legumes, beans, and some fruits. The highest reported intakes of folate occur in populations with the highest consumption of vegetables, such as in countries in which the diet is similar to the Mediterranean diet.6 For example, the mean intake of dietary folate was 559 μg a day in Greece in people who followed the traditional Cretan diet.7 Intakes in the southern regions of Europe (France, Spain, and Portugal) are about 300–400 μg a day, and 200 μg a day in northern European regions (Ireland and Sweden).5 Intakes are also high in countries that fortify grain with folic acid, such as the USA and Canada. Before fortification of grain was introduced, the mean folate intake in the USA was estimated to be 275 μg a day, and 26% of the population had inadequate folate status according to serum concentrations.8 After the introduction of fortification, fewer than 1% of the US population had an inadequate serum folate status.5 In a US study of elderly people, before the introduction of folic acid fortification, homocysteine concentrations were raised in individuals with folate intakes of up to 280 μg a day.

As indicated above, many individuals within populations have folate intakes that might be suboptimum for physiological function.10 Our knowledge about the physiological importance of homocysteine is limited, as is our definition of inadequate folate status. To make more informed dietary recommendations for optimum folate intake, we need randomised trials that take the approach of the FACIT trial.1 In particular, future trials should specify inclusion and exclusion criteria that target individuals at various stages of nutrient balance. They should also include comprehensive monitoring of biochemical concentrations of folate and folate metabolites in addition to monitoring of system function, such as cognitive function.

*Martha Clare Morris, Christine C Tangney
Rush Institute for Healthy Aging, Chicago, Illinois, USA (MCM); and Department of Nutrition, Rush University Medical Center, Chicago, Illinois, USA (CCT)
Martha.C.Morris@rush.edu

We declare that we have no conflict of interest.

Are lipid-lowering guidelines evidence-based?

The last major revision of the US guidelines, in 2001, increased the number of Americans for whom statins are recommended from 13 million to 36 million, most of whom do not yet have but are estimated to be at moderately elevated risk of developing coronary heart disease. In support of statin therapy for the primary prevention of this disease in women and people aged over 65 years, the guidelines cite seven and nine randomised trials, respectively. Yet not one of the studies provides such evidence.

For adults aged between 30 and 80 years old who already have occlusive vascular disease, statins confer a total and cardiovascular mortality benefit and are not controversial. The controversy involves this question: which people without evident occlusive vascular disease (true primary prevention) should be offered statins? With about three-quarters of those taking statins in this category, the answer has huge economic and health implications. In formulating recommendations for primary prevention, why do authors of guidelines not rely on the data that already exist from the primary prevention trials?

We have pooled the data from all eight randomised trials that compared statins with placebo in primary prevention populations at increased risk. Unfortunately, our analysis is imperfect because these trials are not solely primary prevention: 8.5% of patients had occlusive vascular disease at baseline. We used two outcomes to estimate overall benefit (benefit minus harm): total mortality and total serious adverse events (SAEs). Total mortality was not reduced by statins (relative risk 0.95, 95% CI 0.89–1.01). In the two trials that reported total SAEs, such events were not reduced by statins (1.01, 0.97–1.05) (data on SAEs from the other trials were not reported). The frequency of cardiovascular events, a less encompassing outcome, was reduced by statins (relative risk 0.82, 0.77–0.87). However, the absolute risk reduction of 1.5% is small and means that 67 people have to be treated for 5 years to prevent one such event. Further analysis revealed that the benefit might be limited to high-risk men aged 30–69 years. Statins did not reduce total coronary heart disease events in 10 990 women in these primary prevention trials (relative risk 0.98, 0.85–1.12). Similarly, in 3239 men and women older than 69 years, statins did not reduce total cardiovascular events (relative risk 0.94, 0.77–1.15).

Our analysis suggests that lipid-lowering statins should not be prescribed for true primary prevention in women of any age or for men older than 69 years. High-risk men aged 30–69 years should be advised that about 50 patients need to be treated for 5 years to prevent one event. In our experience, many men presented with this evidence do not choose to take a statin, especially when informed of the potential benefits of lifestyle modification on cardiovascular risk and overall health. This approach, based on the best available evidence in the appropriate population, would lead to statins being used by a much smaller proportion of the overall population than recommended by any of the guidelines.

Why the disagreement? The current guidelines are based on the assumption that cardiovascular risk is a continuum and that evidence of benefit in people with occlusive vascular disease (secondary prevention) can be extrapolated to primary prevention populations. This assumption, plus the assumption that cardiovascular risk can be accurately predicted, leads to the recommendation that a substantial proportion of the healthy population should be placed on statin therapy.

A similar set of assumptions underlie the conclusions of the Cholesterol Treatment Trialists’ (CTT) collaboration, a group that undertakes periodic meta-analyses of individual participants’ data on morbidity and mortality from all relevant large-scale randomised trials of lipid-modifying treatment. The CTT Collaborators included seven trials of statins for secondary prevention and seven trials of statins for mostly primary prevention. However, instead of analysing these two groups of studies separately, they combine all the studies and report the overall effect. Because they have individual participants’ data, the CTT Collaborators have the unique opportunity to analyse the data for the 41 354 people in the true primary prevention group that they have identified as included in these studies. However, they do not report on this pure primary prevention population. Instead they calculate and report the absolute benefit of statins in 47 925 patients with no coronary heart disease at baseline; however, this group includes about 6570 patients with pre-existing cerebrovascular or peripheral vascular disease. Combination of these secondary prevention patients (5-year frequency of major vascular events 25–30%) with the true primary prevention group...
(5-year incidence of major vascular events 9%) inflates the estimate of absolute benefit from 1·5% (our estimate) to 2·5%.

The CTT collaborators have primary prevention outcome data that can resolve the issues we raise. Subpopulations of particular interest include: men, women, men aged 70 years or older, women below the age of 70 years, people with diabetes mellitus, 20% of people with the lowest bodyweight, people taking more than five drugs, and tertiles of cardiovascular risk at baseline. The following are the outcomes that would be most informative: total mortality, total SAEs, total incidence of cancer, and total cardiovascular events. This analysis would answer the key outstanding questions. First, do the data on primary prevention confirm that there is no overall benefit in adult women of any age and in men aged 70 years and older? And, second, is there significant heterogeneity between the statin treatment effect in primary prevention subgroups compared with that in secondary prevention subgroups?

If the answer to both these questions is yes, the assumption that the benefits for secondary prevention populations can be extrapolated to primary prevention populations is false and the cholesterol treatment guidelines based on this assumption should be revised.

J Abramson, *J M Wright
Harvard Medical School, Cambridge, Massachusetts, USA (JA); and Department of Anesthesiology, Pharmacology & Therapeutics and Medicine, University of British Columbia, Vancouver, BC, Canada V6T 1Z3 (JMW)
jmwright@interchange.ubc.ca

JMW declares no conflict of interest. JA is an expert consultant to plaintiffs’ attorneys on litigation involving the drug industry, including Pfizer for its marketing of atorvastatin.


Pesticide self-poisoning: thinking outside the box

Self-poisoning with pesticides is a major global public-health problem, with estimates of 300 000 deaths a year in the Asia-Pacific region alone.1 WHO now estimates that pesticide ingestion is the most common method of suicide worldwide, and has responded by launching a global Pesticides and Health Initiative.2,3

Several approaches have been proposed to reduce the high morbidity and mortality associated with pesticide self-poisoning. These strategies include improved clinical management of poisoning, provision of counselling services for vulnerable individuals, and restricted access to toxic pesticides.4,5

Restriction of the availability of pesticides to prevent their use in impulsive acts of self-harm is emerging as a favoured approach.6,7 Suggested measures include the development of agricultural practices in which pesticide use is avoided or reduced to a minimum, national bans on highly toxic pesticides, and promotion of initiatives to store pesticides safely.6 Before one or more approaches are chosen, careful assessment will be required from a combined public-health and agricultural perspective.

The pesticide industry has long argued for secure storage and use of locked boxes to prevent all forms of pesticide poisoning,7 and has started several projects testing and scaling-up the use of safe-storage boxes.8 With the active backing of industry, support for this approach has begun to gather momentum at WHO and the International Association for Suicide Prevention, with three meetings in Durban, Singapore, and Geneva.3,10

The pesticide industry’s concern about this important public-health issue is welcome. However, industry-led initiatives will probably be affected by corporate priorities for shareholders and profits, and could bypass adequate consideration and assessment of alternative strategies.
A second concern about the rapid scale-up and implementation of the locked-box approach is to carefully ensure that the approach will not have unplanned adverse effects. Intuitively, locked boxes are a sensible solution. However, in a pilot study in Sri Lanka, we found that many of the 172 participating households that received an inhouse storage box changed the location of pesticide storage from their fields (0–2 km away) to their homes. After 7 months, the number of households storing pesticides in their household increased from 54% to 98%, and only 84% locked the box. These changes could thus increase access to pesticides at times of stress. The storage box also highlighted where exactly the pesticides were stored; during our study, locked boxes were twice broken into (figure) and pesticides ingested, with one death. Another intervention of simple distribution of boxes without education or support resulted in only 30% of households locking their box.23

So far, no studies assessing the feasibility or effectiveness of safe pesticide-storage devices have been published. Such knowledge is needed before the practice can be widely recommended. Variation in cultural beliefs and agricultural practice in different communities and countries highlights the need for qualitative research to ensure generalisability to local circumstances and to implement appropriate modifications. Practical design issues, including ways to increase the likelihood of boxes being locked, should also be assessed before large-scale trials are undertaken. Infield storage devices or community-run stores could be more effective than the currently promoted inhouse boxes, but acceptable models have not yet been developed.

With the public-health community’s energy focused on safe storage, policymakers could be distracted from more immediate and longlasting solutions such as sales restrictions, product reformulation, import bans, and general reductions in agricultural pesticide use. Safe-storage interventions should be studied and assessed with other options that might not be as attractive to industry.

*Flemming Konradsen, Andrew H Dawson, Michael Eddleston, David Gunnell

Department of International Health, University of Copenhagen, 1014 Copenhagen K, Denmark (FK); South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Peradeniya, Sri Lanka (FK, AHD, ME); Faculty of Medicine and Health Sciences, School of Population Health Sciences, University of Newcastle, Newcastle, New South Wales, Australia (AHD); Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (ME); and Department of Social Medicine, University of Bristol, Bristol, UK (DG) f.konradsen@pubhealth.ku.dk

DG, ME, and AHD are on the scientific advisory group of a Syngenta-funded study to assess the toxicity of a new formulation of paraquat, and have received travel expenses to attend research group meetings. AHD and DG are on the scientific advisory group for a safe-storage project funded by Syngenta.


Adverse-event rates: journals versus databases

Clinical trials prospectively assess therapeutic approaches in specific populations, examining efficacy and adverse side-effects. Variability of adverse-event profiles across trials and populations is expected. From our experience with multicentre clinical trials in cancer research funded by the US National Institutes of Health, coordinating centres are required to monitor trials by ongoing reviews of submitted data, expedited reporting of serious adverse events, data and safety monitoring boards and internal review boards, and regular data transfers to external entities. Data from several trials can be combined for licensure (eg, by the US Food and Drug Administration [FDA]) after extensive review, appearing in summary format in package inserts thereafter (figure). Patients and physicians may select one treatment over another, on the basis of adverse events summarised in package inserts or published work. Finally, pharmacosurveillence after marketing could detect new but rare signals of adverse events.

Orit Scharf and A Dimitrios Colevas recently compared data for adverse events published in peer-reviewed manuscripts with data submitted to and monitored by the US National Cancer Institute (NCI) via the Clinical Data Update System (CDUS). Unless noted, all published adverse events were assumed to be attributable to treatment, which may or may not be true. Their review of 22 multicentre cancer trials funded by the NCI (a non-random sample from more than 200 identified trials) highlighted three problem areas: under-reporting of low-grade adverse events; under-reporting of recurrent adverse events; and inconsistent or incomplete characterisation and reporting of high-grade adverse events. Scharf and Colevas did not summarise the publishing journals, or whether the shortcomings were from a few bad apples in the barrel. We agree that increased access to raw data from clinical trials would be helpful and that the reporting of trials can be improved; however, no single publication standard has been established.

Scharf and Colevas’ report of these observations encourages readers to ask several valid questions. Can we trust the adverse-event data published from a clinical trial? Why are there differences between databases and publications? As an investigator providing data for clinical trials, why am I doing extra work to submit adverse-event data that do not appear in the publication? Stewart Anderson’s accompanying editorial suggested possible explanations for the discrepancies. These included databases that are continually updated over time, publication timelines, representation of the sample, journal constraints, and reporting of only relevant adverse events. Furthermore, in our experience, CDUS submissions are problematic because of the presence of business rules specific to: not accepting a submission with missing or queried data; not accepting reported adverse events occurring during non-treatment phases; and incomplete data mappings. We suspect that, for the sake of having a CDUS report accepted, groups undertaking trials either conservatively suppress problematic findings, or temporarily label missing attributions as “possible”, until resolution. In fact, many researchers in NCI-funded trials see the CDUS as an administrative (as opposed to scientific) duty, focusing their resources on internal quality-control reviews and audits to ensure integrity of data in subsequent publications.

A substantial volume of adverse-event data is obtained during the course of cancer clinical trials. The investigators make a conscious and informed decision to report data at a time that it is considered mature, with the knowledge that the database will continue to be updated. From our experience, of adverse events that are probed for, 85% never occur; only 3% are severe, life-threatening, or fatal; and 11% require inquiries to the local site. Much of this workload is due to assignment of adverse-event attribution, which has repeatedly been shown to be unreliable. Notably, the NCI common-data elements for randomised phase-III trials do not record attribution. Our findings suggest that adverse-event data can be condensed by at least 72% for summary purposes, which focuses resources on events of greatest clinical relevance.

The purpose of publishing results is to disseminate novel findings to the scientific community in a summary fashion. Scharf and Colevas reviewed small phase-II trials (30–100 patients), assessing investigational drugs with premature and developing adverse-event profiles. Unfortunately, in the face of life-threatening or uncommon disease with few treatment options and
scarce data, physicians might need to use such data to guide treatment. Ideally, such guidance should come from standards by medical oversight entities on the basis of randomised phase-III trials, which are better suited to address the relative burden of adverse events of different treatments.20

Should a publication include data similar to those reported via other mechanisms during the trial? Of course. In consideration of continually updated adverse-event databases, we should work to improve the mechanisms creating the problems,7,15 define acceptable rates of discrepancy, and investigate the public sharing of raw data.12,14 Should standards be used in publications? Absolutely. Researchers and journals should be more explicit.13,19 Are publications of phase-II results meant to replace package inserts and guide physicians' treatment decisions? Only with much caution. Scientific publications should be viewed for what they represent; a restricted experience in an often highly selected population. As researchers and journal editors, we are responsible for ensuring accuracy in publications, which represent the primary venue for the dissemination of scientific findings. Resources must be focused on the crucial elements: primary efficacy endpoints, and clinically relevant serious adverse events.

*Michelle R Mahoney, Daniel J Sargent
Division of Biostatistics, Mayo Clinic, Rochester, MN 55905, USA
mahoney.michelle@mayo.edu

We declare that we have no conflict of interest.

Compensation for diethylstilbestrol injury

Society’s long struggle to compensate adequately the victims of drug injury seems to have progressed a little further as a result of two recent developments in the Netherlands and France about the long-running controversy of diethylstilbestrol.

The story of diethylstilbestrol is well known.1,2 Developed in the UK in 1938 as an unpatented low-cost synthetic oestrogen,3 the drug was used widely in pregnant women on the basis of an ill-founded theory that it could prevent miscarriage by countering possible hormonal deficiency.4 However, the many companies that seized on its commercial potential sometimes claimed much more: within a decade of diethylstilbestrol’s introduction, it was promoted as a necessary adjunct to every pregnancy, and as capable of developing “bigger and stronger babies”,5 despite a lack of evidence and in the face of early warnings that the drug was carcinogenic.

Between the late 1940s and the mid 1970s, many expectant mothers routinely received diethylstilbestrol. In the USA, about 5–10 million mothers and their children were exposed to diethylstilbestrol; in the Netherlands, this figure was about 440 000. Only towards the end of this period did it become clear that the drug was not only ineffective (as had long been suspected6), but also that it was harmful. Cases of vaginal tumours, cervical tumours, and reproductive difficulties accumulated in daughters of women who were given diethylstilbestrol during pregnancy. Moreover, treated mothers had a 30–40% increased excess risk of breast cancer,7 and infertility and genital defects were recorded in sons of mothers who received the drug. By the late 1970s, the use of diethylstilbestrol in pregnancy had been abandoned worldwide; however, the damage was done.

Of the countries involved most, the Netherlands initially seemed to address the issue of compensation in the most practical way. Initial claims against manufacturers by so-called diethylstilbestrol daughters stumbled on an inability to prove which manufacturer’s product their mothers had taken. However, the High Court of the Netherlands ruled that a claimant could sue any firm known to have been supplying the drug at the relevant time. After this ruling, the manufacturers, their insurers, and a group representing those exposed to diethylstilbestrol and their advisers formed a settlement. In 2005, a new Law on Collective Settlements for Mass Injury made such an agreement binding on all parties concerned, replacing individual claims before the courts. Furthermore, on June 1, 2006, the Amsterdam Court validated the diethylstilbestrol agreement.8 After 16 years of negotiations, claims can be assessed and the first payments made.

The diethylstilbestrol agreement is based financially on €38 million, made available by the pharmaceutical firms and their insurers. Individuals are eligible for compensation if they have a disorder that can be attributed reasonably to the effects of diethylstilbestrol, provided that such treatment was given before 1977 to their mother during pregnancy. The amount of compensation set for every type of case is intended to reflect the severity of the disorder and the probability of a causal association with diethylstilbestrol.9 However admirable the intentions, is the sum available adequate to provide relief in a country where 440 000 people are thought to have been exposed to diethylstilbestrol and where the overall incidence of injury remains unknown? Nearly 35 years after the
first effects of diethylstilbestrol exposure in utero were reported, new side-effects of this drug continue to emerge. In August, 2006, two studies reported that daughters exposed in utero have a 2–3-times increased risk of developing breast cancer and are 50% more likely to have natural menopause at an early age than are other women. What should we think of awards set at €550 for severe cervical or vaginal dysplasia, €1450 for two or more miscarriages, and €4550 for metastatic breast cancer? Such figures are less than the compensation reported from France in October, 2006, where the court of Nanterre awarded €344 000 to the family of a young woman who died of diethylstilbestrol-related cancer.12 Is it not remarkable that when a woman in the Netherlands has died of metastasised breast cancer, no compensation will be payable? The current agreement has no provisions to compensate daughters who were exposed to diethylstilbestrol in utero and who developed breast cancer (irrespective of survival) because such a risk of breast cancer was suspected, but not scientifically established, when the agreement was reached. Moreover, what happens if new scientific evidence confirms a causal link between diethylstilbestrol and other types of second-generation or third-generation injury that are not considered in the current compensation agreement, thus spreading the funds more thinly? The Netherlands’ victims of diethylstilbestrol might have accepted an inadequate financial settlement too readily.

Drug development and clinical research in the UK

The problem is clear: for every new drug that is approved, US$1 billion in research is spent, 10 years of development are required, and nine of every ten drugs fail.1 With health-care costs soaring and populations ageing, society can simply no longer tolerate such inefficiencies. Clinical Research in the UK attempted to focus on one aspect of this conundrum—late-stage clinical testing. The UK Clinical Research Collaboration, a group of health-care stakeholders (of whom about half are industrial), commissioned McKinsey to study the UK’s strategic position in this arena.

Any bold attempt at nationwide clinical-research planning by so many key stakeholders is to be welcomed. The report accurately perceives the uniqueness of the UK’s single-payer health system, and clearly envisions its potential for common solutions that use information technology. It also correctly highlights the talented academic base in the UK.

By contrast, the report’s narrow focus (late-stage human testing) is surprising. Certainly, large trials contribute disproportionately to the cost of drug development, especially since nine of every ten drugs fail during human testing. Most failures result from unanticipated toxic effects or lack of efficacy, which only surface during such trials. However, neither of these disproportionately expensive inefficiencies is adequately predicted by current methods of preclinical testing, nor would they be fixed by the streamlining
of late clinical trials. Consequently, the very real complexity of efficient drug development, so much in need of a broad rethink by groups such as the UK Clinical Research Collaboration, is not covered by this narrow focus. This limitation is unfortunate for several reasons.

First, the sole focus on large trials reduces the interaction between the UK health-care system and industry to an almost transactional one, since it dwells largely on the costs and inefficiencies of clinical trials. Such a restricted focus runs the risk of portraying industry as merely a disgruntled end-user threatening to move its trial business elsewhere if the UK does not become a more efficient national contract-research organisation to meet their needs. This vision of the UK health-care system also does not engage industry as the true partner in drug discovery that it really needs to be.

Second, several scientific advances now poised to speed drug development are not even mentioned. Establishment of humanised animal models to improve accurate preclinical prediction, development of new mass-spectroscopy-based pharmacokinetic methods, prediction of drug responsiveness within populations by genetic testing, discovery and validation of surrogate biological markers, and use of innovative imaging technologies might all have equally notable benefits on the efficiency of contemporary drug development. Moreover, investigation of these problems or opportunities will need to focus on the positive dynamic of forming new partnerships between industry and the academic base that is correctly envisioned as one of the UK’s greatest strengths. To establish such congruence of goals early on sets this dialogue in a more positive tone.

Third, human testing in drug development needs substantial revision, as the report accurately details. However, the report does not mention the role that industry should have in generating solutions. Previous industrial investments in clinical research have been scant and largely confined to addressing their own needs during human testing of their drugs. Yet the report decries the falling number of clinical investigators, lack of education, dysfunctional infrastructure, lack of allied health-care personnel who are appropriately trained, and deficiencies in public awareness of the value of clinical trials and drug development. The report also strongly advocates for public investment in these areas. Yet little mention is made of a shared responsibility for maintaining the infrastructure commons that all end-users graze from over time.

Finally, most elements of the clinical research enterprise were developed more than 40 years ago and hence were simply not designed to support the current breadth, vigour, and temporal requirements of society’s needs for drug development. To sustain the quality, readiness, and vibrancy of the clinical research enterprise, a fruitful perspective might be to fully redesign the entire system with an eye to the future, as the US Institute of Medicine’s Clinical Research Roundtable and the US National Institutes of Health Director have attempted. We must fully engage and integrate industrial partners, actively involve the intellectual capital of our academic system, enlighten judicious but hopefully efficient governmental oversight, and facilitate the active participation of patients and the public. Such a re-invention will need a nuanced and iterative dialogue that envisions correctly the entire system as it should be, rather than isolating an individual component of an old and failing system without dealing with the full complexity and current opportunities. New solutions should begin with the acknowledgment that all stakeholders should contribute to the system as well as benefitting from it. We can no longer continue to be simple end-users without any obligations.

William Francis Crowley Jr
Massachusetts General Hospital, Boston, MA 02114, USA
crowley.william@mgh.harvard.edu
I declare that I have no conflict of interest.

A device before its time

That quote is a (belated) seasonal example of a Shakespearean anachronism. The more usual one is the striking clock in Julius Caesar. Shakespeare knew about such timekeepers; Caesar’s Romans only had sundials and the clepsydra (water timer). Or did they? The technical know-how of the ancient world never ceases to surprise, and the loss of such knowledge is just as fascinating as (and more baffling than) its acquisition, as the Antikythera mechanism shows. This motley collection of 80 or so damaged and encrusted bronze fragments was found in a Roman shipwreck at the bottom of the sea near the Greek island of that name in 1901. The ship sank around 65 BC. The parts are too fragile to be moved from the National Archaeological Museum of Athens, Greece, and missing items are unlikely now to be found. But today’s technology has been brought to bear on the surviving pieces and is revealing more about what the mechanism did, how it worked, and what the complete object might have looked like.

An early attempt to solve the puzzle was by Derek J de Solla Price, perhaps better known for his work on scientometrics. The device acts as an astronomical calendar or calculator, focused on the position of the sun and on the various lunar cycles, with the extra functions of eclipse prediction and calculation of the positions of some planets. Such interpretations were disputed at first. The ancient Greeks, it was thought, were too interested in philosophy and theatre to be bothered with or have the technology for something as rudely mechanical as this. However, the dating does seem to be sound and an elaborate hoax of more than Piltdownesque proportions can be ruled out. Others, such as Michael Wright, carried on where Price left off. The latest findings, which make use of three-dimensional CT scanning and other techniques, are significant, not least for the increase (from Price’s 923 to 2160) in the legible letters inscribed on the front and back of the machine. Greek lettering changed over the years—for example, Π was written with unequal legs from around 2100 years ago—and epigraphy now dates the mechanism as being a little older than previously thought, at 150–100 BC.

David Sharp
c/o The Lancet, London NW1 7BY, UK
I am a Contributing Editor for The Lancet.

Training traditional birth attendants in Guatemala

Many women choose to deliver with traditional birth attendants in Guatemala—a fact that can’t be ignored, argue local public-health officials. They hope a new, culturally sensitive approach to training TBAs will help improve their quality of care and save lives. Jill Replogle reports.

Two dozen Mayan traditional midwives, or comadronas, watch intently as their colleagues demonstrate manual removal of a retained placenta. Febe Guarcas, an experienced comadrona from the local Vida Association of traditional midwives, leads the training. She claims that in nine months the association has helped save a dozen mothers’ lives by teaching comadronas to recognise signs of risky pregnancies and births, and refer these patients to the nearest health facility.

But training sessions like this for traditional birth attendants (TBAs) are out of style in major international health circles. TBA training, policymakers say, simply hasn’t led to significant reductions in maternal mortality rates. Efforts have instead shifted toward increasing the presence of skilled birth attendants—health professionals who have midwifery training—during pregnancy and delivery, and improving emergency obstetric care.

Still, TBAs deliver more babies than trained professions in many developing countries, including Guatemala—a fact, local public-health officials argue, that can’t be ignored. “If we want to have an influence on maternal mortality, we have to work with [TBAs],” says Alejandro Silva of the Guatemalan Health Ministry’s National Reproductive Health Program.

In the 1970s and 1980s, efforts to reduce high maternal mortality rates focused on educating traditional midwives and other empirically-trained birth attendants—that is, birth attendants with no formal training but often much experience—to recognise the warning signs of a complicated pregnancy, treat basic problems, and refer risky cases to a skilled medical practitioner. However, citing a lack of results, the World Health Organization (WHO) and other major health policymakers shifted funding away from TBA training in the 1990s.

In its World Health Report 2005, WHO clearly states its position on TBA training: “The strategy is now increasingly seen as a failure. It will have taken more than 20 years to realize this, and the money spent would perhaps, in the end, have been better used to train professional midwives.”

The report says that TBAs haven’t helped get women into hospitals as was hoped, and that health professionals don’t have the time or resources to provide the level of supervision that TBAs need to be successful.

“We have to include them…but we cannot give the TBAs the responsibility for maternal health”, says Dr Virginia Camacho, adviser for the Pan American Health Organization’s (PAHO) regional maternal mortality reduction initiative.

An estimated 500 000 or more women die annually of pregnancy-related or birth-related causes, almost entirely in developing countries. Though the highest maternal mortality rates are reported in sub-Saharan Africa, many women still die in comparatively-developed Latin America, and most without access to professional care. These women must rely on family members or TBAs for help.

Attempts to evaluate the effectiveness of TBA training on reducing maternal mortality have yielded inconclusive results. A recent meta-analysis of TBA training, published in 2004 in Midwifery, found that TBA training resulted in significant increases only in vague attributes like “knowledge” and “advice”.

Guatemala appears to be an example of failed TBA training. TBAs attend roughly 60% of births nationwide and over 90% in some rural areas. Workshops and short educational programmes for the estimated 18 000 comadronas in Guatemala have been offered by the public-health ministry and non-governmental organisations for at least 50 years.

Nevertheless, Guatemala still has one of the highest maternal mortality rates in Latin America: 153 deaths per 100 000 livebirths, according to the Guatemalan public-health ministry. In comparison, the average maternal mortality rate for Latin America is 94.7 per 100 000 livebirths.

Deficient health infrastructure and budget (less than 1% of Gross Domestic Product), along with the country’s high poverty and low education levels, all contribute to Guatemala’s high maternal mortality rate. But even in areas where professional health services are available and ostensibly free, many Guatemalan women still choose to have their babies at home with comadronas.

For one thing, comadronas provide an array of services to pregnant women that hospitals and clinics do...
not, including emotional support, massage, and even housework before and after a mother delivers.

Silva, of the reproductive health programme, admits that cultural barriers and the coldness of clinical settings may keep more women from seeking professional health services than the lack of access to those services.

“In studies we’ve done people don’t question the quality of our services, they question the way we treat them”, said Silva. Indigenous, non Spanish-speaking women often face discrimination on top of language barriers.

Traditional midwives who accompany their patients to the hospital also face discrimination—not just in Guatemala but throughout Latin America, says anthropologist Robbie Davis-Floyd, an expert on childbirth and midwifery in the Americas. She says TBAs are often confused by the conflicting advice they sometimes receive from professional groups, says Nicole Berry, a medical anthropologist who has studied traditional midwives in Guatemala.

For example, Maria Angela Ramos, an empirical midwife from a poor neighbourhood near Guatemala City, says that some doctors send their patients to her to receive pre-natal massage, even though the public health ministry warns that such massages can endanger the mother and fetus.

Health analysts and policymakers now recognise the benefits of midwifery-style care for reducing maternal mortality. A recent PAHO document called on all disciplines involved in reproductive health care to use the “midwifery model of care”.

The authors of The Lancet’s recent Maternal Survival Series affirmed that the most promising strategy for decreasing maternal mortality worldwide is “making sure women throughout the world can give birth in a health facility, in the presence of a [professional] midwife”.

Some feel that this strategy should take priority over TBA training. “We’re talking about people’s lives and scarce resources. We have to identify the highest priority”, says Deborah Maine, a professor at the School of Public Health at Boston University.

Still, health officials in Guatemala say moving the majority of births into a clinical setting remains a distant goal, and for the time being, they must continue to work with TBAs.

The reproductive health programme recently began a new training campaign for TBAs, which Silva says relies on a more horizontal and culturally-sensitive approach than previous campaigns. Over 11 800 TBAs are to receive 3-days of training, during which they learn to identify warning signs, refer problem cases, and develop family and community emergency plans.

The Guatemalan public-health system and international agencies are also working to strengthen the referral system and increase the availability of professionally-trained birth attendants in communities with high rates of maternal mortality. The United States Agency for International Development began funding a training programme last year for so-called Mayan auxiliary obstetric nurses.

The eight-month training course teaches basic obstetric skills to auxiliary nurses, who must speak a Mayan language and be willing to work in isolated communities. They serve as professional links between traditional comadronas and the public-health system.

In the province of Sololá, where Guarcas practises, the public hospital hopes to stimulate demand for its services among Mayan women by having a comadrona on staff all times.

Meanwhile, Guarcas and the Vida Association dream of one day opening a birthing centre that would offer both the traditional care of comadronas and professional obstetric services.

Jill Replogle
Human resources for health in the Americas

Many countries in Latin America and the Caribbean have too many specialists and too few primary care providers and community health workers. These countries need to overhaul their training and payment practices to address this imbalance, say human resources experts. Barbara Fraser reports.

Until recently, Mauro Reyes’ hospital, a jumble of pale blue buildings on the north side of Lima, was a neighbourhood health centre. Then the government added some wards and renamed the facility San Juan de Lurigancho Hospital.

“They gave it the name, but they didn’t give me the necessary budget”, Reyes, a gynaecologist and the new hospital’s director, said. “They gave me two new wings, but they didn’t give me the personnel I need.”

Short-staffed and cash-strapped, Reyes must provide care for patients with the myriad of problems common among the urban poor of Latin America’s teeming cities ranging from parasitic infections, tuberculosis and HIV/AIDS to teen pregnancy, depression, and drug addiction.

Only half of Reyes’ staff is on the payroll; the rest are contracted. A contracted physician earns less than $550 a month and receives no benefits. “They don’t take home enough to support their families”, and most hold other jobs as well, Reyes said.

Reyes is not alone. At a recent meeting on Observatories of Human Resources for Health in the Americas in Lima, experts said hiring and retaining qualified staff is a common problem for both the region’s hospitals and community health programmes.

In fact, human resource problems, the experts said, may keep many countries from reaching high priority targets, such as the Millennium Development Goals for reducing maternal and infant mortality. It’s not just a question of pay, they acknowledge, it’s also a question of matching human resources with real needs.

Studies show a correlation between better health outcomes and the number of health-care workers.

Between 1999 and 2004, Mexico, with an average of 26.4 health-care workers per 10 000 inhabitants, had an average infant mortality rate of 19.7 per 1000 livebirths. In comparison, Nicaragua—which is unlikely to meet its MDG for infant mortality—had 9.5 health care workers and an infant mortality rate of 35.

The World Health Organization (WHO) suggests that countries need at least 20 to 25 health care workers—physicians, nurses, and midwives—for every 10 000 inhabitants. While 21 countries in the Americas and the Caribbean meet the threshold and 11 exceed it, 15 countries—with more than 163 million people—are below the minimum.

Disparities also exist within countries. In Peru, the poorest regions—mainly the rural Andean highlands and Amazon basin—have the fewest health workers and highest maternal mortality rates.

The region-wide human resources observatory system, which was launched in 1999 and now includes more than 20 countries in the Americas and the Caribbean, is a forum for research and planning of health care human resources.

To some extent, the human resources crunch is a result of the economic adjustment policies of the 1980s and 1990s, when lenders pressured governments to trim budgets and bureaucracies. Social spending dropped and has been slow to recover. In recent years, Bolivia, Guatemala and Peru have spent less than the equivalent of 1.5% of their GDP on health care.

The human resources picture is often paradoxical. In Colombia, where there are only 15.1 health workers per 10 000 inhabitants, 16.8 percent of the health workforce is unemployed. One factor, international experts say, is that education and allocation of human resources have not been based on real needs. Among other things, medical schools turn out too many specialists and too few family and community health practitioners.

Cuba has long been the exception. With a community-focused approach based on the concept that health is a human right, Cuba’s health indicators have remained good despite the
Brazil is one of many Latin American countries with a high doctor-to-nurse ratio. Its 134.6 health workers per 10,000 inhabitants gives it the highest density of human resources in the hemisphere—accompanied by nearly 100% immunisation coverage and an infant mortality rate of 7.2 per 1000 livebirths, one of the lowest in the region.

Venezuela and Bolivia are beginning to retool their health-care systems to focus more on community medicine. Brazil has made a similar effort, with the formation of 25,000 primary care teams and a commitment to spend US$45 million to beef up family practice and community medicine programmes in 90 medical, nursing and dental schools, according to Francisco Campos, the Brazilian Health Ministry’s secretary of education and labour management.

Charles Godue, head of PAHO’s Human Resources in Health Unit, says there is a growing awareness in the region that human resources management means more than just hiring, firing, and settling strikes—it means careful planning, anticipating changing needs due to demographic and epidemiological shifts.

For example, until recently most Latin American countries were “young” with at least half the population under 25 years. Now, with fertility rates dropping and life expectancy increasing, the population is ageing and chronic diseases are becoming more common. But, because of lack of foresight and planning, there are not enough geriatricians in practice and too few in training.

Many diseases, such as HIV/AIDS, tuberculosis, and malaria, are best tackled with community-based prevention programmes, the types of programs in which nurses can play a key role. But while there are three to four nurses for every physician in Canada, the United States and the English-speaking Caribbean, that ratio is reversed in most of the rest of the hemisphere, with four doctors per nurse in Brazil, Argentina, Paraguay, Uruguay, Costa Rica, and the Dominican Republic. One reason for the differences in ratios is that it is easier to get into a medical school in Latin American countries than it is in English-speaking Caribbean nations.

But even when health workers are trained, there is no guarantee they will stay: although 5000 doctors and 9000 nurses graduated in Peru between 1995 and 2005, the country saw a net increase of only 1200 physicians—and a net loss of 3500 nurses. Peruvian immigration figures show that 4416 physicians emigrated in 1992, a figure that had risen to 14,130 by 2004. Over the same period, the number of emigrating nurses rose from 2726 to 7560.

Between 21% and 32% of the health work force in the United States, Britain, Canada, and Australia is foreign born, and more than half of those workers are from low-income countries. So many health-care workers from Latin America and the Caribbean have moved to the United States, Canada, and Europe that even the destination countries are concerned about the effects on the countries of origin.

“We’re quite aware of the impact we can have on other countries. We’re constantly trying to find the right line between meeting our own needs and not doing so in a way that compromises other countries that face even greater challenges”, said Dr Joshua Tepper, assistant deputy minister of health for Ontario, Canada.

The complexity of the health human resources puzzle in Latin America calls for more comprehensive policies and planning. One challenge is to convince governments to see health care as an investment rather than an expense, said Felix Rígoli, PAHO regional adviser on human resources.

In Peru, efforts to increase the wages of health workers have caused both legislators and citizens to complain that most health funding goes to salaries. “It’s a paradox. If you ask finance ministers, they’ll say a big part of their budgets goes to salaries. If you ask nurses, they’ll say they can’t stretch their pay to make ends meet”, Rígoli said.

Government decentralisation poses another challenge, as local officials must be trained to allocate and manage health human resources effectively. Brazil, which has implemented successful family practice programmes and incentives for rural health workers, is providing human resource management training to health-care professionals in its Amazonian region and the countries along its western border.

Both health officials and educators are becoming aware of the need for joint planning to ensure that the supply of graduates meets the country’s health-care needs. The observatories have provided a forum for educators and health ministry officials to work together on long-range plans.

Once doctors, nurses, obstetricians, dentists, and other health-care professionals graduate, plans must also be in place to encourage them to remain in their home country. Wages are only one factor. Many health-care professionals who have emigrated say they have found better career paths or opportunities to provide more effective care in their destination countries.

According to Rígoli, policies and planning are key to meeting the challenges. “The functioning of health systems depends on the people who work in them”, he said. “It seems obvious, but it’s not.”

Barbara Fraser
Book

On the soma side of the street

Is there anyone who does not acknowledge the importance of psychological or social factors in medical care? Is there anyone left who does not accept that if you want to improve the quality of life and functioning of those with chronic or complex medical problems you need to treat not just the disease, but the person with the disease? It seems there must be, otherwise there would be no need for this book.

Fritz Huyse and Friedrich Stiefel have put together a coherent and evidence-based case for the “integration of the biological, psychological and social” in the care of those with chronic diseases. They call this “integrated medicine”. But why the need for a new term? The case for a truly integrated medicine was most famously articulated by George Engel when he advocated a “biopsychosocial approach” to patients’ care in 1977, and as the authors admit, “the psychological and the social systems of the patient continue to be split off, despite 50 years of the biopsychosocial model”. We still have mountains to climb before achieving a truly integrated medicine.”

Psychosomatics gave way to consultation liaison psychiatry, which had more modest but achievable goals—principally to improve the care of medically ill patients. And across the spectrum of medical care, from the metabolic syndrome, via care of the elderly, to the haemodialysis unit, this book shows clearly and repeatedly the folly of ignoring the psychological in medical practice. Once again the Cartesian dragon is well and truly slain. But is anyone listening? Apparently not, since, as this book tells us, “the psychological and the social systems of the patient continue to be split off, despite 50 years of the biopsychosocial model”. We still have mountains to climb before achieving a truly integrated medicine.

And the size of that mountain is illustrated by the hill where I work: Denmark Hill. For those unfamiliar with London topography, Denmark Hill is a street that dissects the London Borough of Camberwell. On the left hand side is the Maudsley Hospital and the Institute of Psychiatry. On the right hand side is a large general hospital, King’s College Hospital and part of its medical school. Perhaps 3000 people work on the campus on opposite sides of the road. Most belong to the mind on the left or the body on the right. Few belong to both. Of course, it is not that simple. It would spoil my rhetorical flourish to admit that the Institute of Psychiatry is overflowing with neuroscientists of every shape and form, or that many of my colleagues deliver psychological services within the general hospital. On the other hand, as I write this review we, like so many others in the UK’s National Health Service, are being forced to make large-scale “cost improvements”, and one of the things that will be “improved” is our liaison service by losing several key members of staff. The same is happening to the Oxford liaison psychiatry service. When the chips are down, cuts fall disproportionately on those who straddle the physical/mental divide.

Medical services continue to be organised to encourage dualism. Like most of the contributors to Integrated Care for the Complex Medically Ill, my clinical specialty is in liaison psychiatry. My particular interest is those grey areas that lie between medicine and psychiatry—a professional space in that dangerous zone in the middle of the street, and at times it feels that way. We currently call these the unexplained symptoms and syndromes, the latest in a long line of failed attempts to find satisfactory descriptive labels for these conditions. Many of my patients tell me about their physical symptoms—fatigue, pain, weakness, tremor, abdominal disturbances, and so on. These patients will be seen on the soma side of the street, to paraphrase the old Tin Pan Alley song. But if I show interest, they will soon admit to complex emotional lives and distress. Meanwhile, on the Maudsley side of the street, patients talk about their sadness, fear, anger, frustration, anxiety, and occasional despair. But if anyone bothers to ask, it is a rare person who does not admit to often disabling physical symptoms. When it comes to symptoms, mind and body are inexplicably intertwined. As Kurt Kroenke and Judith Rosenblum articulate in this book, there is “no area of medicine that requires tearing
down the walls of mind-body dualism more than the interface between somatic and psychological symptoms. Integrating medical and psychiatric care is essential to the patient-centred and cost-effective care of symptoms’.

But it is not so easy to cross the mind-body divide, and join the two sides of Denmark Hill together. Patients seem to be more comfortable on one or other side. In mental health and general practice settings patients often react with disdain to somatic interventions, such as antidepressants, preferring to see counsellors and not to “mess with my brain”. And on the soma side of Denmark Hill, in the general hospital, the reluctance of some patients with unexplained syndromes to engage with psychologists or psychiatrists is well known, although at the moment it is these disciplines that offer the most successful treatments. But that does not apply to all. Cancer patients across the country lobby for better psychological care. At King’s we have heeded Leonard Egede’s call in this volume for better integration of the physical and psychological into diabetes care, and the new service is immensely popular.

But acceptance of psychological therapies in the oncology clinic or psychiatrists in medical outpatients does not represent the end of dualism. Cancer patients do not lobby for psychologists because they believe that psychological factors are the cause of their cancer. They feel it is safe to engage with psychological therapies precisely because their doctors do not hold with psychosomatic theories.

In brief

Film  Doctor to a dictator

The Ugandan dictator Idi Amin insisted on being called many things: His Excellency President for Life, Conqueror of the British Empire, and Lord of all the Beasts of the Earth and Fishes of the Sea. The man, who butchered 300,000 of this own people in the course of his 8-year rule, also went by “Dr Amin”. This honorific is relevant in The Last King of Scotland, a film that depicts Amin’s tenure through the eyes of a (fictional) Scotsman living in Uganda, but not because Amin lays claim to it. A young physician named Nicholas Garrigan (James McAvoy) does, even after he abandons his humanitarian work in a village to abet one of the most murderous tyrants of the 20th century.

The story begins in Scotland in 1970; Garrigan has a freshly issued medical degree and a wide-open future. He takes a post in rural Uganda, where exotic environs and (this being the pre-AIDS era) sexual exploits await. “Whatever I can do to help”, Garrigan says cheerily on his first day at the village clinic. But he’s in for a rude awakening: the work is hard, and most of the locals prefer the witch doctor. Worse yet, the only female expatriate in town (Gillian Anderson) spurns his advances. So when a chance encounter with the country’s new headman leads to an invitation to the capital, he is happy to skip town.

Like Garrigan, Amin—played with an unnerving intensity by Forest Whitaker—is a brash, charismatic type who likes a good time. He also needs a personal doctor with no ties to the previous regime. Amin dispenses a little charm, offers Garrigan a posh bungalow, and the good doctor is soon on board. Garrigan offers advice here and there, but spends most of his time living the high life and, when necessary, defending his boss to the press as Amin solves political problems with machetes and dynamite and descends into madness. But before Garrigan knows it, a process of elimination has made him Amin’s “closest advisor”; and when he decides, after finally realising he’s got blood on his hands, that he’d like to return to Scotland, he’s not exactly free to go.

This cautionary tale, of how good intentions are betrayed by the callowness and naivety that often hide behind them, dramatises how in volatile Africa, the tie that binds medicine and politics is, tragically, sometimes soaked in blood. The film, based on Giles Foden’s acclaimed first novel, takes to task the gap-between medicine and politics. The new service is excellent monograph do not confront. Ironically, perhaps the best way to improve the psychological support for, and understanding of, patients with a range of illnesses is not to try to combine mind and body. Medical care remains fundamentally dualistic. No matter how overwhelming the evidence, we still seem best able to tackle the social and psychological only when we have solved the physical first.

Simon Wessely
Simon.Wessely@iop.kcl.ac.uk

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No-one in their right mind would have blamed him for fleeing. But as Chechnya tipped slowly into the abyss in December, 1994, Salman Yandarov, the country’s chief trauma and orthopaedics specialist, stayed put. “When many people were already leaving Grozny, I just didn’t believe there would be a war”, he recalls. “And when it all started I kept thinking it will stop in an hour, another hour. And then the bombing went on for a whole month. Most of the doctors left. There weren’t any medical personnel. I was known there and they asked me not to leave. How could I go in such a situation?”

For 10 long weeks Yandarov would live with his family in a filthy basement, darting out to assist the wounded. Fighting raged as Russian planes dropped explosives on the Chechen capital in an attempt to destroy independence fighters. “My apartment was in the centre of the city”, Yandarov explains. “There was shooting all around. We were in the basement. Then the block burned down from the top. We were almost burned to death ourselves.”

More than a decade later much has improved in Chechnya and Yandarov is now Chechnya’s chief trauma and orthopaedics specialist working with Médecins Sans Frontières (MSF) on a reconstructive surgery project in the country’s main reference hospital, Hospital Number 9. But the memories of that brutal time are painfully vivid, especially the chaotic conditions in which he tried to provide medical care. “It was impossible to do operations, we could only give first aid”, remembers 68-year-old Yandarov. “In the basement or in the yard if anybody was injured. A person would be lying there somewhere nearby where mines were exploding. We had to run around to provide help.” When he finally emerged from underground as the battle subsided, Grozny lay in ruins. “If someone had seen me they wouldn’t have believed I was a doctor! We made fires, there was soot everywhere. Our clothes were all covered in dirt. We were like tramps.” Looking at the dapper professor today, the image is hard to conjure up. Yet then it was a harsh reality. Picking their way through the rubble, Yandarov and his wife Natasha made their way to the city’s half-destroyed hospitals. They collected bandages and tugged forceps and scalpels out of the ruins. In a room at Grozny’s central polyclinic the professor set up a makeshift operating theatre and began to work. “Nobody told me to do it, I just decided myself”, he says.

The worst was yet to come. When the conflict flared again in August, 1996, Yandarov was living in a friend’s apartment near a police station with his wife and two daughters. The independence fighters who had been forced into the hills launched a huge offensive on Grozny. “When the police discovered I was a doctor they called me in. There was a jumble of wounded people—soldiers, policemen, civilians—from nearby. Two nurses whom I met in the basement helped me. The whole ground floor was piled with injured people. We worked day and night for 2 weeks.” Such a desperate scramble to save lives was a common occurrence during Chechnya’s first war between 1994 and 1996 and the second conflict in 1999 and 2000. Thankfully, such challenging conditions are no longer part of his Yandarov’s work and his focus is now on rehabilitation.

Yandarov is respected in Chechnya for staying in Grozny during the city’s darkest hours, and well known as an experienced surgeon who trained at a prestigious medical school during the Soviet era. Born in 1938 in Grozny, he went to school in Kazakhstan after Joseph Stalin sent the entire Chechen population into exile there. He returned to Chechnya in 1986 after a long spell training and working in St Petersburg. Now he is acquiring a fresh reputation as the lead doctor in the reconstructive surgery project at Grozny’s Hospital Number 9. Supported by MSF and opened in July, 2006, this project aims to tackle long-standing injuries and chronic disabilities mostly sustained during the conflicts. Manana Anjaridze, MSF’s medical coordinator in Russia, says Yandarov is a perfectionist who is the engine of the project. “He’s very demanding, in a good way. He wants to get the reconstructive operations just right, to have people around him who know how to hold the limbs correctly, who know how to bandage the right way.”

Yandarov describes one case of a woman called Madina who was shot in both hips with exploding bullets when she was 18 years old in 2000. “She had lost a lot of blood and she was brought to us hardly alive. We managed to save her but back then we had to quickly fix each patient and move on to the next one.” Many patients received no follow-up care, he adds. “One of this girl’s hips healed crooked and she was left limping. Then last September she came to us again and we managed to straighten the leg.” Anjaridze says the professor’s meticulous approach is vital. “His main idea is that if we’re going to break people’s bones and re-set them we have to get it spot on first time round”, she says. “He doesn’t want to come back to the patient a few months later and tell them, ‘Look, I’m sorry, we did it wrong, we’re going to have to break it a second time.’” Yandarov hopes the project will build on its initial success and continue to reconstruct limbs and restore lives.

Tom Parfitt
tomparfitt@hotmail.com
Obituary

David V Bates

Respiratory physiologist and leading epidemiologist who studied health effects of air pollution. Born in West Malling, UK, on May 20, 1922, he died of metastatic colorectal cancer on Nov 21, 2006, in Vancouver, British Columbia, Canada, aged 84 years.

David Bates was a young doctor working in the UK at St Bartholomew’s Hospital in 1952 when a cold fog descended on London for 4 days in December, followed by a thick sulphurous smoky fog. Unbeknown to him at the time, a coroner noted that the morgues were full. But in a city that had been subject to deadly bombings and attendant smoke, and was used to fogs, no one bothered to connect the cold fog—and resultant increase in the burning of coal—with the full morgues. “When I arrived at Bart’s Hospital on 10 December 1952, everything was normal for that time of year. Our wards at that time of year always had a number of cases of advanced chronic obstructive pulmonary disease, many in outright heart failure”, Bates would later write in Environmental Health Perspectives. London was, however, also full of cigarette smokers breathing air polluted by low-quality, high-sulphur coal. During the next 2 months 12 000 people died as a result of this fog.

The incident led to new laws on clean air, and it sparked Bates’ interest in respiratory physiology. In 1956, he moved to McGill University, Montreal, Canada, where he studied the effects of ozone on the lung. He and his colleagues published seminal papers on ventilation and lung physiology, and on what happened in the lung when it was damaged by environmental pollutants. Jon Samet, professor of epidemiology at Johns Hopkins University, Baltimore, MD, USA, met him in the late 1970s. By then, Bates had shifted his focus to the epidemiology linking pollution and lung disease. “David was a key figure in beginning to understand how the lung was damaged by environmental agents like tobacco and air pollution and what the physiological effects are”, Samet said. “Then what made him intrigued was how populations are affected, so he moved onto epidemiology.”

Bates joined the University of British Columbia in Vancouver as dean in 1972. He held that post until 1977. In the 1980s, he and Ronnie Sizto published two highly cited papers on air pollution and hospital admissions in southern Ontario, which they called “the acid summer haze effect”. A 1992 paper in Environmental Research on health indices of the adverse effects of air pollution and the question of coherence was also quite popular, Samet said, and influenced the US Environmental Protection Agency’s standards.

In 1991, Bates helped plan the University of Southern California Children’s Health Study, a study of air pollution in southern California that he advised for 15 years. “He knew more about more aspects of the health effects of air pollution than anyone I knew”, said John Peters, who worked with him at the University of Southern California and is director of the university’s division of environmental health. Bates was also a well-respected mentor. “He could tell you that you were wrong without making you feel bad”, Peters said. Bates was a “forceful advocate for environmental protection”, said Frank Speizer, professor of environmental science at Harvard School of Public Health, Boston, MA. He would urge others to go beyond the pure scientific papers and synthesise so that they could campaign for change. In 2003, he and Peters, along with colleagues, published one such paper in the American Journal of Public Health titled “Breathless in Los Angeles”. It concluded: “Our children deserve a visionary public health regulatory policy that addresses these challenges and protects them from sources of air pollution.” In the past few years, Bates co-edited a newsletter for the California Air Resources Board meant for the general public.

Bates was known for the poetry he wrote and as a raconteur, including one anecdote, recalled Speizer, about how, when penicillin was being tested, Bates had the job of administering the shot, then collecting the participants’ urine and carrying it back to the laboratory on his bicycle for analysis. He “kept an open and inquisitive mind both in science and in non-science”, Peters said. Bates is survived by his children, Andrew, Elizabeth, and Joanna, a senior associate dean in medical education at the University of British Columbia. His wife, Margaret Sutton, predeceased him.

Ivan Oransky

ivan-oransky@erols.com
The WHO Director-General election finale

Margaret Chan’s election as the Director-General of WHO (Nov 18, p 1743) raises the question of whether she can deliver in this role. In the Lancet debate between candidates she came through as someone cautious, yet keen to use the potential of corporate skills and the power of communication. However, it is her pledge to champion the Bangkok Charter for Health Promotion that pitches her against a broad range of objectives; achieving these will necessitate ensuring the success of WHO’s ongoing global programmes with time-bound targets, such as polio eradication, as well as its County Cooperation Strategy benchmarks.

Given that these hinge on complex interdependencies, a few issues need closer attention.

First, the question of prioritising the sensibilities of the government over the wellbeing of people is crucial. Extrapolated to the constitutional context “the organization shall not seek or receive instructions from any government or from any authority external to the organization”, this will entail going beyond involving international civil society and calls for redefinition of the intergovernmental agency prerogatives in view of the understanding that these can affect WHO’s role as a custodian of health.

Second, the role played by governments in health is changing as the environment gets dominated by market dynamics with liberalisation of services traditionally in the public domain. WHO will have to broaden its focus outside the traditional sphere of influence to considerations around Member States’ roles in the regulation and financing of care provision, rather than in the direct provision of care, and open avenues for engagement in broader regulatory considerations with new stakeholders, including the private sector and those in the intersectoral domain.

Third, as the lead health agency in the UN family with the legitimacy and mandate, WHO should exercise its interorganisational might to improve cooperation in areas such as joint donor assistance, the multilateral sector-wise approach, drawing together disease-specific initiatives in WHO and other partner organisations, the United Nation’s Disaster Assistance Fund, health-security-related issues, outbreak situations, and disasters. Recent examples of disasters, including the 2005 earthquake in Pakistan and the post-conflict situations in Iraq and Afghanistan, emphasise the value that WHO can bring to such arrangements and the acceptability it has in that role.

Finally, WHO should create the right intraorganisational synergies to garner the support of countries that wish to engage in the normative and standard-setting terms and assist others that need to be supported technically, thus creating options for country engagement.

A radical reform to address these issues seems daunting in view of the vulnerabilities that resource constraints bring in their wake. Ultimately, it might also be a question of prioritising long-term strategic choices over short-term gains. The key to the former is overcoming inherent weaknesses in WHO’s structure; this will necessitate drawing more than just the fine line between being political, which WHO needs to be, and being politicised, which WHO cannot afford to become.

I declare that I have no conflict of interest.

Sania Nishtar
sania@heartfile.org
Heartfile, 1 Park Road, Chak Shahzad, Islamabad, Pakistan

1 The Lancet. WHO 2007–12: the era of Margaret Chan. Lancet 2006; 368: 1743
2 Brown H. WHO’s Director-General candidates respond. Lancet 2006; 368: 1225–28

Prevention of cardiovascular disease with a polypill

Thomas Gaziano and colleagues (Aug 19, p 679) report on the usefulness of a multidrug regimen for prevention of cardiovascular disease in the developing world. However, we disagree with the drugs chosen to treat hypertension and to the overall prevention strategy.

Gaziano and colleagues justify the use of a calcium-channel blocker in treating hypertension by referring to the ASCOT-BPLA trial which showed that an amlodipine-based regimen (amlodipine plus perindopril) was more effective than an atenolol-based one (atenolol plus bendroflumethiazide). This study has already been criticised for the drugs chosen for treatment comparison. As an additional criticism, even though a possible beneficial effect of the calcium-channel blocker regimen might be assumed, it would be marginal, because the estimated number of patients needed to treat per year to prevent one event (NNT) is about 1000. We wonder why, in a cost-controlling health policy, a thiazide diuretic was not included. Since there is no evidence to support a greater efficacy of calcium-channel blockers over thiazides, use of a diuretic instead of a calcium-channel blocker would cost 10–20 times less.

Moreover, we wonder why a strategy to reduce cardiovascular mortality centred on a multidrug regimen and not on a smoking cessation campaign. The importance of smoking in determining the cardiovascular risk profile in lower social classes has been underlined by Jha and colleagues. Prescribing a single pill, without lifestyle changes, to prevent cardiovascular diseases is perverse. Indeed, it could lead to excessive medicalisation, masking the major causes of cardiovascular mortality such as those related to lifestyle or socioeconomic status.

We declare that we have no conflict of interest.


Correspondence

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*Giorgio Costantino, Elisa Ceriani, Anna Maria Rusconi, Nicola Montano. giorgic@libero.it

Medicina Interna II, Azienda Ospedaliera L Sacco, Università degli Studi di Milano, Via Gli Grassi 74, 20157 Milano, Italy


Authors’ reply

Giorgio Costantino and colleagues’ main concern with our drug choices seems to be our use of a calcium-channel blocker over a diuretic in combination with an angiotensin-converting-enzyme (ACE) inhibitor for primary prevention. We agree, as stated in our paper, that the ALLHAT\(^*\) trial and other meta-analyses\(^1,3\) suggest that, as single agents, the thiazides, calcium-channel blockers, and ACE inhibitors seem to work equally well for overall cardiovascular disease endpoints.

But the issue is not really about which single agent is best but about which combination of agents have the best evidence in trials with clinical endpoints. Unfortunately, we know little about the possible effects of drugs in combination on meaningful clinical endpoints. Costantino and colleagues report that the combination regimen chosen in ASCOT-BPLA\(^*\) is not the best, but there are no other trial or evidence-based data with clinical endpoints to confirm an alternative combination therapy. Is it possible that a combination of a diuretic and ACE inhibitor would fare equally well? Certainly, but the evidence base is lacking.

Even if one wanted to speculate that a diuretic and ACE inhibitor were equally as effective as a calcium-channel blocker and ACE inhibitor, this would actually lead to a price reduction of about US$6-7 per year, which would make our cost-effectiveness ratios lower, and therefore even more attractive, not less so. If, in the future, a regimen of diuretic and ACE inhibitor were proven to be equally effective in reducing clinical endpoints, we would certainly advocate its use, given its lower cost.

Regarding the question of whether use of a multidrug regimen should have been the focus of our article and not a smoking cessation programme, the two options are clearly not mutually exclusive. Cost-effective smoking cessation should be promoted as well. Further, there are millions of people globally who are at high risk of cardiovascular disease or death but who do not smoke. We certainly believe that these individuals should not be ignored. Those who are unfortunate enough to be unable to reduce their risk through lifestyle interventions deserve the same access to affordable medications that have significantly reduced the burden of disease in the developed world. We attempted to provide the best evidence-based regimen that is also cost effective in resource poor settings.

We declare that we have no conflict of interest.

* Thomas A Gaziano, Lionel H Opie, Milton C Weinstein
tgaziano@partners.org

Division of Cardiovascular Medicine, Brigham & Women’s Hospital, Boston, MA 02115, USA (TAG); Hatter Institute for Heart Research, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town, South Africa (LHO); and Department of Health Policy and Management, Harvard School of Public Health, Boston, MA, USA (MCW)


Change in blood group in systemic lupus erythematosus

A transient blood group change from A to AB in a 26-year-old woman presenting with systemic lupus erythematosus (SLE), was interpreted by Norio Nakamura and colleagues (Sept 16, p 1022)\(^3\) as being the result of agglutinin to anti-B antibodies, and therefore, essentially, as a false-positive result.

Blood group changes have been reported in leukaemia and stem-cell transplantation,\(^1\) but to our knowledge never before in an autoimmune disease such as SLE. However, more than 30 years ago, Ottensooser and colleagues reported that, in 45 patients with SLE, the frequency of blood groups B and AB exceeded that of controls, the difference reaching twice the standard error.\(^2\) This finding is possibly linked to that of Nakamura and colleagues, irrespective of whether the test results are true or false.

We would like to pose the following question to Nakamura and colleagues: given the clear-cut positivity of the anti-B typing in the figure, could this finding possibly be interpreted in the light of chimeric cells being involved in the development of SLE?\(^3\) Can Nakamura and colleagues trace whether their patient had been pregnant with a
blood group B-positive child, whose fetal cells could have been introduced into her circulation by fetomaternal transfer? If so, a host-versus-graft-like response might have contributed to the development of SLE in this patient.

We declare that we have no conflict of interest.

IJske C L Kremer Hovinga, Marije Koopmans, Emile de Heer, Jan A Bruijn, *Ingeborg M Bajema

Department of Pathology, Leiden University Medical Center, 2300 RC Leiden, Netherlands


Authors’ reply

We showed that blood type changed from A to AB in a female patient with SLE, and that her blood type returned to A after steroid pulse therapy. IJske Kremer Hovinga and colleagues put forward the interesting and exciting hypothesis that our finding could have resulted from a chimeric-cell-associated mechanism, and that a host-versus-graft-like response might have contributed to the development of SLE in this patient.

Chimeric cells could feasibly contribute to the development of immunemediated diseases.1,2 However, we do not have sufficient data to confirm whether or not this was the case in our patient. The patient had a 6-year-old son, but his blood type was A not B. After a more detailed interview, however, we learned that she had had five miscarriages, probably because she had antiphospholipid syndrome.3

Unfortunately, the blood types of her lost embryos were not examined.

We expect that the mechanism will be explained by further experience and investigation.

We declare that we have no conflict of interest.

*Norio Nakamura, Hideaki Yamabe, Ken Okumura
nnakamura@r2.dion.ne.jp

Department of Nephrology, Hirosaki University School of Medicine, S Zaifu-cho, Hirosaki-city, Aomori 036-8562, Japan


Fibromuscular dysplasia and renal transplantation

Vincenzo Tondolo and colleagues (Sept 9, p 946) report what they describe as a non-transplantable kidney with fibromuscular dysplasia. Our experience suggests that their description was inaccurate.

Fibromuscular dysplasia, as shown in the angiography and the macroscopic picture of the kidney of the case presented, is seen in 2.0–6.6% of potential living donor kidney transplantations and therefore represents the second most frequent abnormality.1,2 In two cases of living donor kidney transplantations, we explanted kidneys with severe fibromuscular dysplasia (figure) and replaced the diseased artery with a greater saphenous vein (figure) and replaced the diseased artery with a greater saphenous vein from the recipient. In both cases, the transplantation was successful, although in one bleeding occurred twice and the interposed vein had to be replaced. Both recipients experienced acute rejection controlled medically. Both recipients had stable renal function of the transplant after 23 and 27 months’ follow-up.4 One of the recipients died of concomitant cardiac disease during follow-up, but the other still has stable renal function with creatinine concentrations of 176.8 μmol/L. During follow-up, neither of the recipients developed transplant renal artery stenosis.

In times of ever-growing organ shortage, even organs with diseased arteries can be transplanted if vascular surgical techniques are used. This point emphasises the need for vascular surgical training for transplant surgeons.

We declare that we have no conflict of interest.

*K M Balzer, D Grotemeyer, T Pfeiffer, A Voiculescu, W Sandmann
k.m.b@gmx.de

Department of Vascular Surgery and Kidney Transplantation (KMB, DG, TP, WS) and Department of Nephrology (AV), Heinrich-Heine-University, 40225 Duesseldorf, Germany


Figure: Angiography of renal artery of a potential living kidney donor, showing fibrodysplasia
Authors’ reply
Kai Balzer and co-workers report their experience with fibromuscular dysplasia, suggesting that kidneys with such lesions can be used for transplantation.

Fibromuscular dysplasia is a non-atherosclerotic, non-inflammatory segmental arterial disease and is the second major cause of renovascular hypertension other than atherosclerotic disease. As quoted by Balzer and colleagues, Cragg and colleagues, in reviewing 1862 potential renal donors, showed fibromuscular dysplasia in 71 (3.8%). However, follow-up showed that, of 30 such donors who did not undergo nephrectomy, eight developed hypertension over a mean of 7.5 years, and of 19 patients who did undergo nephrectomy, five developed hypertension over a mean of 4.4 years. By comparison, in a randomised age-matched and sex-matched healthy control group, only 6.1% developed hypertension (follow-up 7.1 years).1

We think that, to discuss the transplantability of kidneys with fibromuscular dysplasia, we should consider cadaveric and living donation separately. In cadaveric transplantation, the decision on transplantability depends on the extent of disease and the feasibility of safe surgical repair. In general, the major site of the lesions is the distal portion of the main renal artery; intrahilar involvement is more rare. In the cases reported by Balzer and colleagues, the diseased tract was confined to the main renal artery and was repaired with a vein graft. In our case, lesions extended into the hilum and involved the three branches of the main renal artery. For this reason, we regarded anastomosis with a triple venous graft unsafe.

In living donation, the main concern is the safety of the donor. Experience shows that donors with fibromuscular dysplasia are more likely to become hypertensive, and sooner, than those without this disorder.2,3 Most surgeons do not accept living donor kidneys with any degree of bilateral fibromuscular dysplasia.1,3 We agree with this policy.

As far as the issue of vascular training for transplant surgeons is concerned, we totally agree with Balzer and colleagues. Their experience shows that, despite excellent surgical techniques, vascular complications are always possible. Indeed, a safe surgical technique is the prerequisite for good long-term transplantation results.

We declare that we have no conflict of interest.

*Vincenzo Tondolo, Giuseppe Nanni, Franco Citterio, Carmine Di Stasi, Marco Castagneto vincenzo.tondolo@rm.unicatt.it

Department of Surgery, Division of Transplantation (VT, GN, FC, MC) and Department of Radiology (CDS), Catholic University, Largo A Gemelli 8, 00168 Rome, Italy


Clinical trials for colonic stents

J E van Hooft and colleagues (Nov 4, p 1573) alert readers to the premature closure of the Dutch Stent-in I colonic stenting study as a result of several late non-procedure-related perforations near the proximal stent end. Global data for the use of colonic stents, and the clinical zeal for their use either as definitive therapy in advanced disease or as a bridge to resection (either open or laparoscopic-assisted), seems to have predated their assessment in randomised trials.

Colonic stenting, largely for malignant disease, is supported by two large systematic reviews2,3 combining more than 2000 patients derived from 88 separate publications in which a minimum of 10 stents were used. These analyses report a combined procedural mortality of less than 1%, a high success rate of decompression, and only a 10% incidence of delayed complications including stent migration or reoclusion. The perforation rate of about 5% mainly comprised early events.

Prospective data that have compared stent insertion and surgery have so far been non-randomised, contrasting stent use with emergency surgery4 or palliative surgery only. At present there are few data on whether stenting compromises longer-term oncological outcome when used as a bridge to resection with curative intent. Given the high perioperative mortality and morbidity (particularly in elderly people) of emergency colorectal resection for obstruction, despite the poor and somewhat unique results of this recent Dutch trial, we advocate the initiation of an international randomised controlled trial to compare self-expanding metallic stents as a bridge to open surgery with open surgery alone for elderly patients in left-sided malignant colorectal obstruction. Such a trial should assess quality of life and cancer-specific survival as well as procedural complication rates and short-term outcome.

We declare that we have no conflict of interest.

*Riccardo A Audisio, Andrew P Zbar, Frank E Johnson
raudisio@doctors.org.uk

Department of Surgery, Whiston Hospital, Prescot L35 5DR, UK (RAA); University of the West Indies School of Clinical and Medicine Research, Queen Elizabeth Hospital, St Michael, Barbados (APZ); and Department of Surgery, Saint Louis University Health Sciences Center, Saint Louis, MO, USA

There is little evidence to support the argument that vaccine development has suddenly become too complex for public research institutes, as is made out. It would be cheaper for the Gates Foundation to invest in vaccine research by academic and public research institutions. The resulting vaccines would be publicly available, regional and national manufacturers could produce them cheaply, uptake would increase, and the poor children of the world would benefit.

We declare that we have no conflict of interest.

Amit Kumar, *Jacob Puliyel
Puliyel@vsnl.com

Department of Pediatrics, St Stephens Hospital, Tis Hazari, Delhi 110054, India


Response from GAVI Alliance

Although we applaud the commitment of Amit Kumar and Jacob Puliyel to child immunisation, many of their contentions are based on a flawed understanding of GAVI’s work. There is overwhelming evidence that immunisation is one of the most cost-effective public-health interventions a country can make. Simply put, the vaccines funded by GAVI are saving lives. GAVI, through its partners, has immunised more than 115 million children, preventing an estimated 1.7 million deaths. GAVI works with its partners, including industrialised and developing countries, vaccine makers, WHO, UNICEF, and others, to ensure that the vaccines adopted by each country are affordable and appropriate for the unique needs of each country.

Sustaining and building on the gains of developing countries continues to be a priority for GAVI, and we are working with countries to help them support the vaccines they have introduced. GAVI provides countries with vaccines over long periods (5–15 years) to enable ministers of health to determine priorities and affordability and to make the kind of decisions about public health trade-offs noted by Kumar and Puliyel.

Vaccine research, although crucially important, is not a substitute for a multifaceted approach to child health and immunisation. Several complementary investments are needed to ensure the appropriate vaccines are developed, manufactured, and accessible to citizens of the developing world. GAVI and other organisations are supporting researchers and vaccine makers in their efforts.

A reinvigorated global movement is needed to increase access to immunisation and to ensure that we reach the Millennium Development Goals. We are well on our way to making this happen.

I declare that I have no conflict of interest.

Jean-Pierre Le Calvez
jplecalvez@gavialliance.org

GAVI Alliance, c/o UNICEF, Palais des Nations, CH-1211 Geneva 10, Switzerland

Adjudication of serious heart failure in patients from PROactive

There has been much discussion of the increased incidence of investigator-reported heart failure with pioglitazone in the PROactive study1 versus the drug’s potential benefit in preventing macrovascular complications in type 2 diabetes.2,3 Because heart failure events were reported as adverse events and


GAVI funding and assessment of vaccine cost-effectiveness

Chunling Lu and colleagues (Sept 23, p 1088)1 found that the Global Alliance for Vaccines and Immunization (GAVI) has had little effect on the coverage of diphtheria, tetanus, and pertussis (DTP) vaccination in areas where baseline coverage was greater than 65%. By contrast, global coverage with hepatitis B vaccine increased from 3% in 1992 to 51% in 2004.2 DTP is not the area of interest to GAVI partners in industry. Industry participation in GAVI was obtained on the specific assurance that it would open up developing country markets for newer vaccines.3 This is progressing well by all reports.

Resolution 45.17 of the World Health Assembly mandates that newer vaccines that are cost-effective be integrated into national immunisation programmes. The first step is for individual countries to establish cost-effectiveness. However, GAVI circumvents this step by providing poor countries with grants to support purchase of new vaccines. With this funding, vaccine costs can come close to zero, and countries are persuaded to start the programme. Funding is withdrawn after a couple of years and nations are effectively lured into a debt trap.

Industry has contributed little to GAVI. Of the US$1 billion spent, $750 million was contributed by the Bill and Melinda Gates Foundation.4
Correspondence

we were not part of the primary composite endpoint and therefore not adjudicated by the Endpoint Adjudication Panel/Committee, there was also the possibility that peripheral oedema, weight gain, or other findings had been mistaken for heart failure.

We did a post-hoc, blinded, independent adjudication of investigator-reported serious heart failure events (those requiring hospital admission; 362 events reported in a total of 257 patients; 47 fatal events), pneumonia (120 events reported in a total of 111 patients; eight fatal events), and death judged by the Endpoint Adjudication Panel/Committee as “other cardiac” (n=130) or “other cardiovascular” (n=29). An adjudication of non-serious episodes of heart failure was not done because the information from the investigators for such patients was limited to that provided on the case record forms. However, cases of non-serious heart failure that deteriorated into a serious event were included.

We recorded whether heart failure was related to the event on heart failure review forms. The forms contained details for each patient, including centre and patient number and a history of events in the study (ie, potential endpoint events and serious adverse events since enrolment). Requirements for the three categories for heart failure events were:

- **Category 1:** Heart failure probable—heart failure suspected on the basis of a combination of symptoms and objective evidence (as revealed by echocardiography or chest radiography [most frequent] or measurements of brain natriuretic peptide or myocardial scintigraphy [infrequent]). As far as possible, considering the retrospective nature of this adjudication, the criteria used were those established in the guidelines issued by the European Society of Cardiology.\(^5\)
  - **Category 2:** Heart failure might have been present—if symptoms and the case history were convincing, even in the absence of any available objective measures of myocardial function.
  - **Category 3:** Heart failure unlikely—all events that did not fulfil the criteria for categories 1 and 2.

The table summarises the data from both the investigator-reported and our independent heart failure review. Although we dismissed a small number of investigator-reported serious heart failure events and identified several new cases, the higher prevalence with pioglitazone than placebo was confirmed (5.5% vs 4.2%). Although fewer deaths were found to be related to heart failure, deaths in which heart failure might have been involved remained similar between treatments (15 patients [0.6%] in each group). Only one case of pneumonia was reclassified as heart failure with pioglitazone and two were reclassified with placebo.

Our independent review of the heart failure confirms the accuracy of the original investigator diagnoses. There were greater rates of serious heart failure in the pioglitazone group than in the placebo group and comparable rates of mortality due to heart failure in these patients with advanced cardiovascular disease.

Takeda provided funding support for adjudication of heart failure data. We declare that we have no conflict of interest.

**Lars Rydén, Inga Thráinsdóttir, Karl Swedberg**

Lars.Ryden@ki.se

Department of Cardiology, Karolinska University Hospital, 171 76 Stockholm, Sweden

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<td>Fatal heart failure</td>
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<td>25 (1.0%)</td>
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*Confirmed by the adjudication as “Heart failure probable”, or “Heart failure may have been present” | Confirmed by the adjudication as “Heart failure contributing to death”

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<th>Placebo (n=2633)</th>
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<td>Investigator-reported</td>
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<td>Fatal heart failure</td>
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Table: Investigator-reported versus post-hoc, independently adjudicated serious heart failure events in the PROactive study
Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study

Lara J Wolfson, Peter M Strebel, Marta Gacic-Dobo, Edward J Hoekstra, Jeffrey W McFarland, Bradley S Hersh, for the Measles Initiative*

Summary

Background In 2002, the UN General Assembly Special Session on Children adopted a goal to reduce deaths owing to measles by half by the end of 2005, compared with 1999 estimates. We describe efforts and progress made towards this goal.

Methods We assessed trends in immunisation against measles on the basis of national implementation of the WHO/UNICEF comprehensive strategy for measles mortality reduction, and the provision of a second opportunity for measles immunisation. We used a natural history model to evaluate trends in mortality due to measles.

Results Between 1999 and 2005, according to our model mortality owing to measles was reduced by 60%, from an estimated 873 000 deaths (uncertainty bounds 634 000–1 140 000) in 1999 to 345 000 deaths (247 000–458 000) in 2005. The largest percentage reduction in estimated measles mortality during this period was in the western Pacific region (81%), followed by Africa (75%) and the eastern Mediterranean region (62%). Africa achieved the largest total reduction, contributing 72% of the global reduction in measles mortality. Nearly 7·5 million deaths from measles were prevented through immunisation between 1999 and 2005, with supplemental immunisation activities and improved routine immunisation accounting for 2·3 million of these prevented deaths.

Interpretation The achievement of the 2005 global measles mortality reduction goal is evidence of what can be accomplished for child survival in countries with high childhood mortality when safe, cost-effective, and affordable interventions are backed by country-level political commitment and an effective international partnership.

Introduction Measles was the single most lethal infectious agent before the licensure in 1963, and subsequent widespread use, of live attenuated measles vaccine. In the early 1960s, as many as 135 million cases of measles and over 6 million measles-related deaths are estimated to have occurred yearly. The immunosuppressive nature of measles reduces patients' defences against complications such as pneumonia, diarrhoea, and acute encephalitis. Pneumonia, either a primary viral pneumonia or a bacterial superinfection, is a contributing factor in about 60% of measles-related deaths. The introduction of routine measles vaccination in most developing countries during the 1980s as part of the Expanded Programme on Immunization had a major effect on global measles mortality. By 1987, WHO estimated that the number of deaths from measles worldwide had been reduced to 1·9 million.

Global measles vaccination activities can be characterised into three broad phases. The first phase involved the introduction of routine vaccination against measles in almost every country in the world through the Expanded Programme on Immunization, beginning in 1974, and the UNICEF-led initiative for Universal Childhood Immunization by 1990. In this phase the recommendation was for one dose of measles vaccine to be administered at or shortly after 9 months of age to at least 80% of children in every country. During the second phase from 1990 to 1999, routine measles vaccination levelled off in the 70–80% coverage range and many industrialised countries introduced a second routine dose, usually at or around the time of school entry, to protect children who did not respond to the first dose. Also during this period, the Pan American Health Organization (PAHO) implemented a strategy that included a second opportunity for measles immunisation for all children to stop endemic measles transmission in the Americas.

The third phase began around 2000 with the realisation that despite the availability of a safe, effective, and relatively inexpensive measles vaccine for over 40 years, measles remained a leading cause of childhood mortality, especially for children living in developing countries. To address this problem, WHO and UNICEF began to target 45 priority countries (panel), together accounting for more than 90% of estimated global measles deaths, to implement a comprehensive strategy for accelerated and sustained reduction in mortality due to measles. The strategy emphasised the PAHO approach to provide all children with a second opportunity for measles immunisation. At present 47 countries are targeted for measles mortality reduction, because Yemen and Timor Leste have been added to the list of priority countries.

The WHO/UNICEF comprehensive strategy for measles mortality reduction has four components: achieving and maintaining high coverage (>90%) for routine measles immunisation in every district; ensuring that all children receive a second opportunity for measles immunisation; effective surveillance for cases of measles,
### Panel: WHO and UNICEF 45 priority countries


including monitoring of immunization coverage; and assuring appropriate clinical management of patients with measles, particularly the provision of vitamin A.8,9,10

Achieving high immunisation coverage for all birth cohorts is the foundation of the strategy for accelerated and sustained measles mortality reduction. Because about 15% of infants who receive measles vaccine at 9 months of age do not develop lasting immunity, even high coverage with a single-dose vaccination policy will result in a substantial proportion of children who remain susceptible to the disease.8 Since measles is highly infectious, the risk of an outbreak increases over time through an accumulation of susceptible children in the population. The ongoing strengthening of routine immunisation services at the district level alone will not result in a rapid reduction in deaths from measles. To obtain a timely reduction of measles deaths, a critical component of the strategy is to provide all children with a second opportunity for measles immunisation. This approach aims to protect children who did not previously receive measles vaccine, as well as those who were vaccinated but failed to develop an immune response.

The second opportunity for measles immunisation can be delivered either through a routine two-dose schedule (in which immunisation services achieve and sustain high coverage), or through periodic supplementary immunisation activities where routine coverage is low to moderate. Supplementary immunisation activities are mass vaccination campaigns that target all children in a defined age group and wide geographical area regardless of previous disease or vaccination history. They use a range of additional strategies (eg, outreach to remote areas, door-to-door canvassing, additional clinic hours, mobile vaccination teams) that reach children who do not routinely access health services and thereby achieve very high vaccination coverage. Catch-up campaigns are one-time only events generally targeting children aged 9 months to 14 years with a goal of rapidly increasing population immunity among pre-school and school-age children.11 The specific target age group depends on the age-specific susceptibility in the population.

To maintain high population immunity in pre-school-age children over time, follow-up campaigns, generally targeting all children aged 9 months to 4 years, are periodically done every 3–5 years. The interval between follow-up campaigns is a function of routine immunisation coverage (the higher the routine coverage, the longer the interval between campaigns). By contrast, in countries that have achieved and maintained high routine vaccination coverage, the second opportunity for measles immunisation can also be provided through implementation of a routine two-dose measles vaccination schedule. This approach usually involves administration of a second dose of measles vaccine at age 12–18 months of age or at school entry.11

In May, 2003, the World Health Assembly endorsed a resolution urging member states to achieve the goal adopted by the UN General Assembly Special Session on Children (2002) to halve the number of deaths due to measles by the end of 2005, compared with 1999 estimates.14,15 We report the achievement of this goal, and outline remaining challenges to reduce mortality further and prospects for the eventual global eradication of measles.

### Methods

**Measuring vaccination coverage**

By July of each year, all Member States of WHO and UNICEF are requested to submit information on routine measles vaccination coverage, supplementary measles immunisation activities, and reported measles cases from the previous year to WHO and UNICEF. WHO/UNICEF estimates of national routine coverage16 with one dose of measles vaccine are based on a review of coverage data from administrative records, surveys, national reports, and consultation with local and regional experts. Coverage achieved during supplementary immunisation activities is calculated by dividing the number of administered doses that are recorded on tally sheets by the estimated target population. Additionally, coverage surveys done after supplementary immunisation activities are often used by countries to revise their administrative coverage estimates. Regional and global coverage were estimated for the routine first dose of measles vaccine and supplementary activities by applying the national WHO/UNICEF coverage estimates and reported supplementary coverage to the UN Population Division estimates of the relevant target populations (surviving infants for routine first-dose coverage, and the specified age groups for supplementary activities).11

A country was defined as providing a second opportunity for measles immunisation if it either had a routine two-dose measles immunisation schedule or had undertaken a nationwide supplementary immunisation activity with coverage of 90% or greater within the previous 5 years.

**Estimating measles deaths**

A major challenge in measuring progress towards the 2005 measles mortality reduction goal has been the absence of complete and reliable mortality surveillance data from many countries, particularly those with the
highest disease burden. Deaths from measles are not routinely reported to WHO, and cases of measles are substantially under-reported even in industrialised countries. To advise WHO on the best methods to monitor global progress towards the 2005 goal, an expert advisory group was convened on Jan 12–13, 2005. The group noted the strengths and weaknesses of various methods for estimating measles mortality but endorsed the approach described in this paper that makes use of surveillance data where reliable, and where surveillance data are unreliable employs a natural history model, which accounts for recent changes in vaccination coverage and is therefore best suited to monitor trends in measles incidence and mortality.

To estimate and monitor trends in yearly numbers of deaths from measles worldwide, a modification of a model proposed by Steink and others was used. In this model the total numbers of cases are estimated and allocated to age groups, and then age-specific case-fatality ratios are applied to the numbers of cases to estimate the numbers of deaths per year.

For countries with good disease reporting (method 1) and routine measles vaccination coverage greater than 80%, the number of cases was derived by dividing an estimated notification efficiency (5%, 20%, or 40%, as appropriate), representing the proportion of cases that are captured and reported through routine surveillance. The reporting efficiency was assigned to groups of countries using published estimates of reporting efficiency for one or more countries in the group.

For the remaining countries (ie, those where average measles vaccination coverage over the past decade has been <80%) an assumption was made that the average yearly number of cases was equal to the number of children in the birth cohort who did not become immune through vaccination (method 2). Because of the highly infectious nature of measles, as well as results from serological surveys showing that by early adulthood most people have immunological evidence of either immunisation or infection-derived immunity, it can be concluded that all individuals who are not effectively immunised are eventually infected with measles. Thus, the average number of cases per year, if immunisation were only given through routine services, would be equivalent to the number of those in the birth cohort who did not become immune through vaccination (although distributed across different age groups).

The number of cases per year was reduced if children received a second routine dose, or if the country had recently used supplementary immunisation activities. A discounting function was then used to calculate the effect of supplementary activities (100%, 90%, 80%, 50%, and 25% for 1, 2, 3, 4, and 5 years after the activity, respectively), on the basis of the observation that such strategies have an effect for about 5 years, and the longer the time since the campaign, the less the effect on reducing the number of cases. This is consistent with the observed effect of mass measles campaigns in 14 countries in the African region during 1998–2001. These average percentage reductions are assumed to apply to countries using similar campaigns in other regions. This static model assumes all the epidemiological parameters remain the same over a 5-year period, and thereby removes the cyclical variations in measles incidence and reflects an average smoothed annual number of cases and deaths. The cases are then distributed across age groups using the age distributions reported by Steink and others (see also webappendix).

Age-specific case-fatality rates are then applied to these estimates of case numbers to estimate the number of deaths.

Data sources for the model included the estimated yearly routine first and second dose measles coverage by country, coverage of supplementary immunisation activities by country (WHO-IVB database, extracted Sept 1, 2006), and population data. Vaccine effectiveness was assumed to be 85% if given before age 1 year and 95% if given to older children. Further details about the model are given in the webappendix.

On the basis of a review of published work, case-fatality ratios for children aged 1–4 years were used as the reference. The values used ranged from 0–0% in industrialised countries of Europe and North America, 0–1% in the industrialised Pacific and South and Central America, 0–8% in the remainder of Asia and the Pacific, and (on average) 3% in Africa, ranging up to 6% in the least developed countries (eg, Sierra Leone). For more than 86% of the world’s population, the case-fatality ratio applied to children aged 1–4 years was less than 3%. We assume that the ratio in children younger than 1 year is larger than that in children aged 1–4 years, which in turn is larger than that in children aged 5–9 years. The case-fatality ratio for children aged 10 years and older is assumed to be 0 (this simplifying assumption has the effect of including any deaths in children older than 10 years in the deaths in the 5–9 age group).

To derive lower and upper bounds for the annual mortality estimates, the output from Markov simulation models implemented in the S-Plus (version 6.1) software package applied to mortality estimates for the year 2000 was reviewed. A series of distributions, including beta, Dirichlet, and multinormal proportions, or were continuous in nature, to represent the uncertainty in the input parameters (routine immunisation coverage, supplementary activity coverage, reported incidence rates, notification efficiency, vaccine effectiveness, distribution of cases across age groups, and age-specific case-fatality ratios). Some parameters had a correlation structure imposed on them (for example, the age-specific case-fatality ratios within a specific country were assumed to vary together, whereas vaccine efficacy and case fatality ratios were assumed to be independent). When distributions had been assessed,
by use of the prior sample size method (see webappendix). 10,000 samples were taken from the input distributions and propagated through the model. The 95% uncertainty intervals for the estimates in the year 2000 were found to vary from –33% to 33% of the point estimate.

The model was found to be most sensitive to two variables: case-fatality ratios and routine measles vaccination coverage. Because it is simpler to implement and more transparent to explain, a deterministic approximation was used; coverage was allowed to vary by plus or minus 5% (absolute) and case-fatality ratios by plus or minus 20% (relative), to derive the lower and upper bounds for the estimates, which for the base year of 1999 yielded a range of approximately plus or minus 33%.

The model was then used to derive yearly estimates of measles cases, deaths, and disability adjusted life years (DALYs), as well as estimates of cases, deaths, and DALYs averted.

**Results**

During the 1980s, worldwide coverage of routine measles vaccination increased to about 70%, and then levelled off during the 1990s. Between 1999 and 2005, coverage of routine immunisation increased from 71% to 77%, with substantial variation across geographical regions (table 1). Moreover, we noted a marked increase in the proportion of countries providing children with a second opportunity for measles immunisation either through a routine two-dose schedule or a nationwide supplementary immunisation activity. In 2005, of 192 countries, 171 (89%) offered children a second opportunity nationally and seven (4%) sub-nationally, compared with 125 (65%) nationally in 1999 (figure 1).

Calculations based on WHO/UNICEF coverage estimates and the estimated number of surviving infants7 showed that more than 29 million 1-year-old children worldwide had not received a dose of measles vaccine through routine immunisation services (table 2). The southeast Asian region had the largest number of unvaccinated 1-year-old children and of children aged 9 months to 14 years without a second opportunity for measles immunisation.

From 2000 to 2005, more than 362 million children aged 9 months to 14 years received measles vaccine through supplementary immunisation activities in the 47 priority countries.11 Of the total doses administered, 84% were given in catch-up campaigns and 16% in follow-up campaigns. Of the priority countries, 34 (72%) had completed nationwide campaigns and 11 (23%) had undertaken subnational campaigns during this period. Reported coverage for supplementary immunisation activities in the priority countries ranged from 65% to 99% (median 96%). By the end of 2005, 45 of the 47 priority countries had completed or begun implementation of a measles catch-up campaign.

Since 1980, implementation of global measles control activities has resulted in about 60% of the worldwide population aged younger than 15 years being protected by routine vaccination (figure 2). Provision of a second opportunity for measles immunisation through supplementary activities or a routine second dose started in the late 1980s and has accelerated since 2000, resulting in protection of an additional 20% of the population younger than 15 years (figure 2).

Starting in 2000, supplementary immunisation activities and improvements in routine coverage accelerated the decline in mortality due to measles (figure 2). Based on results from surveillance data and the natural history model, overall global measles mortality decreased 60% from 873 000 deaths (uncertainty bounds 634 000–1 140 000 deaths) in 1999 to 345 000 deaths (247 000–458 000) in 2005 (table 1, figure 3). The largest percentage reduction in estimated mortality due to
measles during this period was in the western Pacific region (81%), followed by Africa (75%) and the Middle East (62%).

In children younger than 5 years, we estimated that worldwide mortality due to measles decreased from 791 000 (573 000–1 032 000) in 1999 to 311 000 (222 000–415 000) in 2005. Notably, three-quarters of the reduction in measles mortality among children younger than 5 years occurred in Africa, where estimated measles mortality in this age group fell from 459 000 (335 000–597 000) to 114 000 (83 000–148 000). Evidence suggests that case-fatality ratios are reduced in individuals with measles who have been vaccinated but have not become immune and in individuals who receive vitamin A supplementation during supplementary immunisation activities. The model, which assumed that the case-fatality ratio remained constant between 1999 and 2005, might thus have underestimated the reduction in mortality due to measles.

We estimated that measles was responsible for more than 30 million DALYs lost in 1999, falling to 12 million in 2005, and that the number of cases fell from more than 43 million in 1999 to just over 20 million in 2005 (table 3). Cumulatively, from 2000 to 2005, nearly 7.5 million measles deaths had been prevented through immunisation. Given 1999 coverage levels, 2.3 million of these deaths had been prevented through intensified efforts to raise routine coverage and provision of a second opportunity for measles immunisation. Moreover, worldwide distribution of mortality due to measles has drastically shifted. In 1999, 58% of all deaths from measles were estimated to occur in the African region,
and 27% in southeast Asia. However, by 2005, 50% of all deaths from measles occurred in southeast Asia and only 37% in Africa.

Discussion

Intensified large-scale vaccination efforts, particularly in priority countries with the highest burden of measles, have substantially decreased reported incidence of measles and the estimated number of deaths from measles worldwide. Although difficult to quantify, the widespread administration of vitamin A through supplementary immunisation activities against polio and measles and through routine services has also probably contributed to the reduction of measles mortality. Based on modelled estimates, the goal to reduce worldwide measles mortality by 50% between 1999 and 2005 has been met with a 60% decrease, mainly driven by the gains achieved in the African region. Although other published point estimates of measles mortality in children younger than 5 years for 2000–03 differ from those presented in this report, the remarkable progress in reaching more children with measles immunisation and the effect this improvement has had on reported cases of measles suggests that the estimated 60% decline in measles mortality has indeed occurred.

Published estimates of worldwide measles mortality using different modelling approaches vary, but all have wide uncertainty bounds that overlap. Investigators who examined the proportional causes of worldwide child mortality in 42 countries in the year 2000, based on data obtained from verbal autopsies in 18 countries, estimated that deaths from measles represented about 3% (with wide uncertainty bounds) of the more than 10 million yearly deaths in children younger than 5 years.

This point estimate is significantly less than our modelled estimate of 6%, or 669 000 (uncertainty bounds: 485 000–877 000), for the same year, but the estimates are not entirely inconsistent, in view of the wide uncertainty intervals for both approaches. The approach of Morris and others for 2000–03 differ from those presented in this report, the remarkable progress in reaching more children with measles immunisation and the effect this improvement has had on reported cases of measles suggests that the estimated 60% decline in measles mortality has indeed occurred.

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This point estimate is significantly less than our modelled estimate of 6%, or 669 000 (uncertainty bounds: 485 000–877 000), for the same year, but the estimates are not entirely inconsistent, in view of the wide uncertainty intervals for both approaches. The approach of Morris and others has two important weaknesses for investigating mortality due to measles where a highly effective intervention is being rapidly scaled-up. First, it is based on a retrospective cross-sectional rather than a...
cohort approach to examining mortality, and is thus unsuited to monitoring yearly or short-term trends in mortality. Second, the model showed systematic bias towards underestimation of diseases that represent small proportions (<10%) of total child mortality.

Our mortality estimates based on the natural history model are corroborated by data from countries that have implemented the recommended vaccination strategies and have strengthened measles surveillance. An analysis of the effect of intensified vaccination efforts in 19 African countries showed a 92% reduction in reported measles cases. Additionally, only one country (Burkina Faso) experienced a large outbreak after completing a catch-up supplementary immunisation activity. This outbreak was carefully investigated and was largely caused by large scale population migration as a result of civil unrest in neighboring Côte d’Ivoire. Countries in Asia that have implemented the WHO/UNICEF strategy have shown similar results. Cambodia implemented a catch-up supplementary immunisation activity against measles from 2000 to 2003, together with rebuilding of its routine immunisation programme, resulting in a fall in the number of reported measles cases from 12,237 in 2000 to 264 cases in 2005. In Vietnam, the number of reported measles cases decreased by more than 95% (from 16,512 cases in 2000 to 410 cases in 2005) after nationwide supplementary activities aimed at all children aged 9 months to 10 years in 2002–03. In all these countries measles is no longer a public health problem, and in some measles transmission may have been interrupted altogether.

Following a recommendation from an expert review of methods to estimate measles mortality, we attempted to validate the results by comparing this model with surveillance data, as discussed above, and by examining a single-cause proportional mortality model to validate levels of measles mortality in children younger than 5 years for the year 2000.

A systematic review of published studies reporting community-based measures of measles mortality between 1980 and 2000, and overall child mortality, found 28 studies in 16 countries that met the inclusion criteria: that the total number of deaths in each study was greater than 50, and that the proportion of deaths due to measles was less than 20% (to ensure that non-representative studies and outbreak settings were excluded). A weighted logistic regression model was fitted in S-Plus using the total number of deaths in each study as the weights, and using measles vaccination coverage and the proportion of the population that was rural as explanatory variables, with separate slopes against coverage for African and non-African countries. The final model fit these data well (R²=92%), and when applied to current vaccination coverage figures by country, yielded an estimate of 625,000 (95% CI 209,000–1,578,000) deaths in children younger than 5 years for the year 2000, remarkably consistent with our modelled estimate of 669,000 (uncertainty intervals 485,000–877,000).

The natural history method described in this paper has limitations. First, it is a simplification of the actual transmission dynamics, and does not always capture herd immunity effects well, especially in high-coverage settings. Second, the approach to deriving age-specific estimates would be better done in proper cohort-type susceptible-exposed-infected-recovered (SEIR) transmission models. Third, better quality surveillance data and additional field studies for key model inputs are essential to more precisely estimate trends in measles mortality in the future.

The availability of a safe, effective, and inexpensive measles vaccine for more than 40 years has been essential for effective measles control. Additionally, a vaccine delivery strategy that reaches more than 90% of all children is needed. The approach of providing all children with a second opportunity for measles immunisation (using supplementary immunisation activities where necessary) together with ongoing strengthening of routine immunisation services, has proven to be extremely effective in rapidly and sustainably reducing numbers of deaths from measles. A very aggressive implementation of this strategy has interrupted the circulation of indigenous measles virus in the Americas.

A key factor contributing to progress in reducing measles mortality in Africa has been the support of the Measles Initiative. This partnership, which was formed in 2001 and spearheaded by the American Red Cross, the US Centers for Disease Control and Prevention, the United Nations Foundation, UNICEF, and WHO, has played a critical role in supporting African countries in their efforts to reduce measles mortality. With additional resources from the Global Alliance for Vaccines and Immunization and most recently the International Finance Facility for Immunization, the Measles Initiative is expanding its support to high-burden countries in the eastern Mediterranean, southeast Asian, and western Pacific regions of WHO. Every organisation in the Measles Initiative shares the goal of rapidly reducing measles mortality through implementation of the WHO/UNICEF recommended strategies. Additional principles for an effective partnership have included strong country ownership and commitment to measles control, appreciation of the specific role each partner can play, and the need for contributions of all partners to be recognised.

WHO and UNICEF together with its partners have developed the global immunisation vision and strategies for the period 2006–15. This document was welcomed by the 2005 World Health Assembly and includes ambitious—but appropriate—targets of achieving 90% coverage with measles vaccine in every district, and a 90% reduction in worldwide measles mortality, between 2000 and 2010, as an important component of the child...
survival Millennium Development Goals. Important challenges still exist to achieve the 2010 goal for reduction of measles mortality. First, activities need to be fully implemented in large countries that still have a high measles burden such as India, Pakistan, and Indonesia. Second, to sustain the reductions in measles deaths in the 47 priority countries, enhanced efforts are needed to improve immunisation systems to ensure that at least 90% of infants are vaccinated against measles before their first birthday. Third, the priority countries will need to continue to carry out follow-up supplementary immunisation activities every 2–4 years until their routine immunisation systems are capable of providing two doses of measles vaccine to a very high proportion of every birth cohort. Fourth, field surveillance with laboratory confirmation of suspected measles outbreaks will need to be extended to all priority countries to allow programmes to be effectively monitored.

The proven effectiveness of measles vaccine in preventing disease, and of the comprehensive measles immunisation strategy in reducing deaths from measles and interrupting transmission in many countries, has prompted calls for establishment of a global goal for measles eradication.46-52 Indeed, four of the six WHO regions have already established regional measles elimination goals—the Americas (2010), Europe (2010), the eastern Mediterranean region (2010), and the western Pacific (2012). At first glance, measles seems to satisfy most of the five indicators for determining whether a disease is a candidate for eradication.53 First, an effective intervention (ie, measles vaccine) exists to interrupt transmission of the agent. Second, sensitive and specific surveillance and laboratory methods exist to detect and confirm cases. Third, man is the only known natural host of measles virus. Fourth, interruption of measles transmission has been achieved across wide geographic areas over time. Fifth, measles is perceived as an international public-health priority in many (but not all) countries. Despite these characteristics, developed countries have shown little interest in launching another global eradication initiative, especially since efforts to eradicate poliovirus have not yet been completed.44 Even if transmission of measles virus could be interrupted throughout the world, the threat of reintroduction of the virus, either intentionally (eg, as a biological weapon) or unintentionally (eg, in a laboratory accident) makes the possibility that measles vaccination with at least a one-dose schedule could ever be stopped unlikely.45-48

The success of efforts to reduce measles mortality by 50% between 1999 and 2005 has led to a further goal: to reduce mortality due to measles by 90% between 2000 and 2010.49-53 The second opportunity for measles vaccination is one of the most cost-effective child-health interventions available today,54 and international commitments to funding the initiative indicate both the effectiveness and the cost-effectiveness of the measure.46-47 If political will and financial commitments to achieving this goal are maintained, and innovative strategies for linking delivery of measles vaccine with other child survival interventions are used (eg, insecticide treated bednets),55,56 there is good reason to believe that this new target can be met, accelerating progress towards achieving one of the targets of Millennium Development Goal 4, to reduce child mortality by two-thirds.59

The Measles Initiative


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Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis

William J Elliott, Peter M Meyer

Summary

Background The effect of different classes of antihypertensive drugs on incident diabetes mellitus is controversial because traditional meta-analyses are hindered by heterogeneity across trials and the absence of trials comparing angiotensin-converting-enzyme (ACE) inhibitors with angiotensin-receptor blockers (ARB). We therefore undertook a network meta-analysis, which accounts for both direct and indirect comparisons to assess the effects of antihypertensive agents on incident diabetes.

Methods We undertook a systematic review up to Sept 15, 2006, and identified 48 randomised groups of 22 clinical trials with 143 153 participants who did not have diabetes at randomisation and so were eligible for inclusion in our analysis. 17 trials enrolled patients with hypertension, three enrolled high-risk patients, and one enrolled those with heart failure. The main outcome was the proportion of patients who developed diabetes.

Findings Initial drug therapy used in the trials (and the number of patients with diabetes of the total number at risk) included: an ARB (1189 of 14 185, or 8·38%), ACE inhibitor (1618 of 22 941, or 7·05%), calcium-channel blocker (CCB, 2791 of 38 607, or 7·23%), placebo (1686 of 24 767, or 6·81%), β blocker (2705 of 35 745, or 7·57%), or diuretic (998 of 18 699, or 5·34%). With an initial diuretic as the standard of comparison (eight groups), the degree of incoherence (a measure of how closely the entire network fits together) was small (ω=0·00017, eight degrees of freedom). The odds ratios were: ARB (five groups) 0·57 (95% CI 0·46–0·72, p=0·001); ACE inhibitor (eight groups) 0·67 (0·56–0·80, p<0·0001); CCB (nine groups): 0·75 (0·62–0·90, p=0·002); placebo (nine groups) 0·77 (0·63–0·94, p=0·009); β blocker (nine groups) 0·90 (0·75–1·09, p=0·30). These estimates changed little in many sensitivity analyses.

Interpretation The association of antihypertensive drugs with incident diabetes is therefore lowest for ARB and ACE inhibitors followed by CCB and placebo, β blockers and diuretics in rank order.

Introduction The propensity for some antihypertensive drugs to lower glucose tolerance and precipitate diabetes has been known since at least 1958. Because hypertension is often associated in large populations with impaired glucose tolerance, insulin resistance, and obesity, many patients with hypertension develop diabetes, even when treated with placebo. Some long-term clinical trials of antihypertensive agents have shown significant differences in the rates of new cases of diabetes between treatment groups. Four independent meta-analyses have shown that direct inhibitors of the renin-angiotensin system reduce the risk of incident diabetes, but no comparison was attempted in these studies between angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB). Traditional meta-analyses that attempt to summarise all the existing data from clinical trials comparing one drug class with any other treatment show significant heterogeneity for ACE inhibitors, calcium-channel blockers (CCB), diuretics, and β blockers. When the nine trials of an initial CCB versus any other therapy (including placebo in the Felodipine Events Reduction trial [FEVER]) are separated by comparator, the significant p value for homogeneity (<0·001) for the overall meta-analysis becomes less significant. In four trials comparing an initial CCB with an initial ACE inhibitor or ARB, the CCB was associated with a significantly increased risk (by 26%, 95% CI 15–39, homogeneity p=0·77). In six trials that compared an initial CCB with either a diuretic or a β blocker or both, the proportion of patients developing diabetes was significantly smaller in the CCB group than in the other groups (by 21%, 16–26, homogeneity p=0·04). Network meta-analysis is a fairly new statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the strategies have not been directly compared (eg, ACE inhibitor vs ARB). This type of analysis can summarise randomised clinical trials of several different treatment strategies, and provide point estimates (and 95% CI) for their association with a given endpoint, as well as an estimate of incoherence (a measure of how well the entire network fits together, with smaller values suggesting better internal agreement of the model). We therefore used the network meta-analysis technique to estimate the relative odds of developing diabetes during long-term treatment with an initial class of antihypertensive drug, on the basis of the reported numbers of participants with, or at risk of, incident diabetes in randomised clinical trials.

Methods

Identification of trials We undertook a systematic review to identify long-term randomised clinical trials of antihypertensive drugs that reported the number of new cases of diabetes from 1966 to
Sept 15, 2006. This search was repeated four times by one reviewer independently of the other. Data abstraction was done by one reviewer and verified independently by the other. We searched MEDLINE, the Cochrane Collaboration’s Database of Systematic Reviews, PubMed, and OvidWeb using the MeSH terms: “diabetes mellitus-Type 2, anti-hypertensive agents, randomized controlled trials, angiotensin-converting enzyme inhibitors, angiotensin II type 1 blockers, adrenergic beta-antagonists, diuretics, sodium chloride symport inhibitors, calcium channel blockers, placebo, and meta-analysis.” Additionally, we reviewed the reference lists of all the meta-analyses\textsuperscript{15–19} and other publications for other potential data sources (figure 1). A study\textsuperscript{22} that reported results from only one of 83 clinical sites participating in the Study of Left Ventricular Dysfunction (SOLVD) was included only in sensitivity analyses, as were two very recently reported trials.\textsuperscript{23,24} The Study of Trandolapril/verapamil SR And insulin Resistance (STAR)\textsuperscript{23} reported new-onset diabetes in ten of 119 patients randomly assigned initial combination therapy with trandolapril and verapamil, compared with 25 of 121 assigned losartan and hydrochlorothiazide.\textsuperscript{11} In the Trial of Prevention of Hypertension (TROPHY),\textsuperscript{24} new-onset diabetes developed in only 22 of the 809 randomised participants, but those who developed hypertension (which was much more common in those assigned placebo) were given low-dose diuretic or β blocker immediately thereafter, which might have confounded the results of the candesartan cilexetil versus placebo comparison.

**Statistical analysis**

We entered data from all the publications into a computerised spreadsheet (Microsoft Excel), and did traditional meta-analyses using the Mantel and Haenszel

<table>
<thead>
<tr>
<th>Year</th>
<th>Duration (years)</th>
<th>Drug 1</th>
<th>New cases of diabetes/total</th>
<th>Drug 2</th>
<th>New cases of diabetes/total</th>
<th>Drug 3</th>
<th>New cases of diabetes/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASK\textsuperscript{25}</td>
<td>2006</td>
<td>3.8</td>
<td>ACE inhibitor</td>
<td>45/410</td>
<td>β blocker</td>
<td>70/405</td>
<td>CCB</td>
</tr>
<tr>
<td>ALLHAT\textsuperscript{26}</td>
<td>2002</td>
<td>4.0</td>
<td>ACE inhibitor</td>
<td>119/4096</td>
<td>CCB</td>
<td>154/3954</td>
<td>Diuretic</td>
</tr>
<tr>
<td>ALPINE\textsuperscript{27}</td>
<td>2003</td>
<td>1.0</td>
<td>ARB</td>
<td>1/196</td>
<td>Diuretic</td>
<td>8/196</td>
<td>..</td>
</tr>
<tr>
<td>ANBP-2\textsuperscript{28}</td>
<td>2005</td>
<td>4.1</td>
<td>ACE inhibitor</td>
<td>138/2800</td>
<td>Diuretic</td>
<td>200/2826</td>
<td>..</td>
</tr>
<tr>
<td>ASCOT\textsuperscript{29}</td>
<td>2005</td>
<td>5.5</td>
<td>β blocker</td>
<td>799/7040</td>
<td>CCB</td>
<td>567/7072</td>
<td>..</td>
</tr>
<tr>
<td>CAPP\textsuperscript{30}</td>
<td>1999</td>
<td>6.1</td>
<td>ACE inhibitor</td>
<td>337/5183</td>
<td>β blocker</td>
<td>380/5230</td>
<td>..</td>
</tr>
<tr>
<td>CHARM\textsuperscript{31}</td>
<td>2003</td>
<td>3.1</td>
<td>ARB</td>
<td>163/2715</td>
<td>Placebo</td>
<td>202/2721</td>
<td>..</td>
</tr>
<tr>
<td>DREAM\textsuperscript{32}</td>
<td>2006</td>
<td>3.0</td>
<td>ACE inhibitor</td>
<td>449/2623</td>
<td>Placebo</td>
<td>489/2646</td>
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</tr>
<tr>
<td>EMPH\textsuperscript{33}</td>
<td>1991</td>
<td>4.7</td>
<td>Diuretic</td>
<td>29/416</td>
<td>Placebo</td>
<td>20/424</td>
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</tr>
<tr>
<td>FEVER\textsuperscript{34}</td>
<td>2005</td>
<td>3.3</td>
<td>CCB</td>
<td>177/4841</td>
<td>Placebo</td>
<td>154/4870</td>
<td>..</td>
</tr>
<tr>
<td>HAPPHY\textsuperscript{35}</td>
<td>1987</td>
<td>3.8</td>
<td>β blocker</td>
<td>86/297</td>
<td>Diuretic</td>
<td>75/2722</td>
<td>..</td>
</tr>
<tr>
<td>HOPE\textsuperscript{36}</td>
<td>2001</td>
<td>4.5</td>
<td>ACE inhibitor</td>
<td>102/2837</td>
<td>Placebo</td>
<td>155/2883</td>
<td>..</td>
</tr>
<tr>
<td>INSIGHT\textsuperscript{37}</td>
<td>2000</td>
<td>3.0</td>
<td>CCB</td>
<td>126/2508</td>
<td>Diuretic</td>
<td>176/2511</td>
<td>..</td>
</tr>
<tr>
<td>INVEST\textsuperscript{38}</td>
<td>2003</td>
<td>4.0</td>
<td>β blocker</td>
<td>665/8078</td>
<td>CCB</td>
<td>569/8098</td>
<td>..</td>
</tr>
<tr>
<td>LIFE\textsuperscript{39}</td>
<td>2002</td>
<td>4.8</td>
<td>ARB</td>
<td>242/4020</td>
<td>β blocker</td>
<td>320/3579</td>
<td>..</td>
</tr>
<tr>
<td>MRCE\textsuperscript{40}</td>
<td>1992</td>
<td>5.8</td>
<td>β blocker</td>
<td>37/1102</td>
<td>Diuretic</td>
<td>43/1081</td>
<td>CCB</td>
</tr>
<tr>
<td>NORDIL\textsuperscript{41}</td>
<td>2000</td>
<td>4.5</td>
<td>β blocker or diuretic</td>
<td>352/5059</td>
<td>CCB</td>
<td>216/5955</td>
<td>..</td>
</tr>
<tr>
<td>PEACE\textsuperscript{42}</td>
<td>2004</td>
<td>4.8</td>
<td>ACE inhibitor</td>
<td>355/3432</td>
<td>Placebo</td>
<td>399/3472</td>
<td>..</td>
</tr>
<tr>
<td>SCOPE\textsuperscript{43}</td>
<td>2003</td>
<td>3.7</td>
<td>ARB</td>
<td>93/2167</td>
<td>Placebo</td>
<td>115/2175</td>
<td>..</td>
</tr>
<tr>
<td>SHEP\textsuperscript{44}</td>
<td>1998</td>
<td>3.0</td>
<td>Diuretic</td>
<td>140/1631</td>
<td>Placebo</td>
<td>118/1578</td>
<td>..</td>
</tr>
<tr>
<td>STOP-2\textsuperscript{45}</td>
<td>1999</td>
<td>4.0</td>
<td>ACE inhibitor</td>
<td>93/1970</td>
<td>β blocker or diuretic</td>
<td>97/1960</td>
<td>CCB</td>
</tr>
<tr>
<td>VALUE\textsuperscript{46}</td>
<td>2004</td>
<td>4.2</td>
<td>ARB</td>
<td>690/5087</td>
<td>CCB</td>
<td>845/5074</td>
<td>..</td>
</tr>
</tbody>
</table>

Table 1: Summary of clinical trials of antihypertensive drugs that reported new cases of diabetes

Figure 1: Summary of trial identification and selection

RCT=randomised controlled trial.
method and the Riley-Day test for heterogeneity. A separate spreadsheet was produced for the 31 individual two-by-two comparisons, the logarithm of the individual odds ratios, and SE (calculated by the Mantel and Haenszel method), and used for the network meta-analysis.

We did the network meta-analysis using the one-line program published by Lumley,21 (programming language R, version 1.14, framework 2.21). Sensitivity analyses were undertaken by the same methods, after omission of data from specific trials (eg, studies in patients without hypertension), addition of data from unpublished or other trials, attribution of the results of one first-line agent to another agent used in the same randomised group of a trial, or use of data analysed after study closure.

Role of the funding source
PMM was supported in part by National Institutes of Health grant K25 HL68139-01A1. The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Both authors had full access to all the data in the study and had joint responsibility for the decision to submit for publication.

Results
Table 1 shows a summary of the trials included in the base-case network meta-analysis. Figure 2 shows the network of clinical trials according to the comparison of specific classes of initial antihypertensive drugs, as well as point estimates for the results of traditional meta-analyses. In this figure the arrows point towards the class of drug with the higher risk of incident diabetes according to the summary odds ratio for a traditional meta-analysis of studies comparing the two drugs directly. Some estimate of the overall propensity for each drug class to be associated with incident diabetes is shown by the number of arrows pointing away from the drug class.

Figure 3 shows the results of the network meta-analysis, with the diuretic as the standard of comparison, as recommended.45,46 Despite use of information from many disparate studies across different countries, the model has a low degree of incoherence (ω=0·000017). The low value suggests that the overall model is internally consistent, and could provide useful estimates of the effects of individual agents.9 Although standards for incoherence in network meta-analyses have not yet been established (because the technique is new), this degree of incoherence is lower than those seen in a network meta-analyses of 42 clinical trials of various types of antihypertensive drugs in preventing cardiovascular events (which ranged between 0·00022 and 0·0058).45 According to these data, an initial ARB, ACE inhibitor, CCB, or placebo is each associated with significantly fewer new cases of diabetes than an initial diuretic. Since the network meta-analysis technique does not prespecify the standard, but only compares and calculates the interactions across all agents, the referent agent can be changed to placebo. When this was done, the rank ordering of the agents according to their propensity to be associated with onset of diabetes remained the same. However, the odds ratios for the agents differed from when a diuretic was used as the referent agent: only the initial diuretic (odds ratio 1·30, 95% CI 1·07–1·58, p=0·009) and the initial ARB (0·75, 0·61–0·91, 0·003) retain significance. The individual odds ratios for an ACE inhibitor (0·87, 0·75–1·01, 0·064), CCB (0·97, 0·82–1·15, 0·72), and β blocker (1·17, 0·98–1·40, 0·08) were all non-significant.
## Table 2: Results of sensitivity analyses

<table>
<thead>
<tr>
<th>Incoherence</th>
<th>( \omega ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case</td>
<td>0.000017</td>
</tr>
<tr>
<td>Omit CHARM</td>
<td>0.037</td>
</tr>
<tr>
<td>Omit DREAM</td>
<td>0.0099</td>
</tr>
<tr>
<td>Omit HOPE, PEACE</td>
<td>0.0000079</td>
</tr>
<tr>
<td>Add STAR, TROPHY</td>
<td>0.000012</td>
</tr>
<tr>
<td>Attribute results of INVEST and ASCOT to ACE inhibitor</td>
<td>0.000001</td>
</tr>
<tr>
<td>Add STAR, TROPHY</td>
<td>0.0000012</td>
</tr>
<tr>
<td>Omit DREAM, HOPE, PEACE</td>
<td>0.0000079</td>
</tr>
<tr>
<td>Omit DREAM</td>
<td>0.000012</td>
</tr>
<tr>
<td>Omit CHARM</td>
<td>0.0099</td>
</tr>
<tr>
<td>Add SOLVD</td>
<td>0.000001</td>
</tr>
<tr>
<td>Use results of SHEP-2 (instead of SHEP)</td>
<td>0.0000012</td>
</tr>
<tr>
<td>Only patients with hypertension</td>
<td>0.075</td>
</tr>
<tr>
<td>Use only chlortalidone as diuretic</td>
<td>0.000013</td>
</tr>
<tr>
<td>Use no chlortalidone as diuretic</td>
<td>0.068</td>
</tr>
</tbody>
</table>

Data are odds ratio (95% CI). All odds ratios use diuretic as referent agent. See panel for full trial names.

### Panel: Names of trials included in network meta-analyses

- AASK=African American Study of Kidney diseases and hypertension
- ALLHAT=Antihypertensive and Lipid Lowering to prevent Heart Attack Trial
- ALPINE=Antihypertensive treatment and Lipid Profile in a North of Sweden Efficacy evaluation
- ANBP-2=Second Australian National Blood Pressure trial
- ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial
- CAPP2=Captopril Primary Prevention Project
- CHARMS=Canterbury Heart Failure Assessment of Reduction in Mortality and morbidity
- DREAM=Diabetes Reduction Approaches with ramipril and rosiglitazone Medications
- EWPHE=European Working Party on Hypertension in the Elderly
- FEVRI=Felodipine Events Reduction trial
- HAPPHY=Heart Attack Primary Prevention in Hypertension
- HOPE=Heart Outcomes Prevention Evaluation
- HOPE-TOO=HOPE-The Ongoing Outcomes
- INSIGHT=International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment
- INVEST=International Verapamil/trandolapril Study
- LIFE=Losartan Intervention For Endpoint reduction
- MRC-E=Medical Research Council trial of treatment of hypertension in the Elderly
- NORDIL=Nordic Diltiazem study
- PEACE=Prevention of Events with Angiotensin Converting Enzyme inhibition
- SCOPE=Study on Cognition and Prognosis in the Elderly
- SHEP=Study of Systolic Hypertension in the Elderly Program
- SHEP-2=SHEP follow-up study
- SOLVD=Studies Of Left Ventricular Dysfunction
- STAR=Study of Trandolapril/verapamil SR And Insulin Resistance
- STOP-2=Second Swedish Trial in Older Patients with hypertension
- TROPHY=Trial Of Prevention of Hypertension
- VALUE=Valsartan Antihypertensive Long-term Use Evaluation

Perhaps due to the lower statistical power for these comparisons than for those involving the diuretic. Odds ratios did not differ between an ARB and an ACE inhibitor (0.85, 0.68–1.07, \( p=0.16 \)), or between a diuretic and a \( \beta \) blocker (0.90, 0.75–1.09, 0.30).

These base case results were fairly robust when subjected to many one-way sensitivity analyses (table 2), and the changes that result can be explained on the basis of the trials’ attributes. When we omitted the results of CHARMS (see panel for full trial names), because it was (unlike the other trials) done in patients with heart failure and not hypertension, the incoherence increased, but none of the odds ratios changed very much. Also when data from trials in which some participants did not have hypertension (those in DREAM, HOPE, PEACE) were omitted, the odds ratios were fairly stable. The odds ratios for placebo and ACE inhibitor change (in the directions of the results of every trial), but the others stayed about the same. When we added the results of two recently reported trials (STAR and TROPHY), the odds ratios remained much the same (table 2). When the reduction in incident diabetes in INVEST\(^a\) and ASCOT\(^a\) was attributed to the ACE inhibitor used in most patients as second-line therapy, rather than to the initial CCB, the incoherence decreased, the CI for the initial ACE inhibitor’s odds ratio decreased, the odds ratio for the CCB increased (and its 95% CI widened), but the other results changed little. Similarly, when the cases of incident diabetes in CAPP2, \(^b\) NORDIL, \(^b\) and STOP-2\(^b\) were attributed to the diuretic, rather than to the \( \beta \) blocker that was used initially in most patients assigned conventional therapy in these trials, the incoherence decreased, the odds ratios for all drug classes increased, with the biggest increase for the \( \beta \) blocker (the CI for which widened the most). The results of the base-case analysis changed little when we used the results of the HOPE-TOO follow-up\(^a\) (rather than data from the first 4·5 years of the original HOPE study\(^b\)), the current definition of diabetes in SHEP, \(^a\) or when we added the results from one centre in SOLVD, \(^b\) or restricted the analysis to trials done in
patients with hypertension, or according to whether we included data from trials that did or did not use chlortalidone (table 2).

Discussion

Our findings show that ARB and ACE inhibitors are the antihypertensive agents least associated with incident diabetes followed by CCB and placebo, β blockers, and diuretics.

These results summarise international experience of incident diabetes in long-term clinical trials of antihypertensive agents, incorporating both direct and indirect comparisons of agents, including those that have never been compared directly (ie, ACE inhibitor vs ARB). The network meta-analysis technique overcomes the significant heterogeneity in traditional meta-analyses for several drug classes versus all other antihypertensive agents, because it can attribute risk across all classes of initial antihypertensive drugs, rather than being restricted to comparisons of one class versus all other classes. The findings of this network meta-analysis are robust, in terms of both the low estimate of incoherence within the model itself, and in sensitivity analyses (eg, when data from various studies that enrolled patients without hypertension were omitted, or the risk of incident diabetes was allocated to a different agent from the initial randomised drug class).

These results are consistent with those of previous meta-analyses, but go beyond them, because the network technique allows dissection of the individual drug classes’ association with incident diabetes. For example, the meta-analysis of Jandeleit-Dahm and colleagues18 combined three trials of an ARB and four trials with an ACE inhibitor, excluded the results of the amlodipine besilate arm of ALLHAT, which avoided a significant heterogeneity, and did not compare an ARB with an ACE inhibitor. Similarly, Gillespie and colleagues17 did not attempt to separate the effects of the two drug classes in their meta-analysis. They combined the diuretic and CCB groups of ALLHAT into a single comparator, and separated the CHARM-Alternative and CHARM-Preserved groups, without including the CHARM-Added data.5 Their overall conclusion matched that of Scheen:19 an initial ACE inhibitor or an initial ARB lowered the risk of incident diabetes by 22% (95% CI 17–27%, p=0·0001) compared with any and all other drugs to which each had been compared. Scheen used all the data from CHARM and SOLVD, and concluded that the risk reductions with an initial ACE inhibitor were similar to those with an initial ARB. Similarly, Abuissa and co-workers20 attempted to separate the effects of ACE inhibitors and ARB, but showed significant heterogeneity between studies (p=0·008), even with a random-effects model. They attributed the heterogeneity to differences in the types of drugs used, study designs, and methods across the studies, but did not attempt to overcome the heterogeneity by parsing the control groups. Opie and Schall21 undertook traditional meta-analyses of both ACE inhibitors and ARB versus conventional therapy (three trials), CCB versus conventional therapy (four trials), and both ACE inhibitors and ARB versus placebo (two trials, not in patients with hypertension); they concluded that the diuretic or β blocker groups of the trials all had a significantly higher risk of incident diabetes than each group that included the newer drug classes.

There are several reasons why antihypertensive drugs might have differing effects on the risk of diabetes, with diuretics and β blockers apparently increasing the likelihood of diabetes and ACE inhibitors and ARB reducing it.22 Most reasons proposed so far implicate the different actions of these drugs on circulating kinins, pancreatic insulin release, and insulin’s peripheral effects,16–20 particularly since antihypertensive drugs interact with the sympathetic nervous system and adipocytes.22–24

Animal studies have also implicated the γ-subtype peroxisome proliferator-activated receptor.25 Which of these is most important in human beings remains a topic for further research.

Our findings have several inherent limitations. First, incident diabetes has only rarely been a prespecified endpoint in long-term clinical trials of antihypertensive drugs: it was the primary endpoint in ALPINE,27 the most common component of the primary endpoint in DREAM,25 and a low secondary endpoint in VALUE26 and ASCOT.27 Thus, the investigators’ efforts to detect incident diabetes varied between trials: in some studies, formal oral glucose-tolerance tests were done, whereas others relied on self-report,26 or a single fasting glucose test in a convenience sample of participants (eg, only 38% of the eligible ALLHAT participants were tested at 4 years of follow-up).26 Second, the diagnostic criteria for diabetes mellitus changed in 1999, so studies done or reported before then used the older criteria (≥7·8 mmol/L); since then, most studies have used the current threshold of ≥7·0 mmol/L.28 Third, in meta-analyses of clinical trials, observations are grouped by the initial randomised drug (because it is least likely of all variables to be biased), but differences might exist between drugs in the same class (eg, the glycaemic response in people with type 2 diabetes, not incident diabetes, to long-term treatment with carvedilol vs metoprolol29) that are ignored in this approach. In individual network meta-analyses, chlortalidone was associated with a slightly (but not significantly) higher risk of incident diabetes than other diuretics, each compared with placebo: 1·43 (95% CI 1·06–1·92) versus 1·19 (0·90–1·56). In these meta-analyses, the potential effects of poor adherence to assigned therapy, previous treatment regimens,30 or any additional therapies tend to be ignored, even when additional agents might have different effects on the endpoint of interest (eg, INVEST, ASCOT).25–27 For these reasons, we undertook a sensitivity analysis that attributed the effects of therapy to the second-line agent in these two trials. Such confounding is a likely contributor to the different effects of drugs on incident diabetes in many
long-term clinical trials of antihypertensive drugs; even differing proportions of patients taking the same diuretic (eg, in LIFE\textsuperscript{13} or VALUE\textsuperscript{24}) could have affected the results.

The implications of these data for clinical practice are uncertain. By contrast with the recommendation from the US Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure\textsuperscript{20} to use a diuretic for most patients with uncomplicated stage 1 hypertension, the UK National Institute for Health and Clinical Excellence recommends diuretics or β blockers only as third-line or fourth-line agents, partly because of the economic costs of treating people with diabetes.\textsuperscript{27} In clinical trials, the absolute differences between antihypertensive agents for incident diabetes were small, and always less than 3–6%.\textsuperscript{28} Small numbers of affected patients and relatively short follow-up times limit the power of existing studies to detect an increased risk of cardiovascular events in patients with incident diabetes. One longitudinal cohort study from Italy\textsuperscript{29} showed a significant increase, but no increase was seen in people who developed diabetes after randomisation to antihypertensive drug therapy in ALLHAT,\textsuperscript{30} SHEP,\textsuperscript{31} the Finnish MONICA (Monitoring trends and determinants in cardiovascular disease) study,\textsuperscript{32} or VALUE\textsuperscript{44} after mean follow-up of 4–9 years, 14–3 years, 10 years, and 5 years, respectively. Studies with longer follow-up might help define the time taken for incident diabetes to be associated with increased cardiovascular risk.

Future research is likely to provide better quality data to help establish the importance of glycaemic effects of commonly used antihypertensive drugs.\textsuperscript{33,34} Incident diabetes is a prespecified coprimary endpoint in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial (that is under-way), as well as a high secondary endpoint for the Ongoing Telmisartan Randomised Assessment Study in ACE-intolerant patients with cardiovascular disease (TRANSCEND) trials.\textsuperscript{46} The results of these trials might be helpful in establishing whether ACE inhibitors and ARB have significantly different effects on incident diabetes.

Until these trials are reported, however, our network meta-analysis provides a useful and complete picture of the propensity of antihypertensive drugs to be associated with incident diabetes. This technique not only includes the results of all clinical trials that directly compare two initial antihypertensive drugs, but also incorporates indirect comparisons (particularly important for ACE inhibitors versus ARB, which have not yet been directly compared), and results in estimates that are highly coherent and robust to many sensitivity analyses. These attributes make this technique very attractive for summarising the disparate results of many different clinical trials.

References


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Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial

Jane Durga, Martin P J van Boxtel, Evert G Schouten, Frans J Kok, Jelle Jolles, Martijn B Katan, Petra Verhoef

Summary

Background Low folate and raised homocysteine concentrations in blood are associated with poor cognitive performance in the general population. As part of the FACIT trial to assess the effect of folic acid on markers of atherosclerosis in men and women aged 50–70 years with raised plasma total homocysteine and normal serum vitamin B₁₂ at screening, we report here the findings for the secondary endpoint: the effect of folic acid supplementation on cognitive performance.

Methods Our randomised, double blind, placebo controlled study took place between November, 1999, and December, 2004, in the Netherlands. We randomly assigned 818 participants 800 μg daily oral folic acid or placebo for 3 years. The effect on cognitive performance was measured as the difference between the two groups in the 3-year change in performance for memory, sensorimotor speed, complex speed, information processing speed, and word fluency. Analysis was by intention-to-treat. This trial is registered with clinicaltrials.gov with trial number NCT00110604.

Findings Serum folate concentrations increased by 57.6% (95% CI 53.9 to 61.4) and plasma total homocysteine concentrations decreased by 26% (24 to 28) in participants taking folic acid compared with those taking placebo. The 3-year change in memory (difference in Z scores 0.132, 95% CI 0.032 to 0.233), information processing speed (0.087, 0.016 to 0.158) and sensorimotor speed (0.064, −0.001 to 0.129) were significantly better in the folic acid group than in the placebo group.

Interpretation Folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age.

Introduction

Cognitive function declines with ageing, especially cognitive domains related to memory and information processing speed. Changes in cognitive performance, especially memory function, have been linked to risk of dementia in old age. Modifiable risk factors for age-related cognitive decline have been identified, but their causality has not yet been established. Poor folate status is one such suspected risk factor.

A longitudinal study, undertaken in the USA when folic acid fortification of foods was routine, showed greater cognitive decline in people with a high folate intake than in those with low intakes. A systematic review of supplementation with folic acid alone or in combination with other B vitamins showed that no beneficial effect on cognitive performance was conferred. Many of the trials have used small study populations, supplemented for a short duration, or used tests such as the Mini-Mental State Examination, which are unable to detect subtle changes in cognitive function (table I).

We investigated whether 800 μg daily oral folic acid supplementation for 3 years improved cognitive performance compared with placebo in older adults. Cognitive performance was assessed with tests that probe cognitive domains that decline in the ageing process.

Methods

Participants Participants were men and post-menopausal women aged 50–70 years, from the Gelderland region in the Netherlands who participated in the Folic Acid and Carotid Intima-Media Thickness (FACIT) trial (unpublished), a study investigating the effect of folic acid supplementation on atherosclerotic progression. Additional outcomes of the trial were age-related decline in cognitive function and hearing. Here we present data for the effect of folic acid on the cognitive performance aspect of the study.

We used municipal and blood-bank registries to recruit participants. On the assumption that high concentrations of plasma total homocysteine were a risk factor for vascular disease, we selected participants expected to benefit from folic acid’s homocysteine-lowering effect and excluded participants with concentrations of plasma total homocysteine of less than 13 μmol/L (73% of those screened). We excluded participants with raised homocysteine concentrations (>26 μmol/L) that were possibly due to factors other than suboptimal folate concentrations, including: serum vitamin B₁₂ concentration of less than 200 pmol/L (10% of those screened); selfreported medical diagnosis of renal or thyroid disease; or self-reported use of medications that influence folate metabolism. Additionally, we excluded participants with self-reported intestinal disease and participants who...
reportedly used B-vitamin supplements or drugs that could affect atherosclerotic progression. Finally, more than 80% self-reported compliance during a 6-week placebo run-in period was required. The Wageningen University medical ethics committee approved the study and participants gave written informed consent.

Procedures
After the initial measurement sessions, participants were allocated placebo or 800 μg per day folic acid, which is regarded as a low dose for a clinical trial. Patients were allocated treatment or placebo with permuted blocks of sizes four and six, which varied randomly. Specialised staff who were not involved in the study allocated and labelled the capsule boxes with participants’ unique sequence number. Participants in the same household received the same treatment. The folic acid and placebo capsules, produced by Swiss-Caps Benelux (Heerhugowaard, Netherlands), were indistinguishable in appearance. Capsules were individually packaged in foil strips containing 28 capsules per strip, with the days of the week printed on the back. Every year, participants received a 13-month supply of capsules. Compliance was judged by capsule-return counts and a diary that registered missed capsules. Diaries and capsules were returned by participants every 12 weeks.

At the end of the study, the proportion of participants who thought they had received folic acid or placebo did not differ between the two groups (p=0·64). 70% of participants in the folic acid group and 71% in the placebo group thought they had been allocated folic acid; whereas 11% in the folic acid group and 9% in the placebo group thought

<table>
<thead>
<tr>
<th>Duration (in analyses)</th>
<th>Number at follow-up</th>
<th>Mean age, years, SD</th>
<th>Population type</th>
<th>Dose of folic acid (dose of placebo), mg per day</th>
<th>Types of cognitive test</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Folic acid only
| Fioravanti et al10    | 60 days             | 29                  | 80 (6)          | Patients with memory complaints, Mini-Mental State Examination score between 16 and 24, mild to moderate cognitive decline on basis of Global Deterioration Score, 70-90 years, serum folate <7 nmol/L | 15                     | 1 Randt Memory Test a Acquisition and recall b Delayed recall c Memory index d Encoding factor e Cognitive efficiency f Attention efficiency 1 Wechsler Memory Scale 1a Logical memory subtest 1b Associate learning subtest 2 Boston Naming test 3 Controlled Oral Word Association test 4 Trail making test 5 Finger Tapping test 6 Wechsler Adult Intelligence Scale-revised (composite of information, vocabulary and similarities sub-tests) 7 Benton Visual Retention test | Folic acid improved attention efficiency score (p=0·05). When taking into account baseline folate status, folic acid improved acquisition and recall (p=0·007), delayed recall (p=0·007), memory index (p=0·002), encoding (p=0·005). Folic acid seemed to reduce performance on associate learning subtest of Wechsler Memory Scale (p=0·08) and Trails B (p=0·08). |
| Sommer et al11        | 10 weeks            | 7                   | 77 (4)          | Patients meeting DSM-III-R criteria for dementia, ≥65 years, suboptimal folate (serum folate 2-5 ng/mL, red-blood-cell folate 127-452 ng/mL), B12 >200 pg/mL | 2x10                   | 1a Logical memory subtest 1b Associate learning subtest 2 Boston Naming test 3 Controlled Oral Word Association test 4 Trail making test 5 Finger Tapping test 6 Wechsler Adult Intelligence Scale-revised (composite of information, vocabulary and similarities sub-tests) | Folic acid seemed to reduce performance on associate learning subtest of Wechsler Memory Scale (p=0·08) and Trails B (p=0·08). |
| Folic acid with other B vitamins
| Eussen et al12        | 24 weeks            | 152                 | 82 (5)          | Mini-Mental State Examination ≥ 19, ≥70 years, suboptimal vitamin B12 status (B12 100-200 pmol/L or B12 200-300 pmol/L, methylmalonic acid ≥0·32 μmol/L, creatinine ≤120 μmol/L) | 0·4                    | Domains based on clustering of similar tests 1 Attention 2 Construction 3 Sensomotor speed 4 Memory 5 Executive function 1 Mini-Mental State Examination 2 Wechsler Paragraph Recall 3 Category Word Fluency 4 Rey Auditory Verbal Learning 4a composite of trials 1-5 4b trial 7 5 Raven’s Progressive Matrices 6 Controlled Oral Word Association 7 Raven Trail Making, part B 8 Composite score of all tests | Compared with placebo or to vitamin B12 only. No effect of folic acid on cognitive domains. General trend towards reduced performance on tests. In crude analyses significance was reached for the Raven Trail Making test part B (7% slower, 95% CI 2 to 13%) and Wechsler Paragraph Recall test (mean difference -1·19, 95% CI -2·30 to -0·04). After adjustment for baseline performance, sex, and education, the composite score of all tests was lower in the folic acid group than in the placebo group (-0·11, 95% CI -0·22 to 0·00). No effect  |
| McMahon et al13       | 2 years             | 253                 | 74 (6)          | ≥65 years, homocysteine ≥13 μmol/L | 1                      | 1 Mini-Mental State Examination 2 Wechsler Paragraph Recall 3 Category Word Fluency 4 Rey Auditory Verbal Learning 4a composite of trials 1-5 4b trial 7 5 Raven’s Progressive Matrices 6 Controlled Oral Word Association 7 Raven Trail Making, part B 8 Composite score of all tests | Compared with placebo or to vitamin B12 only. No effect of folic acid on cognitive domains. General trend towards reduced performance on tests. In crude analyses significance was reached for the Raven Trail Making test part B (7% slower, 95% CI 2 to 13%) and Wechsler Paragraph Recall test (mean difference -1·19, 95% CI -2·30 to -0·04). After adjustment for baseline performance, sex, and education, the composite score of all tests was lower in the folic acid group than in the placebo group (-0·11, 95% CI -0·22 to 0·00). No effect |
| Stott et al14         | 1 year              | 167                 | 75 (6)          | Mini-Mental State Examination ≥ 19, ischaemic vascular disease, ≥65 years, red-blood-cell folate ≥280 ng/mL, vitamin B12 ≥250 pg/mL | 2·5                    | 1 Telephone Interview for Cognitive Status 2 Letter Digit Coding | Compared with placebo or to vitamin B12 only. No effect of folic acid on cognitive domains. General trend towards reduced performance on tests. In crude analyses significance was reached for the Raven Trail Making test part B (7% slower, 95% CI 2 to 13%) and Wechsler Paragraph Recall test (mean difference -1·19, 95% CI -2·30 to -0·04). After adjustment for baseline performance, sex, and education, the composite score of all tests was lower in the folic acid group than in the placebo group (-0·11, 95% CI -0·22 to 0·00). No effect |
they had been allocated placebo. All staff, including all authors, were unaware of group assignment until completion of the trial and after data analyses.

We assessed cognitive function using five separate tests used in the Maastricht Aging Study.21 These five tests were used to construct five a-priori-defined cognitive domains: memory, sensorimotor speed, complex speed, information processing speed, and word fluency.22 Descriptions of the tests are in panel 1.23–27 Although not part of the cognitive tests used for our study outcome, we used the Mini-Mental State Examination9 to screen for participants with possible dementia, defined as a score of less than 24 points.

All participants underwent the measurements after an overnight fast, followed by a glass of fruit juice and a bread product for breakfast. Two trained research assistants oversaw the tests during a 40-min session; they used standard wording to instruct participants. A third research assistant periodically observed the testing to ensure that the two research assistants did not deviate from the protocol. All cognitive tests were done in the same room with the same props. We repeated cognitive testing at the end of the study using variations of the tests used at baseline (parallel versions). We repeated the verbal fluency test because the validity of a parallel version of the animal-naming part of the test has not been established.

Fasting venous blood was processed and samples were stored at –80ºC. We measured serum folate, erythrocyte folate, serum vitamin B₁₂, plasma total homocysteine, plasma vitamin B₆, serum creatinine, and lipids as described elsewhere.22 The C677T polymorphism in the gene encoding methylenetetrahydrofolate reductase (MTHFR)28 and apolipoprotein E genotype were determined by PCR of DNA and restriction digestion with HinFl and HhaI, respectively.

Self-reported medical history, including current drug use and smoking habits, were ascertained by questionnaire.

Table 1: Summary of randomised controlled trials examining effect of folic-acid-containing supplements on cognitive function

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Participants</th>
<th>Mean Age</th>
<th>Outcome Measures</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan et al21</td>
<td>5 weeks</td>
<td>104</td>
<td>51 (20)</td>
<td>Healthy women 0.75</td>
<td>Folic acid reduced Verbal Fluency performance (p&lt;0.05). When stratifying by age, folic acid improved Rey Auditory-Verbal Learning test (recognition task) in older participants (&gt;65 years, p&lt;0.05).</td>
</tr>
<tr>
<td>Toole et al26</td>
<td>2 years</td>
<td>3097</td>
<td>66 (10)</td>
<td>Previous stroke, homocysteine &gt;9 μmol/L 2.5 or 0.02</td>
<td>1 Mini-Mental State Examination No effect</td>
</tr>
<tr>
<td>Vital Trial Collaborative Group17</td>
<td>12 weeks</td>
<td>128</td>
<td>Range</td>
<td>Mini-Mental State Examination score &gt;26 or mild cognitive impairment assessed by modified Telephone Interview of Cognitive Status 2</td>
<td>1 Mini-Mental State Examination No effect</td>
</tr>
<tr>
<td>Leverin et al18</td>
<td>4 months</td>
<td>171–179</td>
<td>76 (4)</td>
<td>Community-dwelling 0.8</td>
<td>1 Digit Span Forward 2 Digit Span Backward 3 Identical forms 4 Visual reproduction 5 Synonyms 6 Block design 7 Digit Symbol, 90s 8 Thurstone’s Picture Memory test 9 Figure Classification</td>
</tr>
<tr>
<td>Obeid et al19</td>
<td>45 days</td>
<td>80 (6)</td>
<td>Mini-Mental State Examination score &gt;15, &gt;65 years 5.0 orally or 1.1 (intravenously three times a week for 3 weeks) 1 Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-infarct Dementia and Dementia 2 Orientation abilities 3 Memory 4 Intellectual abilities</td>
<td>No treatment effect reported, only differences in performance within groups</td>
<td></td>
</tr>
</tbody>
</table>

DSM-III-R=Diagnostic and Statistical manual of Mental Disorders, 3rd edition revised.
and reviewed by a research assistant with the participant. Education was grouped according to highest attained level.29 Height and weight were measured and body-mass index calculated. Blood pressure was measured with an automated meter (Dinamap Compact Pro 100, General Electric). Eight blood-pressure measurements were taken and the average calculated. We used a food-frequency questionnaire to estimate dietary folate intake during the past 3 months.

We measured genotype and attained educational level at the beginning of the study. Plasma total homocysteine, serum folate, and vitamin B₁₂ concentrations and information about medical status and drug use were recorded yearly and all other measurements were taken at the beginning and end of the study.

Statistical analyses

Our sample size calculation was based on the mean intima-media thickness progression of the common carotid artery (the primary endpoint of the FACIT trial). We assumed that if the progression of the mean carotid intima-media were 0·01 mm (SD 0·06 mm), then 251 participants would be needed in each group to detect a difference of 0·015 mm (power 80%, two-sided α=0·05). We assumed that 30–40% of the population could be lost to follow-up.

The cognitive domains were constructed with Z scores (panel 2).21 Sensorimotor speed measures basic speed, and shows direct stimulus-response connections with little central processing, whereas complex speed measures time needed for higher-order information processing. As other investigators have done,30,31 we present global cognitive function (an average of the domains). The test scores at the beginning and end of the study were pooled to calculate the grand mean and SD per test; this information was used to calculate the Z scores (panel 2). At baseline, one participant missed 50% or more of the subtests for complex speed and three participants did not have an information processing speed score. These participants were assigned the median score of these domains of the total population at baseline. 17 participants lost to follow-up were assigned the median score of these domains of the total population at the end of the study. Analyses were done on an intention-to-treat basis with SPSS 11.0. No adjustments were made for multiple testing.

The outcome of this study was the difference between the folic acid and placebo groups in the 3-year change in cognitive performance for memory, sensorimotor speed, complex speed, information-processing speed, and word fluency.

We used the t test to determine whether the change in cognitive performance differed between treatment groups. We did all analyses without knowledge of follow-up folate or homocysteine concentrations. The treatment code was broken once an independent statistician had verified the data and all authors had formally approved the tables showing the main effects.

In secondary analyses, we determined whether the effect of folic acid supplementation was dependent on initial concentrations of folate or homocysteine or MTHFR C677T genotype. We determined the effect of folic acid

Panel 1: Description of cognitive function tests

**Word learning test**

Measures the storage and retrieval of newly acquired verbal information. Participants were instructed to memorise 15 commonly used monosyllabic words. The words were printed on a card and were presented in a fixed sequence for 2 s. Immediately after the 15 words were presented, the participants are asked to recall the words. This procedure was done three times. 20 min after presentation of the words, participants were prompted to recall the 15 words. The maximum and total number of correctly repeated words of the immediate recall tests were recorded, as well as the number of correctly repeated words in the delayed recall test.

**Concept shifting test**

A timed test with four subtests that measure the ease of switching between two psychological concepts. Each subtest was printed on one sheet of paper, which contained 16 circles (15 mm diameter) arranged in a larger circle (16 cm diameter). For the first subtest, participants were asked to cross off the circles in numerical and alphabetical order (eg, 1, A, 2, B, 3, C, etc).

**Stroop colour-word test**

Measures selective attention and susceptibility to behavioural interference and consists of three subtests. Each subtest was presented on a separate sheet containing four rows of ten columns of colour names of coloured blocks. For the first subtest, participants were instructed to read words printed in black ink (words were “red”, “blue”, “green”, and “yellow”). Participants were asked to name coloured blocks in the second subtest, for the final subtest, participants were asked to name the colour of the ink, rather than read the word (eg, say blue when the word “RED” was printed in blue ink).

**Verbal fluency test**

Measures word fluency or the ability to draw on one’s encyclopaedic memory in a strategic manner. Participants were asked to name as many animals as possible in 1 min. This test indicated the amount of organisation among clusters of related words (eg, pets, zoo animals, etc).

**Letter digit substitution test**

Assesses general speed of visual information processing. Nine different letters were assigned a unique number (1–9) in a key at the top of the form. The participants were presented with a random series of letters in cells and were instructed to add the corresponding digit to the letters. The number of correctly copied corresponding digits in 90 s was recorded.

Panel 2: Construction of cognitive domains with Z-scores

| Memory= (Z_{word learning test ‘total immediate recall’}+Z_{word learning test ‘maximum immediate recall’}+Z_{word learning test ‘delayed recall’})/3 |
| Sensorimotor speed= (Z_{concept shifting test ‘numbers and letters’}+Z_{concept shifting test ‘numbers’}+Z_{concept shifting test ‘letters’}+Z_{group color-word test ‘word reading’})/4 |
| Complex speed= (Z_{concept shifting test ‘numbers and letters’}+Z_{group color-word test ‘word reading’})/2 |
| Information processing speed= Z_{letter digit substitution test} |
| Word fluency= Z_{verbal fluency test} |
supplementation per stratum (median cut-off) using an independent sample t test. We used linear regression models to examine whether the difference in treatment effects between strata was significant.

Role of the funding source
The sponsors had no role in the design or implementation of the study, data collection, data management, data analysis, data interpretation, or in the preparation, review, or approval of the manuscript. 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
Patients were randomised between November, 1999, and April, 2001, and the study was undertaken from September, 2000, to December, 2004. The figure shows the trial profile.

The participant with headache complaints dropped out of the trial prematurely. 17 participants (2%) did not return for the cognitive function measurements after 3 years, and six participants stopped treatment prematurely. The proportion of participants lost to follow-up or who stopped treatment early did not differ between the groups (p=0·25). Apart from these participants, the compliance of the participants was high, with 99% of the capsules reportedly consumed. Table 2 shows baseline clinical characteristics of the participants.

In both groups, plasma total homocysteine concentrations at baseline were lower than at screening, a likely result of regression to the mean (table 3). After 3 years, serum folate concentrations were significantly higher in the folic acid group than in the placebo group (table 3). Baseline scores on the cognitive tests and domains were similar between the two groups (table 4). At baseline, one participant in the folic acid group and six in the placebo group scored less than 24 points on the Mini-Mental State Examination (p=0·05). Whereas sensorimotor speed, information-processing speed, and complex speed declined significantly during the 3-year study in the placebo group,
the rate of decline was slower in these domains in the folic acid group (table 5). Both groups improved on memory tests, because of procedural learning effects. However, the improvement was significantly greater in the folic acid group than in the placebo group.

The 3-year change in cognitive function was significantly better in the folic acid group than in the placebo group in terms of information-processing speed. Folic acid did not affect sensorimotor speed, complex speed, or word fluency. Global cognitive function, defined as the average of the five domains, improved significantly (table 5). Performance on the Mini-Mental State Examination was not affected by folic acid group (p=0·63). The median score for both groups after 3 years was 29 points (IQR 28–30) ranging from 21 to 30 points in the folic acid and 16 to 30 points in the placebo group.

In addition to memory and information-processing speed, sensorimotor speed improved significantly (p<0·05) when other imputation techniques were used (eg, last value carried forward, expectation maximisation), when 17 participants lost to follow-up were excluded from the analyses, and when seven participants with initial Mini-Mental State Examination scores of less than 24 points were excluded from the analyses. Finally, at baseline, a greater proportion of participants with a low educational level, an important determinant of cognitive performance, were randomised into the folic acid group. Additionally, a higher proportion of participants in the folic acid group had dyslipidaemia and self-reported vascular disease. Our results did not change when we adjusted for these variables.

51 participants received the same treatment and lived in the same households. Hence these observations were not independent of one another. When partners were excluded from the analyses, the results did not change, except that folic acid supplementation significantly improved sensorimotor speed (difference in Z scores 0·079 [95% CI 0·014–0·145]).

To show the relevance of our findings we compared the regression coefficient of age—adjusted for sex, education, and treatment calculated with linear regression models with initial performance as the dependent variable—with the treatment effect. 3-year folic acid supplementation confers an individual the performance of someone 6·9 years younger (95% CI 2·1–11·8). This improvement is similar to a performance of an individual 6·9 years younger (95% CI 2·1–11·8).

The effect of folic acid supplementation was not modified by initial folate status or MTHFR C677T genotype. Compared with placebo, participants with initial plasma total homocysteine concentrations greater than the population median of 12·9 μmol/L showed a greater improvement in information processing speed than participants with concentrations lower than the population median (interaction term p=0·034). Information-processing speed of the latter group improved by 0·013, (95% CI 0·066 to 0·073), whereas participants with higher homocysteine concentrations improved by 0·166, (0·064–0·267). Outcomes of the other four domains and global cognitive function were not affected by initial plasma total homocysteine concentrations.

In post-hoc analyses, we examined whether low concentrations of vitamin B12 modified the effect of folic acid supplementation on cognitive performance. Folic acid supplementation improved sensorimotor speed (difference in Z score 0·112, 95% CI 0·001–0·223) and information processing speed (0·190, 0·055–0·325) in 230 participants with initial low or normal concentrations of vitamin B12 (<250 pmol/L), but not in 588 participants with vitamin B12 concentrations of 250 pmol/L or greater (0·046, –0·033 to 0·126 and 0·048, –0·036 to 0·131, respectively).

| Age (years) | 60 (5) | 60 (6) |
| Male | 294 (72%) | 292 (70%) |
| High / middle / low education | 154 (38%)144 (36%)107 (26%) | 169 (41%)168 (41%)76 (18%) |
| Mini-mental state examination (points) | 29 (28–30) | 29 (28–30) |
| Range (points) | 18–30 | 15–30 |
| Folate acid | 0.079 (0.014–0.145) |
| MTHFR C677T allele 0, 1, 2* | 143 (36%), 187 (46%), 73 (18%) | 168 (41%), 191 (46%), 52 (13%) |
| Vitamin B12, (pmol/L) | 268 (24/–363) |
| Vitamin B12 (pmol/L) | 30 (28–240)8 | 368 (24/–483) |
| Creatinine (mmol/L) | 92 (7.12) | 92 (7.12) |
| Total cholesterol (mmol/L) | 58 (3.11) | 58 (7.11) |
| LDL cholesterol (mmol/L) | 40 (1.00) | 40 (1.00) |
| HDL cholesterol (mmol/L) | 12 (0.3) | 12 (0.4) |
| Dyslipidaemia | 156 (39%) | 138 (33%) |
| ApoE e4 allele, 0, 1, 25 | 272 (67%), 122 (30%), 11 (3%) | 282 (69%), 116 (28%), 12 (3%) |
| Systolic blood pressure (mm Hg)* | 133 (16) | 133 (16) |
| Diastolic blood pressure (mm Hg)* | 77 (8) | 77 (9) |
| Hypertension* | 94 (23%) | 88 (21%) |
| Body-mass index|| 26.6 (3.6) | 26.5 (3.6) |
| Current smokers | 84 (21%) | 83 (20%) |
| Diabetes mellitus | 12 (3%) | 14 (3%) |
| Self-reported cardiovascular disease** | 58 (14%) | 39 (9%) |

**Diagnosis of angina pectoris, myocardial infarction, arrhythmia, stroke, or peripheral arterial disease, or having undergone angioplasty, coronary bypass surgery, or aortic aneurysm surgery. Data are mean (SD), median (IQR) or number (%) unless otherwise indicated.

Table 2: Baseline clinical characteristics

Articles

Folic acid (n=405) | Placebo (n=413)
---|---
**Word learning test**
Total of three immediate recall trials (number of words) | 26.9 (5.9) | 26.8 (5.4)
Maximum of three immediate recall trials (number of words) | 11.2 (2.2) | 11.2 (2.0)
Delayed recall (number of words) | 8.9 (2.8) | 9.0 (2.7)

**Concept shifting test**
Empty (s)* | 5.37 (1.16) | 5.43 (1.28)
Numbers (s) | 23.26 (5.82) | 23.40 (6.07)
Letters (s)† | 27.01 (7.40) | 27.46 (9.51)
Numbers and letters (s)†‡ | 35.95 (12.28) | 36.34 (13.35)

**Stroop colour-word test**
Word reading (s)* | 16.34 (2.75) | 16.38 (3.09)
Naming colour of ink (s)† | 42.62 (10.65) | 43.68 (11.79)
Letter digit substitution test, number of digits in 90 s¶ | 48.86 (8.96) | 48.24 (8.99)

**Verbal fluency test, number of words** | 24.8 (6.3) | 24.1 (5.7)

Performance did not differ between two groups. *Data available for 412 participants in placebo group. †Data available for 403 participants in folic acid group and 411 participants in placebo group. ‡Data available for 409 participants in placebo group. ¶Data available for 404 participants in folic acid group and 411 participants in placebo group.

Table 4: Performance on cognitive function tests at baseline

Discussion

In 818 older adults, daily oral folic acid supplementation for 3 years beneficially affected global cognitive function, and specifically memory, and information processing; functions that are sensitive to ageing. The decline in memory seen with ageing is generally preceded, and might be affected, by a decline in speed functions. Nonetheless, folic acid supplementation might beneficially affect both memory and speed simultaneously, since high concentrations of homocysteine have been associated with atrophy of the hippocampus, an area of the brain which is important for memory consolidation. Complex speed, a domain sensitive to ageing, was not affected by folic acid supplementation. The effect of folic acid might be restricted to basic aspects of speed and information processing, rather than high order information processing. Word fluency was not affected by folic acid supplementation, perhaps not surprisingly, because encyclopaedic memory is a component of crystallised intelligence that stays relatively intact as one grows older.

Our study might have yielded demonstrable effects of folic acid on cognitive function because we used sensitive tests that exist in parallel versions. We also improved the robustness of the underlying cognitive constructs by clustering raw test scores for several tests in compound performance measures. This procedure decreased variation associated with the individual tests. Finally, clustering of raw tests scores limited our cognitive performance outcomes to five a-priori defined outcomes.

By contrast with other trials, we were able to detect an effect of folic acid on several cognitive functions, for several reasons. First, assuming that high plasma total homocysteine concentrations are a causal risk factor for cognitive decline, we selected a population likely to benefit from folic acid supplementation. Second, we had a fairly large study population and supplemented for quite a long period. Third, although we did not attempt to measure the prevalence of dementia at baseline nor its incidence during the duration of the trial, our population is unlikely to have included many cognitively impaired or demented participants, since the general performance on a dementia screening test such as the Mini-Mental State Examination was high, both at the beginning and end of the study. That treatment with folic acid or other B vitamins might feasibly be too late in populations with mild cognitive impairment and dementia. Finally, sensitive tests such as our own—not the commonly used Mini-Mental State Examination, which is a dementia screening device—were needed to detect the subtle effects of B vitamins on cognitive ageing. Importantly, given the general scarcity of positive findings from other trials (table 1) and the multiple comparisons made in our trial, our results need to be confirmed by other investigators to ascertain whether the significant positive effects of folic acid on cognitive performance were due to type I error.

A strength of our study is the low attrition rate; a high attrition rate might have biased our findings of cognitive change, since participants with poor cognitive function are likely to withdraw from studies. In our study, the 12 participants in the folic acid group and five participants in the placebo group who did not return for the end measurements had low scores only on baseline tests of

### Table 3: Folate status and total homocysteine concentrations throughout the study

<table>
<thead>
<tr>
<th></th>
<th>Folic acid</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum folate (nmol/L)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12 (9–15)</td>
<td>12 (10–15)</td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>13 (4–46)</td>
<td>22 (19–52)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Year 2</td>
<td>20 (4–52)</td>
<td>22 (19–52)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Year 3</td>
<td>27 (5–70)</td>
<td>23 (19–52)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td><strong>Erythrocyte folate (nmol/L)</strong>†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>630 (494–829)</td>
<td>671 (535–815)</td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>404 (1741–2549)</td>
<td>697 (546–1888)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td><strong>Dietary folate intake (μg per day)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>192 (159–230)</td>
<td>195 (158–242)</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>212 (152–281)</td>
<td>179 (152–224)</td>
<td>0·946</td>
</tr>
<tr>
<td><strong>Plasma total homocysteine (μmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.0 (11.6–14.4)</td>
<td>12.9 (11.6–14.8)</td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>9.4 (8.3–10.5)</td>
<td>12.4 (10.4–14.6)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Year 2</td>
<td>9.6 (8.4–10.9)</td>
<td>12.5 (11.0–15.0)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Year 3</td>
<td>10.1 (9.0–11.3)</td>
<td>13.4 (11.5–15.2)</td>
<td>&lt;0·001</td>
</tr>
</tbody>
</table>

Data are median (IQR). At the time of our study folic acid fortification of foods was prohibited in the Netherlands. p values based on non-parametric tests. *At baseline, data available for 405 participants in folic acid group and 413 participants in placebo group. †Data available for 394 participants in folic acid group and 403 participants in placebo group. At Year 1, data available for 395 participants in folic acid group and 407 participants in placebo group. At Year 2, data available for 399 participants in folic acid group and 403 participants in placebo group. At Year 3, data available for 394 participants in folic acid group and 406 participants in placebo group. #At baseline, data available for 405 participants in folic acid group and 413 participants in placebo group. At Year 1, data available for 405 participants in folic acid group and 413 participants in placebo group. At Year 2, data available for 405 participants in folic acid group and 408 participants in placebo group. At Year 3, data available for 405 participants in folic acid group and 413 participants in placebo group. At Year 1, data available for 405 participants in folic acid group and 413 participants in placebo group. At Year 2, data available for 405 participants in folic acid group and 408 participants in placebo group. At Year 3, data available for 405 participants in folic acid group and 406 participants in placebo group.

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A strength of our study is the low attrition rate; a high attrition rate might have biased our findings of cognitive change, since participants with poor cognitive function are likely to withdraw from studies. In our study, the 12 participants in the folic acid group and five participants in the placebo group who did not return for the end measurements had low scores only on baseline tests of...
memory (0.558 Z score, 95% CI 0.116–1.000). Their absence from year-3 tests is unlikely to have affected our estimates for several reasons: the effect of folic acid supplementation on memory was not dependent on baseline performance on the memory tests (data not shown), the number of participants lost to follow-up was minimal, and the effect estimates based on participants with follow-up data were similar to the intention-to-treat analyses. A second strength was the standardised test conditions that reduced variation due to factors such as caffeine and varying breakfasts.36

Our study also had some limitations. First, we studied participants with high plasma total homocysteine concentrations: 3044 out of 4200 participants were excluded from the study because of low plasma total homocysteine concentrations. Thus, the effect of folic acid supplementation on cognitive function might be greater than would be expected in populations with lower plasma total homocysteine concentrations—eg, in countries such as the USA, with mandated fortification of flour with folic acid. Second, our findings pertain only to vitamin B12-replete individuals. Suggestions have been made that folic acid supplementation exacerbates neurological symptoms in people with vitamin B12 deficiency.37 The possibility of folate-mediated exacerbation of neuropathological disorders in people with low concentrations of vitamin B12 needs to be addressed by studies that monitor both vitamin B12 status and neurological function. As an improvement to our own study, transcobalamin in addition to vitamin B12, should be measured, because transcobalamin is a better marker of vitamin B12 status than is vitamin B12 itself.38

Will folic acid supplementation lead to a reduced incidence of dementia? Whereas some have argued that cognitive decline is the beginning of a continuum leading to dementia,39 others have argued that the cause of age-related cognitive decline differs from that of dementia40 and that age-related cognitive decline is not an early state of mild cognitive impairment or dementia.41 Cognitive tests differ in their ability to identify individuals who worsen to more advanced states such as mild cognitive impairment or dementia. Of our test battery, memory is the most clinically relevant domain. Memory can be used to distinguish between cognitively normal and cognitively impaired people.42 Memory storage (delayed recall), in particular, can distinguish between people with non-progressive mild cognitive impairment and preclinical Alzheimer’s disease.43 Although folate improved performance on tests of memory, including delayed recall, additional research is needed to determine whether folic acid supplementation can reduce the risk of mild cognitive impairment or Alzheimer’s disease.

We have shown that 3-year folic acid supplementation improves performance on tests that measure information-processing speed and memory, domains that are known to decline with age, in older adults with raised total homocysteine concentrations. Randomized, controlled trials are underway to examine the effect of homocysteine-lowering on recurrent vascular disease and cognitive function assessed by the Mini-Mental State Examination or modifications thereof; these and other homocysteine-lowering trials should include sensitive measures of cognitive function. Additionally, trials similar to our own should be repeated in other populations to provide greater insight into the clinical relevance of folic acid supplementation, such as in populations with mild cognitive impairment and dementia.

**Contributors**

All authors participated in the study design, study implementation, and in the interpretation of the results.

**Conflict of interest statement**

Jane Durga currently works at Nestle Research Center in Lausanne, Switzerland and Petra Verhoef currently works at the Unilever Food and Health Research Institute in Vlaardingen, the Netherlands. The work at both food companies entails examining the health benefits of a variety of

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### Table 5: Change in cognitive performance within groups during 3 years and difference in cognitive change attributed to folic acid supplementation

<table>
<thead>
<tr>
<th></th>
<th>Folic acid (n=405)</th>
<th>Placebo (n=413)</th>
<th>Folic acid vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 0</td>
<td>Year 3</td>
<td>3-year change in cognitive performance, mean (SD)</td>
</tr>
<tr>
<td>Global cognitive function, mean (SD) Z score</td>
<td>0.006 (0.673)</td>
<td>0.073 (0.694)</td>
<td>0.067 (0.338)</td>
</tr>
<tr>
<td>Memory, mean (SD) Z score</td>
<td>-0.207 (0.959)</td>
<td>0.273 (0.965)</td>
<td>0.480 (0.724)</td>
</tr>
<tr>
<td>Sensorimotor speed, mean (SD) Z score</td>
<td>0.054 (0.706)</td>
<td>0.011 (0.753)</td>
<td>-0.042 (0.458)</td>
</tr>
<tr>
<td>Complex speed, mean (SD) Z score</td>
<td>0.033 (0.803)</td>
<td>0.026 (0.868)</td>
<td>-0.027 (0.651)</td>
</tr>
<tr>
<td>Information processing speed, Z score</td>
<td>0.039 (1.008)</td>
<td>0.021 (0.967)</td>
<td>-0.072 (0.513)</td>
</tr>
<tr>
<td>Word fluency, mean (SD) Z score</td>
<td>0.038 (1.056)</td>
<td>0.036 (1.028)</td>
<td>-0.002 (0.864)</td>
</tr>
</tbody>
</table>

* One sample t test(0). † Independent sample t test.
food ingredients, including folic acid. However, the study reported in the current manuscript was completed and submitted to The Lancet before the authors joined the companies, when they were still employed by Wageningen University and Wageningen Centre for Food Sciences. All authors declare that they have no conflict of interest.

Acknowledgments
We thank all study participants for their time and motivation; the FACIT trial research team for their dedication and enthusiasm; and Dick Willems (Maastricht University, Netherlands) for data verification. The trial research team for their dedication and enthusiasm; and Dick Willems (Maastricht University, Netherlands) for data verification. The trial research team for their dedication and enthusiasm; and Dick Willems (Maastricht University, Netherlands) for data verification.

Wageningen University and Wageningen Centre for Food Sciences. Wageningen Centre for Food Sciences is an alliance of major Dutch food industries, research institutes and the Dutch government. Wageningen Centre for Food Sciences does long-term strategic research for the development of new and innovated food with attention to health aspects.

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36 Campbell NRC. How safe are folic acid supplements? Arch Intern Med 1996; 156: 1638–44.
CAT scan reveals BAT sign

Fadi Braiteh, Philip R Cohen, Razelle Kurzrock

Computed axial tomography scanning (CAT or CT scan), introduced into clinical practice three decades ago, offers clear axial cross-sectional imaging, and in-vivo visualisation of anatomical structures. The bony structures on the pelvic imaging section, at the level of the first sacral vertebrae (S1), show the image of a flying bat (figure A). This finding is consistent and almost identical, with minor variants, in most people of both sexes. The recognition of the bat sign on CT allows clinicians to quickly and easily identify the first sacral vertebrae and the appropriate anatomical structures. The head of the bat represents the first sacral vertebral body, and its wings correspond to the inominate bones of the pelvis. The nose is the sacral canal (through which run the second and third sacral roots), the ears are the ala, the orbits are the anterior sacral foramina, and each eye represents the anterior division of the first sacral nerve (figure B). The fifth lumbar root (L5) can be identified at the junction of the bat’s ears and head, and the femoral nerve lies within the groove of the iliacus and psoas muscles. The bat sign is a very helpful method for clinicians to make anatomical correlations to clinical findings and vice versa.

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1 Rogers LF. “My word, what is that?”: Hounsfield and the triumph of clinical research. AJR Am J Roentgenol 2003; 180: 1501.

Lancet 2007; 369: 217
Phase I Program, Division of Cancer Medicine (F Braiteh MD, Prof R Kurzrock MD), University of Texas, MD Anderson Cancer Center, Houston, TX 77030-4009, USA; and Department of Dermatology (P R Cohen MD), University of Texas, Houston Medical School, Houston, TX, USA
Correspondence to: Dr Fadi Braiteh fbraiteh@mdanderson.org

Figure: Pelvic axial CT (A) and diagrammatic representation of the scan (B)
**Huntington’s disease**

Francis O Walker

Huntington’s disease is an autosomal-dominant, progressive neurodegenerative disorder with a distinct phenotype, including chorea and dystonia, incoordination, cognitive decline, and behavioural difficulties. Typically, onset of symptoms is in middle-age after affected individuals have had children, but the disorder can manifest at any time between infancy and senescence. The mutant protein in Huntington’s disease—huntingtin—from an expanded CAG repeat leading to a polyglutamine strand of variable length at the N-terminus. Evidence suggests that this tail confers a toxic gain of function. The precise pathophysiological mechanisms of Huntington’s disease are poorly understood, but research in transgenic animal models of the disorder is providing insight into causative factors and potential treatments.

### The hereditary nature of chorea was noted in the 19th century by several doctors, but George Huntington’s vivid description led to the eponymous designation of the disorder as Huntington’s disease.

Over the next few decades, the worldwide distribution of the disorder and its juvenile form were recorded. The discovery of the causal *HD* gene (table 1) has stimulated research, and work is now focusing on molecular mechanisms of disease.

### Clinical findings in Huntington’s disease

Individuals with Huntington’s disease can become symptomatic at any time between the ages of 1 and 80 years; before then, they are are healthy and have no detectable clinical abnormalities. This healthy period merges imperceptibly with a prediagnostic phase, when patients show subtle changes of personality, cognition, and motor control. Both the healthy and prediagnostic stages are sometimes called presymptomatic, but in fact the prediagnostic phase is associated with findings, even though patients can be unaware of them. Diagnosis takes place when findings become sufficiently developed and specific. In the prediagnostic phase, individuals might become irritable or disinhibited and unreliable at work; multitasking becomes difficult and forgetfulness and anxiety mount. Family members note restlessness or fidgeting, sometimes keeping their partners awake at night. Eventually, this stage merges with the diagnostic phase (see webmovie), during which time affected individuals show distinct chorea, incoordination, motor impersistence, and slowed saccadic eye movements.

Cognitive dysfunction in Huntington’s disease, often spares long-term memory but impairs executive functions, such as organising, planning, checking, or adapting alternatives, and delays the acquisition of new motor skills. These features worsen over time; speech deteriorates faster than comprehension. Unlike cognition, psychiatric and behavioural symptoms arise with some frequency but do not show stepwise progression with disease severity. Depression is typical and suicide is estimated to be about five to ten times that of the general population (about 5–10%). Manic and psychotic symptoms can develop.

Suicidal ideation is a frequent finding in patients with Huntington’s disease. In a cross-sectional study, about 9% of asymptomatic at-risk individuals contemplated suicide at least occasionally, perhaps a result of being raised by an affected parent and awareness of the disease. In the prediagnostic phase, the proportion rose to 22%, but in patients who had been recently diagnosed, suicidal ideation was lower. The frequency increased again in later stages of the illness. The correlation of suicidal ideation with suicide has not been studied in people with Huntington’s disease, but suicide attempts are not

### Table 1: History of Huntington’s disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1872</td>
<td>George Huntington characterises Huntington’s disease</td>
</tr>
<tr>
<td>1900</td>
<td>Paracelsus suggests CNS origin for chorea</td>
</tr>
<tr>
<td>1953</td>
<td>DNA structure elucidated</td>
</tr>
<tr>
<td>1955</td>
<td>Huntington’s disease described in Lake Maracaibo region of Venezuela</td>
</tr>
<tr>
<td>1967</td>
<td>World Federation of Neurology meeting on Huntington’s disease</td>
</tr>
<tr>
<td>1968</td>
<td>Thomas Sydenham describes post-infectious chorea</td>
</tr>
<tr>
<td>1976</td>
<td>First animal model (kainic acid) of Huntington’s disease</td>
</tr>
<tr>
<td>1983</td>
<td>Gene marker for Huntington’s disease discovered</td>
</tr>
<tr>
<td>1993</td>
<td>HD gene identified, Huntington study group formed for clinical trials</td>
</tr>
<tr>
<td>1996</td>
<td>Transgenic mouse developed</td>
</tr>
<tr>
<td>2000</td>
<td>Drugs screened for effectiveness in transgenic animal models</td>
</tr>
</tbody>
</table>

*Approximate number of publications on Huntington’s disease cited for that year in the Current List of Medical Literature (before 1966) and in PubMed (1967 onwards).

### Search strategy and selection criteria

I searched Pub Med from 1965-2005 for the term “Huntington’s Disease” cross referenced with the terms “apoptosis”, “axon transport”, “mitochondria”, “animal model”, “proteosome”, “transcription”, “juvenile”, “suicide”, “neurotransmitters”, “age of onset”, “identical twins”, “neurodegeneration”, and “imaging”. I translated all non-English language publications that resulted from this search strategy. I mainly selected articles from the past five years, but did not exclude commonly referenced and highly regarded older publications. I also searched the reference lists of articles identified by this search strategy and selected those that I judged relevant. Several review articles and book chapters were included because they provide comprehensive overviews beyond the scope of this Seminar. The reference list was further modified during the peer-review process based on comments from the reviewers.
uncommon. In one study, researchers estimated that more than 25% of patients attempt suicide at some point in their illness.19 Individuals without children might be at amplifi ed risk,19,20 and for these people access to suicidal means (ie, drugs or weapons) should be restricted. The presence of affective symptoms, specifi c suicidal plans, or actions that increase isolation (eg, divorce, giving away pets) warrants similar precautions.20 Although useful for diagnosis, chorea (fi gure 1) is a poor marker of disease severity.21,22 Patients with early-onset Huntington’s disease might not develop chorea, or it might arise only transiently during their illness. Most individuals have chorea that initially progresses but then, with later onset of dystonia and rigidity, it becomes less prominent.21,22

Another fi nding in Huntington’s disease that contributes to patients’ overactivity is motor impersistence—the inability to maintain a voluntary muscle contraction at a constant level (fi gure 2).23 This diffi culty leads to changes in position and sometimes compensatory repositioning. Incapacity to apply steady pressure during handshake is characteristic of Huntington’s disease and is called milkmaid’s grip. Motor impersistence is independent of chorea and is linearly progressive, making it a possible surrogate marker of disease severity.7

Fine motor skills, such as fi nger-tapping rhythm and rate, are useful for establishing an early diagnosis of Huntington’s disease: gross motor coordination skills, including gait and postural maintenance, deteriorate later in the disorder’s course. Such changes, unlike chorea, directly impair function, a fi nding that is, in part, indicated by the modern preference for the terminology Huntington’s disease rather than Huntington’s chorea. As motor and cognitive defi cits become severe, patients eventually die, usually from complications of falls, inanition, dysphagia, or aspiration. Typical latency from diagnosis to death is 20 years.4 Huntington’s disease in juveniles (onset before age 20 years and as early as 2 years) and some adults can present with rigidity without signs of chorea.24,43 Such individuals can be misdiagnosed with Parkinson’s disease, catatonia, or schizophrenia. Slowed saccadic eye movements are usually prominent in these patients—jerking of the head to look to the side is characteristic. Seizures are fairly typical in young patients and cerebellar dysfunction can arise.44,45 A decline in motor milestones or school performance is sometimes an early fi nding in children with Huntington’s disease.

Differential diagnosis
Differential diagnosis of Huntington’s disease is straightforward in patients with typical symptoms and a family history. However, dentatorubropallidoluysian atrophy,26 Huntington’s disease-like 2 (frequent in black Americans and South Africans),27 and a few other familial disorders28,29 are phenotypically indistinguishable from the disorder. Furthermore, about 8% of patients do not have a known affected family member.30,31 Neuroacanthocytosis can also mimic Huntington’s disease,32 but areflexia, raised creatine kinase, and the presence of acanthocytes are distinctive. Huntington’s disease should not be confused with tardive dyskinesia, chorea gravidarum, hyperthyroid chorea, vascular hemichorea, the sometimes unilateral post-infectious (Sydenham’s) chorea, and chorea associated with antibodies against phospholipids. By comparison with Huntington’s disease, these disorders have a different time course, are not familial, and do not have motor impersistence, impaired saccades, and cognitive decline as characteristics. In young people, Huntington’s disease can be confused with hepatolenticular degeneration and subacute sclerosing panencephalitis.

Neuropathology
Neuropathological changes in Huntington’s disease are strikingly selective, with prominent cell loss and atrophy in the caudate and putamen.31–33 Striatal medium spiny neurons are the most vulnerable. Those that contain enkephalin and that project to the external globus pallidum are more involved than neurons that contain substance P and project to the internal globus pallidum.31,34 Interneurons are generally spared. These fi ndings accord with the hypothesis that chorea dominates early in the course of Huntington’s disease because of preferential involvement of the indirect

Figure 1: EMG recording of chorea in patient with stage I Huntington’s disease
Recording is made with standard belly tendon using surface disc electrodes placed over the fi rst dorsal interosseous muscle. Note the irregular pattern of discharges, with variable amplitude, duration, and rise times of every EMG burst. Healthy individuals at rest show no EMG activity.

Figure 2: EMG recording of motor impersistence
The patient is instructed to maximally abduct the second digit against resistance and to maintain it. Note that motor activity fades repeatedly. The parenthetical inclusion is a copy of the fi rst 400 ms of resting chorea shown in fi gure 1, adjusted for the different amplitude settings, for comparison. Note that choreiform bursts intermittently exceed the EMG activity from maximum volitional eff ort. Healthy individuals show consistent EMG amplitude during this task.
pathway of basal ganglia-thalamocortical circuitry.11 Other brain areas greatly affected in people with Huntington’s disease include the substantia nigra, cortical layers 3, 5, and 6, the CA1 region of the hippocampus,12 the angular gyrus in the parietal lobe,13,14 Purkinje cells of the cerebellum,15 lateral tuberal nuclei of the hypothalamus,16,17 and the centromedial-parafascicular complex of the thalamus.12

In early symptomatic stages of Huntington’s disease, the brain could be free of neurodegeneration.44–45 However, evidence of neuronal dysfunction is abundant, even in asymptomatic individuals. Cortical neurons show decreased staining of nerve fibres, neurofilaments, tubulin, and microtubule-associated protein 2 and diminished complex 2 concentrations.46–47 These elements are associated with synaptic function, cytoskeletal integrity, and axonal transport and suggest an important role for cortical dysfunction in the pathogenesis of the disorder.

One of the pathological characteristics of Huntington’s disease is the appearance of nuclear and cytoplasmic inclusions that contain mutant huntingtin and polyglutamine.48 Although indicative of pathological polyglutamine processing, and apparent in affected individuals long before symptom onset,49 mounting evidence suggests that these inclusions are not predictors of cellular dysfunction or disease activity, which instead seem to be mediated by intermediate stages of polyglutamine aggregates.49 In some transgenic mouse models of Huntington’s disease, inclusions arise only after symptoms begin.50 Cells that have inclusions seem to survive longer than those without,51 and little correlation is seen between the various cellular and animal models of the disorder and human Huntington’s disease, in terms of the appearance of inclusions in histopathological specimens and the onset of dysfunction or neurological symptoms.52–54 A compound that enhances aggregate formation might actually lessen neuronal pathological findings.55

Imaging
Routine MRI and CT in moderate-to-severe Huntington’s disease show a loss of striatal volume and increased size of the frontal horns of the lateral ventricles,56 but scans are usually unhelpful for diagnosis of early disorder. Data from PET and functional MRI studies have shown that changes take place in affected brains before symptom onset,57–59 and some MRI techniques can precisely measure cortex and striatum.60–62 In fact, with these techniques, caudate atrophy becomes apparent as early as 11 years before the estimated onset of the disease and putaminal atrophy as early as 9 years.58 In presymptomatic individuals carrying the HD gene who show no evidence of progression by clinical or neuropsychological tests over 2 years, tensor-based magnetic resonance morphometry shows progressive loss of striatal volume.59

Clinical genetics
The gene for Huntington’s disease (HD) is located on the short arm of chromosome four and is associated with an expanded trinucleotide repeat. Normal alleles at this site contain CAG repeats, but when these repeats reach 41 or more the disease is fully penetrant.54,63,64 Incomplete penetrance happens with 36–40 repeats, and 35 or less are not associated with the disorder. The number of CAG repeats accounts for about 60% of the variation in age of onset, with the remainder represented by modifying genes and environment.55–57

Trinucleotide CAG repeats that exceed 28 show instability on replication, which grows with increasing size of the repeat; most instability leads to expansion (73%), but contraction can also take place (23%).65–69 Instability is also greater in spermatogenesis than oogenesis, in that large expansions of CAG repeats on replication happen almost exclusively in males.70–72 These findings account for the occurrence of anticipation, in which the age of onset of Huntington’s disease becomes earlier in successive generations, and the likelihood of paternal inheritance in children with juvenile onset symptoms. Similarly, new-onset cases of Huntington’s disease with a negative family history typically arise because of expansion of an allele in the borderlin or normal range (28–35 CAG repeats), most usually on the paternal side.73

Somatic instability of CAG repeats also happens in Huntington’s disease. Although fairly minor, somatic mosaicism with expansion has been noted in the striatum in human beings and in animal models of the disease,74–76 and this finding could contribute to selective vulnerability. Mosaicism in lymphocytes might rarely complicate genetic testing.77–79

Identical twins with Huntington’s disease typically have an age of onset within several years of each other, but in some cases they show different clinical phenotypes.80–82 Homozygous cases of the disorder show no substantial differences in age of onset,83 but the rate of progression can be enhanced.84

Genetic testing and diagnosis of Huntington’s disease
Despite early surveys that suggested a high amount of interest, fewer than 5% of individuals at risk for Huntington’s disease choose to actually pursue predictive genetic testing.85 Those who undergo testing generally do so to assist in making career and family choices; others elect not to test because of the absence of effective treatment. Predictive testing for the disorder is not without risk. Suicide can follow a positive result,86,87 and people who are misinformed about the nature of Huntington’s disease might seek testing inappropriately. Current protocols are designed to exclude testing for children or those with suicidal ideation, inform patients of the implications of test results for relatives (ie, identical twins), identify sources of subsequent support, and
protest confidentiality. Genetic discrimination against individuals with Huntington’s disease has been reported but, at least for now, has been rare. Few centres are sympathetic with requests from doctors for help if recommended testing protocols have been ignored.

For individuals who undergo pretest counselling, evidence suggests that the overall experience with the process is positive. Although anxiety and stress increase immediately after being given a positive test result, these symptoms return to baseline. Overall, at 2 years, distress is lower and well-being higher irrespective of the outcome of the test. People who receive a negative result can sometimes have stress, known as survivor guilt, and subsequent counselling can be of value. Prenatal testing is requested substantially less frequently than predictive presymptomatic testing, a finding attributed to denial, resistance to abortion (an option not needed for preimplantation genetic testing), and concern about fetal risks. Parents who opt not to test express hope that treatment will become available for affected offspring.

A positive genetic test is cost effective and provides confirmation for patients who have developed signs and symptoms consistent with Huntington’s disease irrespective of family history. Negative test results could lead to diagnosis of a syndrome that resembles Huntington’s disease. At-risk individuals who have survived to advanced age without developing signs or symptoms sometimes undergo exclusionary testing to allay fears that their children or grandchildren might have inherited the disorder. Experience with genetic testing in Huntington’s disease has served as a model for testing protocols for other late-onset disorders and points out the challenges and opportunities of genome technology.

Epidemiology and genetic fitness

Huntington’s disease shows a stable prevalence in most populations of white people of about 5–7 affected individuals per 100 000. Exceptions can be seen in areas where the population can be traced back to a few founders, such as Tasmania and the area around Lake Maracaibo in Venezuela. In Japan, prevalence of the disorder is 0·5 per 100 000, about 10% of that recorded elsewhere, and the rate is much lower in most of Asia. African populations show a similarly reduced prevalence, although in areas where much intermarriage with white people takes place the frequency is higher.

Currently, the higher incidence of Huntington’s disease in white populations compared with African or Asian populations relates to the higher frequency of huntingtin alleles with 28–35 CAG repeats in white individuals. In people with dentatorubropallidoluysian atrophy, which is frequent in Asia, expanded alleles for the causal gene (ATN1) are much more typical in Asian populations.

Why do population differences in huntingtin alleles persist? What is the genetic fitness of Huntington’s disease? Findings have shown no consistent increase or decrease in the number of children of affected individuals. Furthermore, the HD gene does not seem to confer any promising health benefits other than a possible lower incidence of cancer, perhaps related to an upregulation of TP53 in Huntington’s disease. No data suggest that expanded huntingtin alleles protect against epidemic infectious disease.

Huntingtin and pathogenesis of Huntington’s disease

Huntingtin is expressed in all human and mammalian cells, with the highest concentrations in the brain and testes; moderate amounts are present in the liver, heart, and lungs. Recognisable orthologs of the protein are present in many species, including zebrafish, drosophila, and slime moulds. The role of the wild-type protein is, as yet, poorly understood, as is the underlying pathogenesis of Huntington’s disease.

One mechanism by which an autosomal-dominant disorder such as Huntington’s disease could cause illness is by haploinsufficiency, in which the genetic defect leads to inadequate production of a protein needed for vital cell function. This idea seems unlikely because terminal deletion or physical disruption of the HD gene in man does not cause Huntington’s disease. Furthermore, one copy of the HD gene does not cause a disease phenotype in mice. Whereas homozygous absence of the HD gene is associated with embryonic lethality in animals, people homozygous for the HD gene have typical development.

Findings suggest that the mutant HD gene confers a toxic gain of function. A persuasive line of evidence for this idea comes from nine other known human genetic disorders with expanded (and expressed) polyglutamine repeats: spinocerebellar ataxia types 1, 2, 3, 6, 7, 12, and 17; dentatorubropallidoluysian atrophy; and spinobulbar muscular atrophy. For none of these disorders is there evidence to suggest an important role for haploinsufficiency. In spinobulbar muscular atrophy, complete deletion of the androgen receptor is not associated with neuromuscular disease. All nine diseases show neuronal inclusions containing aggregates of polyglutamines and all have a pattern of selective neurodegeneration. One of the most striking features of these disorders is the robust inverse correlation between age of onset and number of polyglutamine repeats (figure 3). Results suggest that the length of the polyglutamine repeat indicates disease severity irrespective of the gene affected, with the longest repeat lengths associated with the most disabling early-onset (juvenile) forms of these disorders. Although difficult to confirm, some data also suggest that the rate of progression might be faster with longer CAG repeats, particularly for individuals with juvenile-onset disease.
The most convincing evidence for a gain of function in Huntington’s disease is the structural biology of polyglutamine strands. In-vitro evidence suggests that polyglutamines will begin to aggregate, initially by forming dimers, trimers, and oligomers. This process needs a specific concentration of protein and a minimum of 37 consecutive glutamine residues, follows a period of variable abeyance and proceeds faster with higher numbers of glutamine repeats. These findings might account for both delayed onset of disease and the close correlation with polyglutamine length. The rate of aggregation increases with the number of glutamine residues, which accords with evidence showing that length of expansion is associated with early age of onset. Huntington’s disease arises only in patients with 36 repeats or more, corresponding to 38 glutamine residues (a normal huntingtin sequence after the poly-CAG tract contains CAA and CAG, which both code for glutamine). Individuals with 36–40 CAG repeats (38–42 residues) show variable penetrance with respect to the Huntington’s disease phenotype, with fewer people having symptoms with 36 repeats and only rare cases showing no symptoms at 40 repeats. Other CAG-repeat disorders have closely related, but somewhat different, repeat ranges (figure 3) associated with age of onset, but it is noteworthy that only in Huntington’s disease is the polyglutamine strand at the N-terminus of the expressed protein. Other characteristics of the expressed proteins in these disorders probably affect aggregation.

The mechanism whereby polyglutamine aggregation leads to selective neuronal dysfunction in Huntington’s disease and eventually neurodegeneration has not yet been elucidated, but several key processes have been identified. The first steps seem to involve proteolysis and aggregation, as outlined above. Mutant huntingtin is at higher risk of proteolysis than wild-type protein and its truncation facilitates aggregation. The polyglutamine strand in the mutant protein occupies only a small proportion of its length, and a shorter protein could reduce steric interference. Evidence suggests that aggregates of truncated huntingtin are toxic and likely to translocate to the nucleus. Prolonged mutant huntingtin production and aggregate formation are believed to eventually overcome the ability of cells to degrade them, via either proteasomes or autophagic vacuolisation, leading to an increased load of unmanageable aggregate proteins. Aggregates also interfere with normal proteins by recruiting some of them into their matrix. Such proteins include those that usually interact with wild-type huntingtin, suggesting that perhaps truncated and aggregated mutant huntingtin retains active binding sites. Through

Figure 3: Composite graphs plotting age of onset against number of CAG repeats in eight human polyglutamine disorders. Note the tight inverse correlation and the clustering of number of repeats for every genetic disorder. SCA=spinocerebellar ataxia. SBMA=spinobulbar muscular atrophy. DRPLA=dentatorubropallidoluysian atrophy. HD=Huntington’s disease.
these and possibly other mechanisms, mutant huntingtin affects several nuclear and cytoplasmic proteins that regulate transcription, apoptosis, mitochondrial function, tumour suppression, vesicular and neurotransmitter release, and axonal transport. Through the many mechanisms described above, mutant huntingtin might not only have a toxic gain of function but also exert a dominant negative effect, in which it interferes with the typical function of wild-type huntingtin.

Another step in the pathogenesis of Huntington’s disease might entail cell-cell interactions. Mutant huntingtin might cause harm to a neuron, by disrupting the function of nearby neurons or glia that provide important support to that neuron. For example, in a transgenic mouse model of Huntington’s disease, interference of mutant huntingtin with the axonal transport and vesicular release of brain-derived neurotrophic factor in corticostriatal neurons seems to contribute to intrinsic dysfunction of striatal neurons.

Animal models of Huntington’s disease

The earliest animal models of Huntington’s disease were developed in the 1970s on the basis of selective vulnerability of striatal neurons to excitotoxic aminoacids. These neurons have many glutamate receptors because corticostriatal pathways use this excitatory aminoacid as a primary neurotransmitter. Striatal neurons have also proven to be selectively vulnerable to 3-nitropropionic acid, a mitochondrial toxin, suggesting that Huntington’s disease might affect energy metabolism in neurons.

Transgenic animal models of Huntington’s disease were first created in mice and subsequently in Drosophila spp and Caenorhabditis elegans. The fly and mouse models consistently show neuronal polyglutamine inclusions and indicate that pathology is dependent on polyglutamine length, is late onset, progressive, motor, and degenerative, with neuronal dysfunction followed by neuronal death. Similar animal models of other inherited polyglutamine disorders have been developed.

Although post-mortem human brain tissue from end-stage Huntington’s disease patients is available, animal models are invaluable because they provide material for histopathological and biological studies in the earliest stages of disease pathogenesis and for assessment of cell-cell interactions. The transgenic animal models also allow insertion of modifying genes and blinded drug treatment trials. For example, in a transgenic mouse model in which expression of mutant huntingtin protein with 94 polyglutamines could be switched off, not only was the clinical syndrome reversed but also...
pathological inclusions were resolved. Work done in transgenic animal models might not always be applicable to human Huntington’s disease because of species differences and variations in huntingtin gene length, promoters, and mechanisms of expression. Nonetheless, the ability to test drugs in an animal that has a lifespan of days or months provides a useful model for screening compounds that would need years of testing in patients.

Symptomatic treatment of Huntington’s disease
Diagnosis of Huntington’s disease usually happens when patients seek medical advice with respect to difficulties with work. In such situations, a diagnosis might be partly welcome because it helps to establish disability. People who are doubtful about having Huntington’s disease, however, could benefit from a delay in diagnosis until a follow-up visit, when laboratory confirmation is available and they are supported by a family member. The visit at which a diagnosis of Huntington’s disease is made is especially important clinically. Family members might recall it in particular detail, so providing accurate information about genetics and sources of support is vital. Making the experience as positive as possible—by dispelling myths and identifying strategies for good family experiences—establishes a professional bond that can be helpful later should difficulties arise.

Like other chronic diseases, managing patients with Huntington’s disease requires a proper appreciation of the limitations of medical management. Despite research advances in the past 20 years, medical treatment has made little progress. The survival of affected individuals in the Lake Maracaibo region of Venezuela, where medical technology is largely unavailable, is similar to that of populations with ready access to treatments. Antichoreic drugs such as tetrabenazine or neuroleptics offer patients with severe chorea a respite from their constant involuntary movements. However, declining function might not be an indication for increasing these drugs because they can cause bradykinesia, rigidity, and depression or sedation. Affective disorders in Huntington’s disease are amenable to psychiatric treatment, so prompt intervention is advisable.

Counselling can be helpful for patients, their spouses, and individuals at risk for Huntington’s disease. Even though only a few patients take advantage of predictive or prenatal testing, frank discussions can help them deal with the complex issues of family, financial, and career planning. Affective disorders in Huntington’s disease are amenable to psychiatric treatment, so prompt intervention is advisable.

Panel: Behavioural difficulties and symptoms in patients with Huntington’s disease

Apathy or lack of initiative
Dysphoria
Irritability
Agitation or anxiety
Poor self-care
Poor judgment
Inflexibility

Frequent symptoms (20–50% of patients)
Disinhibition
Depressed mood
Euphoria
Aggression

Infrequent symptoms (5–12%)
Delusions
Compulsions

Rare symptoms (<5%)
Hypersexuality
Hallucinations

Table 2: Potential treatments for Huntington’s disease tested in transgenic animal models

<table>
<thead>
<tr>
<th>Drugs with reported benefit</th>
<th>Interventions with reported benefit</th>
<th>No benefits noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Stem cell transplants</td>
<td>Rofecoxib</td>
</tr>
<tr>
<td>Creatine</td>
<td>Environment enrichment</td>
<td>Dichloroacetate</td>
</tr>
<tr>
<td>Trehalose</td>
<td>Intrabodies</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Asialoerythropoietin</td>
<td>S-PBN</td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td></td>
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<tr>
<td>Mercaptamine</td>
<td></td>
<td></td>
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<tr>
<td>Sirolimus</td>
<td></td>
<td></td>
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<tr>
<td>Remacemide</td>
<td></td>
<td></td>
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<tr>
<td>Minocycline</td>
<td></td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
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<tr>
<td>Thioctic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin-lactam</td>
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<td></td>
</tr>
</tbody>
</table>

Table 3: Potential treatments for Huntington’s disease tested in human trials

<table>
<thead>
<tr>
<th>Drugs with reported symptomatic benefit (chorea only)</th>
<th>Drugs in clinical trials</th>
<th>No protective benefit recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Creatine</td>
<td>Backfen</td>
</tr>
<tr>
<td>Remacemide</td>
<td>Riluzole</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Ethyl eicosapentaenoic acid</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>Mercaptamine</td>
<td>Remacemide</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coenzyme Q 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OPC-14117 (Otsuka Pharmaceuticals, Tokushima, Japan)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tauroursodeoxycholic acid</td>
<td></td>
</tr>
</tbody>
</table>

dystonia or chorea, and might need direct questioning to describe treatable affective disorders or disruptive symptoms such as irritability or compulsions. Poor hygiene, impaired judgment, impulsiveness, and aggression can happen as well (panel). Sometimes, acknowledging the difficulties faced by families and caregivers is all that can be done.

Patients with Huntington’s disease love to eat, yet weight loss is typical in these individuals. Discussion of food preferences is an enjoyable part of seeing such patients in the clinic. However, as their disease progresses, feeding becomes increasingly difficult, with dysarthria, dysphagia, and difficulty getting food into the mouth. Smaller bites, use of thickening agents, and reminders not to eat quickly may be of benefit.

**Experimental treatments**

Currently, several drugs for Huntington’s disease are in clinical trials to slow the progression of the disease; a few agents have shown promise in work done in animal models. The most intriguing research to date has been with coenzyme Q10, which has shown effectiveness in transgenic animal models of Huntington’s disease and a possibility of improvement in a human trial. This substance is believed to work by enhancing mitochondrial function in Huntington’s disease. A long-term clinical trial of high doses of coenzyme Q10 in patients with Huntington’s disease has received federal funding and will begin soon.

However, for completion, standard clinical trials of drugs such as coenzyme Q10 take several years and entail many patients. One way to speed up assessment of promising treatments is with futility studies. This type of study design—by prudent use of historical controls and predetermination of what constitutes a desirable magnitude of effect—can be used as an intermediate step to screen compounds for definitive trials. Such studies are especially useful when risks of long-term side-effects from treatment are possible or when funding and suitable volunteers are in limited supply. This type of study is currently being used to test minocycline, a drug with unique anti-inflammatory and antiapoptotic effects, in Huntington’s disease. Tables 2 and 3 list other potential drugs.

The development of surrogate markers of Huntington’s disease for clinical trials might also be a promising way to assess new treatments quickly and safely. Use of disease markers to monitor progression of cancer or HIV has accelerated the pace of drug discovery for these disorders. Current interest in Huntington’s disease has focused on imaging biomarkers, but the potential for serological markers is also of interest. A promising study has shown that Huntington’s disease transgenic mice without caspase 6 do not develop symptoms. Therefore, treatment of Huntington’s disease in humans by interfering with the catabolism of mutant huntingtin by this enzyme could be possible.

**Future work**

The best therapeutic option for Huntington’s disease could entail starting treatment in the asymptomatic phase of the disorder. Currently, in several observational studies of at-risk individuals, the feasibility of using the onset of the clinical Huntington’s disease phenotype or other biomarkers of disease (such as changes on imaging studies) is being investigated as a potential endpoint for future clinical trials. Success in animal models, identification of possible surrogate markers, progress in symptomatic treatment, and design of efficient study designs all provide tangible reasons for optimism in the Huntington’s disease community. With adequate funding for continued research, the discovery of meaningful treatment seems imminent.

**Conflict of interest statement**

I declare I have no conflict of interest.

**References**

11. Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide onset of the clinical Huntington’s disease phenotype or phase of the disorder. Currently, in several observational studies of at-risk individuals, the feasibility of using the onset of the clinical Huntington’s disease phenotype or other biomarkers of disease (such as changes on imaging studies) is being investigated as a potential endpoint for future clinical trials. Success in animal models, identification of possible surrogate markers, progress in symptomatic treatment, and design of efficient study designs all provide tangible reasons for optimism in the Huntington’s disease community. With adequate funding for continued research, the discovery of meaningful treatment seems imminent.

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**Child development in developing countries 3**

**Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world**

Patrice L Engle*, Maureen M Black*, Jere R Behrman, Meena Cabral de Mello, Paul J Gertler, Lydia Kapiriri, Reynaldo Martorell, Mary Eming Young, and the International Child Development Steering Group†

This paper is the third in the Child Development Series. The first paper showed that more than 200 million children under 5 years of age in developing countries do not reach their developmental potential. The second paper identified four well-documented risks: stunting, iodine deficiency, iron deficiency anaemia, and inadequate cognitive stimulation, plus four potential risks based on epidemiological evidence: maternal depression, violence exposure, environmental contamination, and malaria. This paper assesses strategies to promote child development and to prevent or ameliorate the loss of developmental potential. The most effective early child development programmes provide direct learning experiences to children and families, are targeted toward younger and disadvantaged children, are of longer duration, high quality, and high intensity, and are integrated with family support, health, nutrition, or educational systems and services. Despite convincing evidence, programme coverage is low. To achieve the Millennium Development Goals of reducing poverty and ensuring primary school completion for both girls and boys, governments and civil society should consider expanding high quality, cost-effective early child development programmes.

**Introduction**

This is the third paper in a series that addresses the lost developmental, educational, and economic potential of more than 200 million children under the age of 5 years in developing countries.1 The second paper identified risks with the strongest evidence base and highest prevalence as stunting, iodine and iron deficiencies, and inadequate cognitive and social-emotional stimulation.2 Less well-documented, but with consistent epidemiological evidence, are risks related to social conditions (maternal depression and violence), environmental factors (lead and arsenic), and some infectious diseases (malaria and HIV). Risk factors often co-occur and interfere with children’s development, thereby contributing to a trajectory that includes poor health, lack of readiness for school, poor academic performance, inadequate preparation for economic opportunities, and perpetuation of the intergenerational cycle of poverty.

This paper examines the effectiveness of intervention programmes in developing countries. Based on the recommendations from earlier papers in this series,3 we assess programmes that promote child development through preventing or ameliorating the effects of stunting, iodine deficiency, iron deficiency anaemia, and inadequate stimulation. We also identify examples of interventions to reduce the effects of social, environmental, and infectious risks. We include only evaluations that report cognitive or social-emotional outcomes. Developing country interest in early child development programmes

Awareness of child development is increasing in developing countries. The health sector has advocated for early child development programmes for children with low birthweight,4 developmental delays,1 and from low-income disadvantaged environments.4 Child development information is often incorporated into growth monitoring charts. Government-supported preschool programmes for children are increasing; in the past 15 years, at least 13 developing countries have instituted compulsory preschool or pre-primary programmes.5 By 2005, the World Bank had financed loans to 52 developing countries for child development programmes, for a total of US$1680 million, at least

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**Search strategy**

Databases searched were MEDLINE (PubMed), Embase, Psych Info, the Cochrane Review, the Educational Resources Information Center (ERIC), the World Health Organization, the World Bank and the International Bureau of Education for UNESCO (United Nations Educational, Scientific and Cultural Organization), SIGLE (grey literature from Europe), LILACS (Latin American and Caribbean Health Services), and UNICEF. The UNICEF and World Bank databases were searched and queries were sent to international organisations that may have had access to unpublished evaluations, including Plan International, Save the Children, Christian Children’s Fund, Aga Khan Foundation, Bernard Van Leer Foundation, Consultative Group for Early Child Care and Development, and regional early child development networks.

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This is the third in a Series of three articles about child development in developing countries

†Steering group listed at end of the paper

UNICEF, New York, NY, USA
(P L Engle PhD); Department of Pediatrics, University of Maryland Baltimore, MD, USA
(Prof M M Black PhD); Department of Economics, University of Pennsylvania, PA, USA (Prof J R Behrman PhD); World Health Organization, Geneva, Switzerland
(M Cabral de Mello DES psy clin); World Bank, Washington, DC, USA (M Young DrPH); Haas School of Business, University of California, Berkeley, CA, USA
(Prof P J Gertler PhD); University of Toronto, Toronto, Canada
(L Kapiriri PhD); and Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA (Prof R Martorell PhD).

Correspondence to:
Prof Patrice Engle,
Department of Psychology and Child Development, Cal Poly State University, San Luis Obispo, CA, USA
Pengle@calpoly.edu

30 developing countries had policies on early child development,19 and UNICEF was assisting governments in supporting parenting programmes in 60 countries.10 Despite this interest, there have been few systematic evaluations of early child development programmes in developing countries.

**Early child development programmes**

**Improving food intake and reducing stunting**

Both efficacy trials and programme evaluations have shown that improving the diets of pregnant women, infants, and toddlers can prevent stunting21,22 and result in better motor and mental development.2,13,14 Food supplementation during the first 2–3 years of life improves cognition at 3 years of age and beyond.15,16 One trial showed an improvement in motor development with exclusive breastfeeding.19 The longest follow-up duration is from Guatemala, where supplementation before age 3 years showed beneficial effects on schooling, reading, and intelligence tests during adulthood (25–42 years).20

Conditional cash transfers provide funds dependant on behaviour, such as participation in nutrition monitoring and supplementation programmes.18 Evidence from a conditional cash transfer programme in Mexico for more than 20 million people showed that transfers to women plus direct nutritional supplements for young children and nutrition education were associated with children’s improved growth and motor development.21,22 Conversely, analysis of such a transfer programme in Brazil noted that recipient children grew slower than non-recipients, perhaps because families feared that benefits would be discontinued if their child grew well.23

**Reducing iodine and iron deficiencies**

Assessments of efficacy trials and programmes of iodine interventions provide conclusive evidence of a significant effect on cognition and behaviour.7 Salt iodisation remains the most cost-effective way of delivering iodine and of substantially improving cognition. At least 30 developing countries have reached the 2005 goal of sustainable elimination of iodine deficiency through universal salt iodisation;79 69% of households consume iodised salt, with rates of 86% in Latin America, 85% in east Asia, but only 47% in central Europe and central Asia.80

Iron deficiency anaemia impedes child development.2 Detrimental effects in infants and toddlers might not be readily reversed by iron therapy, suggesting the need for a preventive approach.81 Iron supplementation to prevent anaemia in young children has positive effects on motor, social-emotional, and language development.7 Innovations for iron supplementation include: microencapsulated ferrous fumarate plus ascorbic acid supplied as sprinkles added to complementary foods;21 growing plant varieties with higher iron content;24 removing phytates from plants that inhibit iron absorption; soaking maize flour in excess water with phytase and decanting the water before cooking the flour;25 and new iron fortification methods that eliminate aftertaste, reduce risk of excess intake, and maintain bioavailability.26,27 These approaches are promising for the reduction of iron deficiency and anaemia in young children.83,84 A 6-month trial in South Africa assessed the effect of iron and other micronutrient-fortified maize porridge on infant development and reported better motor development in the fortified porridge group than the non-fortified group.85

Concerns have been raised about giving iron supplements to iron replete infants, eg, decreased linear growth86,87 or increased hospitalisations and death in a malarial region.88 These issues should be studied further and need to be considered in public health programming.

**Stimulation combined with nutrition and health programmes**

Stimulation occurs through responsive and increasingly complex developmentally appropriate interactions (matched to the child’s emerging abilities) between caregivers and children that enhance child development.89,90 Both cognitive and social-emotional skills provide the basis for later academic and employment success.91,92

Inadequate stimulation and interactions can affect child development through disrupting basic neural circuitry. Neural disruptions are measured through stress hormones,93 brain images,94 and event-related potentials.95 Early stimulation may enhance neurocognitive processing and brain functioning, particularly for premature infants.96 The effects of early stimulation are also evident in the dramatic improvements in child development in undernourished, institution-raised children adopted into middle-class homes. A study of Korean girls adopted into middle-class families illustrates the synergistic effects of malnutrition and environmental deprivation on children’s intelligence.97,98 IQ scores of children adopted after 2 years of age and with a history of malnutrition scored worse than equally malnourished children adopted at less than age 2 years (figure 2), but both were close to average.
Similar age-related findings have been reported in institutionalised Romanian children adopted into middle-class homes.44–46 In developed countries, long-term benefits from high-quality early intervention programmes for disadvantaged children include higher verbal and mathematics achievement, greater success at school (ie, less grade repetition, higher graduation rates), higher employment and earnings, better health outcomes, less welfare dependency, and lower crime rates than similar non-participants.47–49 For children younger than 3 years, combining family and centre-based components is more effective than either alone.49,50 Cost-benefit ratios for seven programmes in developed countries ranged from 1.8 to 17.0.45 Programmes for disadvantaged children during early childhood have a better rate of return than programmes introduced later in life.44

Myers51 reviewed the effects of nutrition and child development programmes on school progress (repetition, promotion, and dropout) in developing countries before 1990. Three of the four nutrition programmes, and six of the nine programmes with schooling data, showed significant effects of early intervention, particularly for the most disadvantaged. The absence of effect in four studies was attributed to automatic promotion, poor quality of the schools, and methodologically weak evaluation.

![Figure 2: IQ scores among female Korean orphans varying by history of malnutrition and age of adoption](Data taken from references 40 and 41)

<table>
<thead>
<tr>
<th>Sample size*</th>
<th>Intervention</th>
<th>Age</th>
<th>Outcome measure</th>
<th>Significant effects</th>
<th>Effect size of cognitive measure</th>
<th>Scale†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre-based</td>
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<td></td>
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<tr>
<td>Guinea52</td>
<td>877</td>
<td>Informal community-based early learning centres</td>
<td>2–6 years</td>
<td>Cognitive development (Simplified Boehm Basic Concept Test) at 5 years</td>
<td>Cognitive development controlling for socioeconomic status p&lt;0.05</td>
<td>0.33 0.66 socioeconomic status controlled</td>
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<td>Cape Verde 53</td>
<td>803</td>
<td>Formal preschool</td>
<td>3–6 years</td>
<td>Cognitive development (Simplified Boehm Basic Concept Test) at 5 years</td>
<td>Cognitive development with socioeconomic status controlled p&lt;0.05</td>
<td>0.29 0.48 socioeconomic status controlled</td>
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<tr>
<td>Bangladesh54</td>
<td>208</td>
<td>Preschool run by NGO, feeding</td>
<td>4.5–6.5 years</td>
<td>(1) Cognitive development from WPPSI–III (2) Local school readiness assessment test (3) Play observation scale</td>
<td>(1) Treatment&gt;control p&lt;0.05 (2) Treatment&gt;control p&lt;0.05 (3) Treatment&gt;control p&lt;0.05</td>
<td>(1) 0.20–0.23 (2) 1.0 (3) 0.19–0.72</td>
</tr>
<tr>
<td>Burma55</td>
<td>(1) 1880 (2) 268</td>
<td>Community-based early child development centre and community support</td>
<td>3–5 years</td>
<td>(1) Primary school pass rate (2) Academic achievement tests (language, mathematics, thinking skills)</td>
<td>(1) Treatment=85%, control=72% (2) Treatment=86%, control=69% in language and mathematics; treatment=82%, control=73% in thinking skills</td>
<td>Not available 2</td>
</tr>
<tr>
<td>Nepal56</td>
<td>935</td>
<td>Community-based early child development centre (education and health)</td>
<td>3–6 years</td>
<td>(1) Primary school pass rate (2) Repetition rate for grade 1 (3) Yearly dropout rate after 4 years</td>
<td>(1) Grade 1: treatment&gt;control by 32% Grade 2: treatment&gt;control by 38% (2) 5.5% (1/20) of national norm (3) 1.2% (1/10 of national norm)</td>
<td>Not available 2</td>
</tr>
<tr>
<td>Vietnam57</td>
<td>313</td>
<td>Centre and home (education, parenting, nutrition)</td>
<td>0–3 years for nutrition; 4–5 years for education</td>
<td>Raven's Colored Progressive Matrices at 6.5–8.5-year-old</td>
<td>Early child development &gt; nutrition &gt; than nutrition only on Raven's Colored Progressive Matrices. Greatest effect in malnourished children</td>
<td>Roughly 0.25 based on estimated SD 1</td>
</tr>
<tr>
<td>Colombia58</td>
<td>333 children all underweight 570 at follow up (all but higher socio-economic status group underweight initially)</td>
<td>Day care centre-based feeding and stimulation; 5 groups: food alone; food+different periods of stimulation, and high socio-economic status group</td>
<td>42 months up to 75 months (varying amounts)</td>
<td>Stanford-Binet IQ test</td>
<td>Greatest effect for children enrolled for the maximum time (4 years) and beginning earliest (age 4 years). Supplementation without stimulation had no effect on psychological development. Duration benefited performance.</td>
<td>Not available 1</td>
</tr>
<tr>
<td>Argentina59</td>
<td>More than 125 000 children</td>
<td>Increase in preschool places</td>
<td>3–5 years</td>
<td>Third grade mathematics and Spanish achievements</td>
<td>1 year of pre-primary increased mean third grade test score by 8% of mean or by 23% of SD. Child attention, effort, class participation, and discipline were also significantly higher in experimental group</td>
<td>0.23 3</td>
</tr>
</tbody>
</table>

(Continues on next page)
We reviewed programmes implemented in developing countries since 1990 using six criteria: (a) randomised controlled trial or matched comparison group; (b) intervention before age 6 years; (c) effectiveness or programme evaluations (not efficacy trials); (d) child development assessed; (e) targeted disadvantaged children; and (f) developing country. 35 studies from developing countries were identified, of which 20 met the criteria (tables 1 and 2 and search strategy). The programmes fell into three groups: centre-based early learning (N=8); parenting or parent-child (N=6); and comprehensive (N=6), including health and nutrition interventions.

Centre-based programmes

All eight evaluations recorded a substantial effect on children’s cognitive development. Preschools were provided in Guinea and Cape Verde, Bangladesh, Burma, Nepal, Vietnam, and Colombia, and pre-primary schools were expanded in Argentina. Most reported gains in non-cognitive skills such as sociability, self-confidence, willingness to talk to adults, and motivation. Longitudinal studies
Parenting and parent-child programmes

Four parenting programmes used home visiting, and all reported positive effects on child development. In Jamaica, parenting practices improved when children and parents were actively involved in a home-visiting programme, but not when the parent component was limited to information sharing. In Bolivia, information and skill building about health, hygiene, nutrition, and development, linked with a literacy programme for indigenous women and home visits, resulted in higher test scores for participants' children than those of matched non-participants.

Two programmes used group sessions with mothers. In Turkey, where mothers practised skills to play with their children, there were short-term and long-term effects on child development. In Bangladesh, mothers’ knowledge of child development and child rearing increased after information-based sessions, but there was no effect on child development, perhaps because there were no practise or skill-based activities with families.

Comprehensive programmes

Six programme evaluations met the criteria for this group (table 2) and show the changes in programme models from 1975 to the late 1990s. The Integrated Child Development Services (ICDS) in India began in 1975, and provided counselling to pregnant and lactating women about nutrition, growth monitoring for children 0–5 years, and feeding and preschool centres for children 3–6 years old. The programme has been implemented at low cost, and currently serves more than 30 million children.

In 1992, the National Institute of Public Cooperation and Child Development in India compared around

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### Table 2: Comprehensive programmes for child development in developing countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Sample size</th>
<th>Intervention</th>
<th>Age</th>
<th>Outcome measure</th>
<th>Significant effects</th>
<th>Effect size of cognitive measure</th>
<th>Scale†</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>3724</td>
<td>Integrated childcare centre; preschool education, support for pregnant and lactating mothers, growth monitoring, feeding, assistance for child immunisation and some emergency health</td>
<td>3–6 years</td>
<td>Motor and mental development using WHO Milestones assessment</td>
<td>Integrated Child Development Services significantly better than controls; stronger effect for younger; both nourished and undernourished performed better than matched controls</td>
<td>Not available</td>
<td>3</td>
</tr>
<tr>
<td>Peru</td>
<td>304</td>
<td>Preschool and non-formal preschool, community nutrition programmes</td>
<td>3–5 years</td>
<td>Grades (A–C) in mathematics and language (Spanish) as assessed by the first grade teacher</td>
<td>Both students in formal and non-formal preschool performed better than no pre-school</td>
<td>Not available</td>
<td>3</td>
</tr>
<tr>
<td>Bolivia</td>
<td>1198</td>
<td>Child care centres in home for stimulation; feeding and health and nutrition monitoring; education of mother</td>
<td>6–72 months</td>
<td>Gross and fine motor skills, language and auditory skills, and psychosocial skills</td>
<td>Effects stronger at younger age (2–3 years) with longer duration (&gt;17 months)</td>
<td>0.4–1.5 depending on test</td>
<td>2</td>
</tr>
<tr>
<td>Uganda</td>
<td>2010</td>
<td>Communication on early child development, health and nutrition, child health days, village grants on nutrition or early child development centres</td>
<td>0–6 years</td>
<td>(1) Ugandan version of the British Abilities Scale (2) Parenting practices (3) Nutritional status</td>
<td>(1) No significant difference (2) Significant difference in parent attitudes and behaviour towards early child development (3) Significant difference for younger than 1 year</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td>6693</td>
<td>Family day-care programmes, home visits on parenting and nutrition, improved health and nutrition services, feeding</td>
<td>0–4 years</td>
<td>Early child development checklist of gross and fine motor skills, receptive and expressive language, social-emotional skills, cognitive skills, and self-help skills and development index</td>
<td>For Developmental Index, all differences significant (p&lt;0.05) for children with duration of exposure &gt;17 months, and for all children aged 2–3 years at enrolment for all durations. Strongest effect for language</td>
<td>Ranged from 0.5–1.8 for specific scales, ages, and durations</td>
<td>2</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>300 children with growth faltering</td>
<td>Stimulation in therapeutic feeding centre, home visits, and group meetings (treatment–centres with child development interventions; control 1–nutrition centres without child development programmes, control 2–well-nourished)</td>
<td>6–24 months</td>
<td>Bayley Scales of Infant Development</td>
<td>Treatment&gt;control 1 for mental development, not motor; control 2&gt;control 1 in mental and motor development. No effect of stimulation intervention on nutritional status</td>
<td>0.37</td>
<td>1</td>
</tr>
</tbody>
</table>

*Sample size for the assessment, not for the whole programme. †Scale: 1=coverage fewer than ten villages; 2=coverage of ten or more villages, or a district but not national programme; 3=national-level government programmes.

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(Nepal, Argentina, Burma, and Colombia) recorded improvements in the number of children entering school, age of entry, retention, and performance.

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14 000 ICDS children with 2000 control children from non-participating communities that had similar services, and reported less likelihood of ICDS children being severely malnourished and greater likelihood of attending school.70 To three of the wealthier states, participating 3–5-year-old children scored higher on measures of child development than matched non-participants from neighbouring towns, with greater effects for younger and for malnourished children in two of the three states.70

These assessments indicate that the ICDS can be effective, but a World Bank evaluation in 2002 indicated that the ICDS had “only modest positive effects”,70 probably because of low funding, work overload of community workers, and insufficient training.71

In the early 1980s, Peru developed a community preschool and feeding programme for disadvantaged children. An evaluation in 1999 showed that first graders who had attended the programme did not differ on indices of school performance from those in formal preschools, but both groups had higher scores than children who did not attend the programme, controlling for socioeconomic variables.72

Three projects, supported by the World Bank, in Bolivia, Uganda, and the Philippines illustrate various models for early child development. In the early 1990s, the PIDI (Proyecto Integral de Desarrollo Infantil) programme in Bolivia trained low-income urban women to run child-care centres in their homes for malnourished children 6–72 months, and funded them to upgrade their homes, provide food for the centres, and run health and nutrition monitoring and educational activities.73 Non-participants were compared with children who had at least 6 months of exposure. There were benefits in growth in children younger than 36 months and benefits in cognitive and psychosocial development, irrespective of age. The estimated cost was US$43 per month per child, 40% of which was for food.

The Uganda Nutrition and Early Child Development Project began in the late 1990s.73 Communities within 25 districts were divided into intervention and control. Intervention communities received radio and newspaper messages on child stimulation, positive parenting, health, hygiene, and nutrition. Child health days every 6 months for the whole community provided growth monitoring and promotion, immunisation, deworming, and health care. Each intervention community could receive community grants for nutrition or early child development, and most chose nutrition. After 2 years, there were substantial improvements in breastfeeding practices, growth rates in the youngest children, and parental attitudes and behaviour supporting early child development, but there were few effects on cognitive development of children aged 3·5–6 years, possibly because of the low intensity of the intervention.

In the late 1990s, the Philippines increased training and supplies to existing services for children aged 0–5 years using an integrated, multi-sectoral approach for delivering a combination of services,74,75 and added community child development workers responsible for parenting education on health, nutrition, and child development. The evaluation showed that programme communities had more feeding programmes, parent education, and home-based child care programmes than control communities, adjusting for child age and programme duration.74,75 Children who had been exposed for more than 18 months showed a benefit in cognitive development, with effect sizes up to 1·8 SD in language development for 2–3 year-old children (figure 3). There was no effect on haemoglobin, despite an iron supplementation programme, nor on stunting, but participating children older than 4 years were heavier than non-participants.

Panel 1: Characteristics of successful early child development interventions

- Integration of health, nutrition, education, social, and economic development, and collaboration between governmental agencies and civil society.
- A focus on disadvantaged children.
- Sufficient intensity and duration and include direct contact with children beginning early in life.
- Parents and families as partners with teachers or caregivers in supporting children’s development.
- Provide opportunities for children to initiate and instigate their own learning and exploration of their surroundings with age-appropriate activities.
- Blend traditional child-rearing practices and cultural beliefs with evidence-based approaches.
- Provide early childhood education staff with systematic in-service training, supportive and continuous supervision, observational methods to monitor children’s development, practice, and good theoretical and learning-material support.

Figure 3: Effects of the Philippine Early Child Development Programme on standardised Developmental Index score as a function of child’s age at enrolment and duration

Developmental index varies by child’s age at programme enrolment and duration of time in programme, favouring younger children with longer duration. All differences are significant (p<0·05) for 17–25 months duration and for 2-year-olds and 3-year-olds for all durations compared with non-programme children. Adapted from data available in Armecin.74

*Adapted from Jaramillo and Mingat.111
A component of psychosocial stimulation was added to the Bangladesh Integrated Nutrition Project, a national nutrition programme for malnourished children. A 12-month randomised controlled trial of home-visiting and mothers’ group sessions in community centres reported substantial benefits to the children’s cognitive development and behaviour (fear, timidity), but no effect on growth.\(^5\)

In summary, five of six early child development programmes showed beneficial effects. The recent programme models have been integrated into existing community-based systems and include families more effectively than earlier models. However, as the Uganda results indicate, low-intensity programmes that do not direct services toward children might have limited effect on child development outcomes.

**Factors consistently associated with programme effectiveness**

Numerous factors are associated with success of interventional programmes (panel 1). Providing services directly to children is more effective than only providing information to parents; demonstrations and opportunities for skill building and practice with parents increased effectiveness.\(^6\) Disadvantaged children, including children who are stunted, benefit more than advantaged children.\(^7\) Younger children (2–3 years) benefit more than older children (5–6 years), even after adjusting for duration.\(^8\) Longer exposure results in more consistent and larger effect on child development.\(^9\) For example, disadvantaged preschoolers in Cali, Colombia, with 4 years of intervention achieved test scores that were similar to a middle-class sample, whereas children with less intervention lagged behind (figure 4).\(^10\)

Evaluations from Guinea, Cape Verde, and Bangladesh recorded associations between multiple measures of preschool quality and children’s cognitive performance.\(^11\)\(^12\) The International Association for the Evaluation of Educational Achievement (IEA)’s assessment of pre-primary programmes involving 1500 children from ten countries (three developing countries) identified programme quality (eg, more child-initiated activities and small-group rather than large-group activities) as a critical contributor to cognitive development.\(^13\) Dimensions of quality that are important for child development are programme structure (children to staff ratio, group size, staff training, and physical environment), and processes (warmth and responsiveness of the caregiver, emotional tone of the setting, and variety of activities).\(^14\)\(^15\)

Programmes that have assessed intensity report a linear relationship between frequency of home visits and improvements in child development.\(^16\) Beneficial effects of combined programmes have been found on efficiency of delivery, cost savings, and effect.\(^17\)\(^18\)\(^19\)\(^20\) Most evaluations did not have the design or sample size to isolate the effects of individual components or to test for synergistic effects.\(^21\)

### Monitoring child development

Currently, there are no globally accepted indicators for child development. Indicators would improve countries’ abilities to set targets, allocate resources, monitor progress, and ensure accountability, but a simple measure is hard to construct. Child development is often measured through individual assessments of developmental changes in multiple domains (eg, cognitive, language,
Social, environmental, and infectious risks

Social risks

There have been few evaluations of social protection interventions designed to mitigate the effects of social risks (eg, maternal depression, exposure to domestic and community violence, and stigma and loss due to HIV/AIDS) on children from developing countries. Women in developing countries have high rates of stress and depressive symptoms, often associated with poverty, lack of support, and negative life events. Children of depressed mothers are at risk for poor development, in part mediated through inconsistent and unresponsive parenting. Reductions in maternal depressive symptoms with moderate to large effect sizes were shown in four psychosocial interventions, but no substantial effect was seen on child competence in the one study that looked at these effects. In Jamaica, mothers’ depression scores declined after participating in a parenting intervention, similar to evidence from developed countries showing that teaching mothers practical caregiving skills has beneficial effects for both mothers and children.

Violence toward young children often occurs through excessive corporal punishment, child abuse and neglect, and exposure to violence. Responses include law reform on standards of care and mechanisms for surveillance and improving parenting practices. In some countries, supportive and therapeutic services (including therapeutic day-care) for young children who have witnessed or experienced violence have been established. Although there is evidence that home visiting can be an effective strategy for preventing child abuse, results are not consistent. There are few programmes directed toward young children in developing countries, and no evaluations were located.

Parental loss is often associated with violence or disease-related mortality, including the HIV/AIDS pandemic. In 2004, there were 43.4 million orphans (age 0–17 years) in sub-Saharan Africa, of which 28% were due to HIV/AIDS. A breakdown of these data by age showed that 7 million orphans (16%) were younger than 6 years and 23 million (52%) were younger than 12 years. Interventions for younger children affected by AIDS, such as home visiting, support for families, ensuring access to care, and community-based child care are limited in scale and have not been rigorously assessed.

Environmental risks

The evidence that environmental toxins such as lead and arsenic can compromise child development is a major reason for reducing exposure. Chelation, even oral chelation or the removal of lead from children’s blood and bone stores, although successfully reducing body burden, has not resulted in improvements in children’s developmental functioning. Mitigation programmes (including provisions of deep water-wells and education) successfully reduce arsenic concentrations in exposed individuals, but there are no findings on whether they result in improvements in child development. Systematically preventing exposure is probably a more effective and efficient strategy than treatment, but the challenge is the extensiveness of environmental toxin exposure.

Infectious risks

Severe malaria and HIV/AIDS have been associated with poor child development. Effective malaria prevention and control include insecticide treated bednets and artemisinin-based combination therapies. Until recently, coverage of treated bednets for children under 5 years of age was estimated at less than 5%, but countries are now rapidly scaling up coverage, with around 50 million nets expected to be delivered in 2006 and some countries expected to exceed the Abuja targets in 2006. Although the effect on children’s development has not been sufficiently studied, benefits to later cognitive abilities following chemotherapy before the age of 6 years have been reported. Mother-to-child transmission of HIV can be prevented, but in 2005, only 9% of pregnant women in low-income and middle-income countries received services to prevent transmission to their newborn babies, and only 9.2% of HIV-positive pregnant women received prophylactic antiretrovirals.

Future directions and crucial issues

In the final section we discuss priorities for improving the development of the 200 million children younger than 5 years at risk for cognitive and social-emotional deficits.
Investing in early child development programmes

Despite the substantial evidence that comprehensive early development programmes are effective in increasing children’s chances of success, government investment is low. Preschool or kindergarten enrolment, the only early development programme that is monitored worldwide, was 35% in developing countries in 2001. The rate has increased during the past 15 years in east and west Asia and the Pacific, although the regions with the highest need (assessed by grade 1 repetition and dropout) have shown slower progress (table 3). Programme coverage is negatively associated with countries’ general poverty index (figure 6), leaving the poorest countries with almost no investment in early child development. However, some countries, such as India, have invested in programmes, despite poverty. If the current rate of progress continues, the disparity between rich and poor countries in preschool attendance (figure 6) will increase. Jaramillo and Mingat estimate that in Africa, an increase in the preschool gross enrolment rate to 40% during the next decade could reduce repetition rates and increase the proportion of grade 1 students who reach grade 5 from 65% to 78%.

Investments are low for multiple reasons. For example, governments are organised sectorally and no one sector is responsible for early child development. The problem is not visible, and governments might be unaware of the cost to individual and society of not investing in early child development programmes (panel 2).

There are human rights and economic reasons to invest in child development programmes (panel 3). The Convention for the Rights of the Child established the principle that children have the right to survival and to develop, and governments are responsible for supporting families in their childrearing.

Evidence indicates that early development programmes are beneficial for their costs. There are many considerations when estimating reliable benefit-to-cost ratios, including: measuring all benefits and costs in monetary terms, such as the value of increased academic performance; assessing diverse resource costs; and balancing between immediate gains versus long-term benefits. Recent estimates of benefit-to-cost ratios for interventions for early child development yield ratios substantially above 1 in developing countries, and in developed countries. In PIDI (Bolivia), the benefit of a 5% increase in cognitive scores and a 2% increase in height translated into a benefit of between $1·8 and $3·66 per dollar of project cost.

Reducing disparities

Achievement differences in children from different socio-economic groups widen over time. Early interventions can reduce disparities. If enrolment in high-quality programmes were increased to 100% for low-income children in the USA, disparities in readiness for school would be reduced up to 24% between black and white children and up to 36% between Hispanic and white children. In Cali, Colombia there was a difference of

Figure 6: Change in preschool gross enrolment ratios from 1970 to 2003–04 by region


Panel 2: Reasons that governments do not invest in early child development interventions

• Children’s loss of developmental potential, and the cost of loss of developmental potential, both for individual children and poverty alleviation, are not recognised.
• There are no globally accepted indicators for child development to monitor progress or ensure accountability.
• Governments respond to short-term effects and find difficulty in justifying the long-term investment in human development.
• There are multiple organisational stakeholders for young children, so the responsibility for early child development is not assumed by any entity.
• There is not a single strategy for promoting early child development.

Some items were modified from Heaver and the World Bank.

Panel 3: Why governments should invest in interventions for early child development

• It is the most cost-effective period in the child’s life to invest.
• Events in the early years of a child’s life influence the child’s productivity and learning ability throughout the life course, and are effective strategies for reducing poverty among disadvantaged populations.
• Programmes increase the efficiency and effectiveness of school expenditures by reducing drop-out and repetition.
• Increased schooling for girls has a long-term effect on their children’s survival, growth and development.
• Interventions are more sustainable because parents and families carry these changes over to subsequent children.
• There is a strong evidence base on effective interventions for early child development.
• The Convention on the Rights of the Child ensures every child the right to

To estimate the effects of early child development on schooling and adult earnings among disadvantaged groups in developing countries, we used longitudinal data beginning before age 5 from 152 Brazilian males, 18 years of age, and 1471 Guatemalan adults, age 25–42 years. Both data sets included standardised assessments of preschool development and schooling attainment, as well as controls for maternal schooling and parental income or socioeconomic status, and birth year and sex for Guatemala. We used effect sizes from the review of programmes (tables 1 and 2), ranging from 0·3 to 1·8, to obtain the individual benefits on increased schooling attainment, and we varied the assumed programme coverage rates from 0% to 100% to obtain aggregate average benefits. Analyses across the two data sets found that with 90% coverage, an increase of 1 SD in pre-school cognitive skills is associated with an aggregate benefit of around two-thirds to more than one grade of additional schooling (figure 7 has the derivation of estimated benefits). Estimates for Guatemala that control for random measurement error find effects over five times as large. The estimates from Brazil and Guatemala (not controlling for measurement error) and estimates from developing countries of the economic returns of schooling suggest that preschool participation contributes to increases of around 5–10% in lifetime labour income.

Integration of early child development programmes into other systems

Policy decisions on programmes often span multiple ministries (eg, health, education, welfare) and need coordination across sectors. The health system is often the only infrastructure that reaches children younger than 3 years and therefore can initiate programmes to promote early development and prevent risks. Health visits or growth monitoring sessions have added recommendations for child development. The Care for Development Intervention, a module of WHO’s Integrated Management of Childhood Illness, is based on interactive learning and includes strategies for improving psychosocial care and responsive feeding. Two pilot studies showed the feasibility of delivering the intervention in resource-poor settings, and a controlled evaluation trial in Turkey showed that the Care for Development Intervention had a positive effect on parenting behaviours. In the Congo, surveyed parents reported that they would like more information about their children’s development in their health visits, and in the USA, incorporating developmental counselling into primary care has improved quality of care and parenting practices. These innovations are promising but their effect on child development has not yet been assessed.

Panel 4: Policy and programme recommendations

- Implement early child development interventions in infancy through families and caregivers, and add group learning experiences from 3 to 6 years, particularly for disadvantaged children as a poverty reduction strategy.
- Ensure that development programmes combine health and nutrition services with early learning, rely on families as partners, and have adequate quality, intensity, and duration to affect children’s development cost effectively.
- Incorporate early child development into existing services and systems to increase programme coverage.
- Monitor the effectiveness of programmes with outcome measures of child development.
- Increase advocacy on the importance of early child development and the consequences of the loss of developmental potential to individuals and to society.
- Include programmes in policies and financial allocations at national, local, or international levels.
- Create coordinating mechanisms for ministries that share the responsibility for early childhood development.
- Ensure that all children are adequately nourished, including micronutrients, such as iodine and iron.

Figure 7: Estimated changes in number of years of school passed as a function of aggregate effect size and coverage of early child development programmes

Effect sizes are based on the range of estimates in tables 1 and 2. Benefits are the increases in schooling attainment for individuals based on estimates of the relation between preschool cognitive tests and completed schooling attainment using longitudinal data that started in pre-school ages and continued through young adulthood in Brazil (age 18 years for 152 males) and Guatemala (ages 25–42 years for 1471 females and males), controlling for maternal schooling, parental family income (Brazil), or socioeconomic status (Guatemala), and birth year and sex for Guatemala. The lines probably would be less steep as coverage became very high.
The educational system can promote child development by supporting comprehensive programmes for early child development. If the programmes are of high quality, have family involvement, and when needed, provide health care and food supplementation or micronutrients, evidence suggests that disparities among the most disadvantaged children can be reduced before school entry. Linking early development programmes administered through the health system with programmes in the educational system increases the likelihood of building intervention follow-up for children at risk.

Early child development programmes can be coordinated across ministries, non-governmental organisations (NGOs), and civil society. In Turkey, parenting messages are provided by the health care system, the Ministry of Agriculture, the Ministry of Labor, and even the Military. In Cuba, the Educate parenting messages are provided by the health care organisations (NGOs), and civil society. In Turkey, coordinated across ministries, non-governmental organisations provide health care and food supplementation or micronutrients, evidence suggests that disparities among the most disadvantaged children can be reduced before school entry. Linking early development programmes that can be adapted across countries for monitoring, planning, and assessment.

Improving and assess strategies to increase effectiveness of outreach to disadvantaged children, including orphans. Strengthening the evidence base for the effects of maternal depression, exposure to violence, parental loss, toxins, malaria and other infectious diseases on child development and identify effective interventions to reduce their risks and adverse consequences.

Create and test a method for estimating the costs of different models of early child development programmes.

Panel 5: Research recommendations

- Identify the characteristics of child development programmes that are effective and can be expanded and implemented through existing health, nutrition, education, and social protection services.
- Examine the role of early child development programmes in mitigating the effects of multiple disadvantages, including poverty.
- Research parenting interventions to identify the most effective and scaleable strategies.
- Assess possible synergies among programme components to guide implementation recommendations.
- Define a core set of globally accepted measurements and indicators for child development that can be adapted across countries for monitoring, planning, and assessment.
- Improve and assess strategies to increase effectiveness of outreach to disadvantaged children, including orphans.
- Strengthen the evidence base for the effects of maternal depression, exposure to violence, parental loss, toxins, malaria and other infectious diseases on child development and identify effective interventions to reduce their risks and adverse consequences.
- Create and test a method for estimating the costs of different models of early child development programmes.

Conclusion

Effective interventions are available to reduce the developmental loss currently estimated to affect more than 200 million children under 5 years of age in developing countries, by promoting child development and preventing or ameliorating developmental loss. The most effective interventions are comprehensive programmes for younger and disadvantaged children and families that are of adequate duration, intensity, quality, and are integrated with health and nutrition services. Providing services directly to children and including an active parenting and skill-building component is a more effective strategy than providing information alone.

The papers in this series show that early interventions promote child development and prevent or ameliorate developmental loss. Despite the strength of the findings and the evidence for the effectiveness of investing in child development early in life, the response, particularly in the poorest countries, has been slow. Children’s rights are threatened by the failure of countries to develop their human capital, resulting from the lack of attention to early development. Interventions to promote early child development are cost-effective investments to ensure that children are prepared for educational and economic opportunities, thereby reducing disparities and achieving the Millennium Development Goals of reducing poverty and hunger and ensuring primary school completion for girls and boys. Countries can make a commitment to the future by investing in early child development programmes that reach all young, disadvantaged children through comprehensive child development programmes of quality and by developing the financing and policy mechanisms for sustainability.

Contributors
P L Engle and M M Black are the lead authors and are responsible for the overall manuscript. The other authors (J B Behrman, M Cabral de Mello, P J Gertler, I Kapiriri, R Martorell, and M E Young) contributed to various sections of the manuscript. All authors, including the members of the International Child Development Steering Group, revised and edited the entire manuscript.

International Child Development Steering Group

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

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HIV self-testing: a time to revise current policy

Lucy Frith

A review of government policy about self-testing for HIV is needed in the UK. Since 1992 to sell or otherwise provide a member of the public with any form of self-test for HIV has been illegal in that country. This policy, which was developed at a time when HIV was regarded as different from other diseases (ie, exceptionalism) in public health measures, is now outdated. New technologies that enable rapid and accurate HIV testing are now becoming available. To increase the uptake of HIV testing and truly respect patient autonomy we need to challenge this outmoded practice and remove the legal obstacles to self-testing for HIV.

On Nov 3, 2005, the US Food and Drug Administration’s (FDA) blood products advisory committee met to debate the issues raised by a self-test for HIV based on oral fluids, after its manufacturers declared their intention to seek over-the-counter status. The committee’s meeting is the first stage in a long approval process, but it suggests that self-testing for HIV is being considered in the USA. Most of the experts who spoke at the meeting argued that the introduction of self-testing for HIV was long overdue.

Self-tests for HIV need to be distinguished from home-sample-collection test kits. With these tests, the patient takes his or her own blood sample at home, then sends it to a laboratory for testing and receives the results by telephone. Such tests have had FDA approval since 1996. With self-testing for HIV all stages of the test would take place in the patient’s home, in the same way as a home pregnancy test. The patient would obtain the sample, such as an oral-fluid swab, and the result develops in about 20 min. If the UK were also to legalise HIV self-testing, there are good grounds to believe that legalisation would increase the uptake of HIV testing—a major UK government health target.

An estimated 31% of people with HIV in the UK are unaware of their HIV status, and with advances in highly active antiretroviral therapy the patient should be diagnosed quickly so that the illness can be managed effectively. Early diagnosis also has public-health benefits because people who are HIV positive and are aware of their status are more likely to change their behaviour to reduce the risk of transmitting HIV to others. Self-HIV testing has been suggested as one means of increasing the uptake of HIV testing—a major UK government health target.4

Preliminary investigations in the USA suggest that there is a demand for self-testing. Some sectors of the population would find self-testing more satisfactory than HIV testing in a medical setting and for others it would be more satisfactory than testing of samples taken at home. Whether self-tests result in an overall increase in HIV testing in the UK would have to be monitored, but results from studies in the USA are encouraging. Along with a probable increase in overall uptake, self-testing would enhance patients’ choice. People would have more say over where, how, and when they would be tested for HIV. This promotion of patient autonomy is central to the case for self-testing.

There is a trend in health care towards an emphasis on patient autonomy, which has led to greater self-diagnosis and screening. People are encouraged to take responsibility for their own health, with the recognition that they can make informed decisions without direct intervention from health-care professionals. The restriction of HIV testing to clinical settings is unwarranted, because it prevents individuals from fully exercising their autonomy. As an editorial in the Canadian Medical Association Journal said, “Where the technology exists, why should the public not have autonomy and privacy in obtaining important health information [on their HIV status]?”

Since patient autonomy is important in current medical practice, there should be good and weighty reasons to justify restriction of that autonomy. If self-testing for HIV could be harmful in some way, there would be grounds for keeping HIV testing in a clinical setting. However, none of the arguments put forward to justify the harmfulness of self-testing are strong enough to merit the continued illegality of such tests.

The most common argument used against self-tests is that the person would not receive face-to-face counselling before or after the test. Mandatory pretest face-to-face counselling in HIV is a legacy of exceptionalism: something that is increasingly questioned. Although such counselling can be beneficial, for some people a requirement for pretest face-to-face counselling can actually deter them from being tested.

The argument about the absence of pretest counselling with self-testing needs to be considered in the context of the general re-evaluation of the role of HIV counselling. In practice, the way HIV testing and counselling are done is beginning to change. In response to calls to increase the numbers tested and reduce waiting times, the British Association of Sexual Health and HIV draft guidelines suggest that genitourinary medicine clinics should stop routine pretest counselling. Before undertaking the test patients are recommended to have a pretest discussion, the primary objective of which is to ensure informed consent for the test. Traditional counselling should be reserved for those making a specific request and those who are at high risk of a positive result. The most radical change in HIV testing and counselling is perhaps universal antenatal testing for HIV. All pregnant women in the UK are routinely asked to give their consent to an HIV test, but most will not receive counselling. Guidelines issued by the UK General Medical Council state that counselling needs to be available only for women assessed as at medium or high risk of HIV infection.
view of the changes in genitourinary clinics and the universal antenatal HIV testing, the opposition to self-testing on the grounds that there is no pretest face-to-face counselling is severely undermined.

Although practice in pretest counselling is changing, the predicted lack of counselling after a self-test is the most serious concern.\(^{19}\) Many health professionals have argued that people receiving a positive HIV test result on their own would suffer greater distress and anxiety than those receiving their results in a health-care setting.\(^{14}\) However, self-testing does not necessarily mean there would be no counselling or support. Although there would be no face-to-face counselling, telephone counselling would have to be available. In the UK, the Parliamentary Office of Science and Technology has argued that there should be a requirement on the manufacturers of any self-test to provide some form of counselling as part of their testing service.\(^{18}\) Fears about the lack of face-to-face counselling were raised when the US FDA was considering home-sample-collection HIV tests in the early 1990s,\(^{6}\) but studies on the implementation of these tests, for which telephone counselling was available, did not show any adverse consequences such as increased suicides associated with their introduction.\(^{19}\)

Counselling would also be available when people sought a confirmatory test. As with any HIV test, a second test in a health-care setting would be needed to confirm positive results of a self-test. Information directing people to the relevant NHS services and support in their area would have to be available with every test. People who used HIV self-test kits would then have access to face-to-face counselling.

Although it is a possibility that some individuals would not arrange a second test, this situation might also apply in medical settings, in which a proportion of people will not return to collect their test results.\(^{20}\) Studies in the USA in people who used the home-sample-collection HIV test showed that many of those with positive results took up referrals for follow-up care.\(^{19}\) Although these people would have received their results from telephone counsellors, these referrals show willingness of those who have been tested to go to a health-care provider for further care.

Other concerns raised by self-tests are accuracy and the ability of people to provide adequate samples for testing. The test discussed by the FDA in November, 2005, was the OraQuick rapid HIV test (OraSure Technologies, Bethlehem, PA, USA), an oral-fluid testing system for which the individual takes a swab at home and the result develops within 20 min. This test was licensed for use in clinical and community health-care settings in the USA in 2004,\(^{20}\) but there have been concerns about unacceptable numbers of false-positive results generated.\(^{6}\) OraQuick therefore might not have the required accuracy for a self-test for HIV. However, other methods will be developed and we can reasonably predict that a test will soon meet required standards of accuracy. If we can agree in principle that self-tests for HIV are ethically acceptable and desirable, the law should be changed so that the process of scrutinising self-tests can begin.

Accuracy of an HIV test can also be affected by the ability of the person doing the test to collect the sample and interpret the results correctly. Therefore, self-tests for HIV might not be suitable for home use. For instance, false results produced by the inexpert use of the test could cause high personal distress in the case of false-positives, or increased health risks in false-negatives.\(^{1}\) However, Branson\(^{19}\) noted in his study of the home-sample-collection HIV test that people were able to use such tests to produce accurate results.\(^{18}\) Spielberg and colleagues\(^{5}\) showed high congruence between laboratory tested results and home results. The evidence so far suggests that people’s ability to use self-test kits need not be a major obstacle to their introduction.

The final concern about self-tests for HIV is the possibility of abuse—ie, the testing of someone without their consent, either secretly or under duress. This undoubted drawback with self-testing does not apply to tests done in a medical setting. A solution would be to make testing for HIV by non-health care professionals without their consent illegal, as is being done for non-consensual DNA testing.\(^{21}\) Although such a law could not prevent testing, it would stop the results being used legally (eg, for employment dismissal). The effect of self-testing for HIV on other areas such as domestic violence would also need to be closely monitored when self-tests are piloted.\(^{7}\)

HIV testing practices have changed substantially since self-tests were made illegal in the UK. With the incontrovertible benefits of increasing the numbers tested for HIV, the acceptability of self-tests should be reconsidered. If practitioners truly believe in patient autonomy, people should be allowed to choose where, when, and how they are tested for HIV, where the technology exists. When appropriate self-test kits become available, the UK needs to be in a position to benefit from their use.

**Conflict of interest statement**

I declare that I have no conflict of interest.

**References**

Myocardial infarction in sickle-cell disease

Jiří Pavlů,* Riaz E Ahmed,* Declan P O’Regan, John Partridge, David C Lefroy, D Mark Layton

A 50-year-old woman was admitted to our hospital in December, 2005, with a 5 h history of central chest pain of sudden onset. She described dull pain across her chest with radiation to the right arm accompanied by nausea and vomiting. The pain was worse on deep inspiration but not associated with dyspnoea, and it failed to improve after glyceryl trinitrate. She had a history of homozygous sickle-cell disease with frequent painful episodes; she managed most of these episodes at home with diclofenac and dihydrocodeine phosphate, although intermittently needed exchange transfusion.

The presenting chest pain was different in character from her typical sickle-cell crises. She had no history of coronary heart disease, diabetes, hypertension, or dyslipidaemia, and was a non-smoker. She was apyrexial. Other than mild icterus, physical examination was unremarkable. Electrocardiography showed sinus rhythm with T-wave inversion in V1 to V3, and biphasic T-waves in V4 to V6. A chest radiograph was normal. Arterial blood gas analysis showed PaO2 of 10·6 kPa and SpO2 of 91·1% on room air. Haemoglobin concentration was similar to her steady state at 107 g/L. Serum biochemistry showed increased troponin I at 1-78 μg/L with normal creatinine and electrolytes. Acute coronary syndrome was suspected and enoxaparin sodium, aspirin, and clopidogrel bisulfate were started. Her troponin I peaked at 8·23 μg/L, 12 h after admission, by which time her pain had been superseded by dull pressure over the precordium. Coronary angiography (preceded by automated red-cell exchange to haemoglobin S level of 19%) showed smooth coronary arteries with no occlusion. No ventilation-perfusion mismatches were shown on lung scintigraphy, and the patient proceeded to a cardiac MRI. An inversion recovery gradient echo sequence acquired 15 min after injection of intravascular gadolinium contrast demonstrated a region of myocardial enhancement. Bright-blood cine sequences showed that this anomaly was associated with a wall motion abnormality. Her chest pain resolved fully and electrocardiography became normal within 4 days. When seen for follow-up in August, 2006, she remained asymptomatic.

Sickle-cell disease was first described in 1910 by the Chicago physician J B Herrick who contemporaneously postulated that thrombosis in the coronary artery leads to myocardial infarction.1 Such thrombus generally forms where the coronary arteries are narrowed as a result of atherosclerotic plaque. Case reports of myocardial infarction in sickle-cell disease are uncommon, and in most cases coronary angiography showed no significant coronary-artery occlusion.2 An autopsy study demonstrated myocardial infarction in the absence of significant obstructive or atherosclerotic lesions in 9·7% of patients.3 In contrast to the normal findings in major coronary vessels, the small arteries are narrow in many patients with sickle-cell disease.4 On this background, aggregation of blood cells and their interaction with coagulation factors can cause acute occlusion. Release of inflammatory mediators from leucocytes and platelets induces coronary vasospasm,1 to which scavenging of nitric oxide by haemoglobin liberated through intravascular haemolysis may contribute further. Fat embolism, secondary to bone-marrow infarction, has been implicated in occurrence of myocardial infarction during painful sickle-cell crisis.4 A strength of cardiac MRI is its ability to provide non-invasive myocardial-tissue characterisation at a high spatial resolution. Hyperenhancement of infarcted tissue occurs owing to an increased volume of distribution and delayed wash-out of contrast. Late enhancement can be seen in other causes of cardiomyopathy and in myocarditis, but ischaemic infarction is always characterised by subendocardial enhancement.5 Myocardial infarction should be included in the differential diagnosis of chest pain in sickle-cell disease despite normal coronary angiography.

References

Figure: Cardiac MRI

Inversion recovery gradient echo sequence of the left ventricle in short (left) and long (right) axis shows a hyperenhancing infarct in the lateral wall (arrows).