access and the adequacy of dialysis. They have, however, been questioned for their reliance on expert opinion and because of the close relations between the Foundation, the Kidney Disease Outcomes Quality Initiative (KDOQI) that formulates its recommendations, and the drug industry.3,12 In fiscal year 2005, according to its annual report, the Foundation received $19.7 million—57% of its total support—from various “corporate and organizational partners”.13 In calendar year 2005, it received $41.1 million from Amgen and $3.6 million from Ortho Biotech, a subsidiary of Johnson & Johnson, the current marketers of epoetin products in the USA.4,6 Amgen supported the development of the anaemia guidelines and is acknowledged as “the founding and principal sponsor of KDOQI”.11 Of the 18 members of the workgroup, two-thirds disclosed financial associations with Amgen or other epoetin manufacturers or marketers.21 In October, 2006, fact sheet, the Foundation responded to “some controversy [that] has arisen due to the fact that KDOQI guidelines have been supported by industry. The NKF continually reviews its policies and procedures to safeguard the work product of KDOQI and to ensure that no sponsorship funds contributed to the NKF ever influence the content of any of the KDOQI guidelines.”14

On the basis of the available data, the maintenance of haemoglobin concentrations above 130 g/L appears to be unsafe in patients with chronic renal failure. There is considerable doubt that values between 120 and 130 g/L are as safe as those between 110 and 120 g/L. Maintaining higher haemoglobin values requires substantially more epoetin, greatly increases the cost of care, and is not in accord with the prescribing information. Although ongoing trials will provide more information, results are not imminent. Physicians and dialysis facilities need updated guidance about the management of anaemia and what is best for patients. Given the billions of dollars at stake for the drug and dialysis industries, such guidance is likely to receive the broadest acceptance if developed without industry support, and by experts without relevant financial associations. This might be accomplished under the auspices of the National Institutes of Health Consensus Development Program or the Agency for Healthcare Research and Quality.

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I declare that I have no conflict of interest.


Dengue: setting the global research agenda

The global incidence of dengue has increased exponentially over past decades (figure). Fuelled by conditioning factors such as rapid urbanisation, demographic change, large-scale migration, and travel, the disease is now endemic in most countries of the tropics, and about 925 million people now live in urban areas that are at risk of dengue infection.1 The increasing incidence, intensity, and geographical expansion of dengue epidemics pose a growing threat to the health and economic well-being of populations living in endemic areas, where the introduction of new virus strains to regions affected by existing serotypes is a risk factor for outbreaks and severe disease. Dengue is a major international public-health concern, as expressed...
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in World Health Assembly resolution WHA 55.17 and in the 2005 revision of the International Health Regulations (WHA 58.3).2,3 We do have strategies, methods, and guidelines with which we can greatly reduce dengue case-fatality rates and virus transmission, but weak implementation of these plans and an inability to respond effectively to conditioning factors (such as those mentioned above) outside the health sector is causing concern.

This worry was expressed at a meeting of our Scientific Working Group on Dengue (UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training on Tropical Diseases), which was held in Geneva on Oct 2–5, 2006, attended by 60 experts from dengue research and control programmes around the world. We met to discuss research in progress and work needed to reverse the epidemiological trend and geographical expansion of dengue. The practical relevance of science for dengue prevention and control was underlined by WHO, which organised a back-to-back meeting to update global guidelines on dengue, which reminded us of the value of close interaction between scientists and public-health practitioners.

Without vaccines, drugs, and even useful diagnostic tests, the only available responses to the challenge of dengue are clinical management, vector control for prevention, and a surveillance system to identify outbreaks at an early and treatable stage. Implementation of these strategies is, however, hampered by the complexity of the clinical guidelines (which are difficult to use when health-care levels are low),4,5 by the scarcity of information on the cost-effectiveness of vector-control measures and alternative delivery strategies, and by the lack of political will in allocating resources to disease and vector surveillance and to prevention and control initiatives.

However, the outlook is optimistic because dengue research is beginning to attract not only increased funding from national and international sources but also a diversity of young researchers ranging from molecular biologists to behavioural scientists. Findings are contributing to the design and validation of new intervention packages, to accelerated development of diagnostics, vaccines, and drugs through better understanding of pathophysiology, immunology, and viral factors, and to improved dengue case-management through evidence from prospective clinical studies. New vector-control methods6 and approaches for vector surveillance7 are being developed and made available to control programmes and partners, and modern information technology is being tested for its cost and usefulness in supporting district-level decision-making, where vector control is taking place.

Recommendations made by the Scientific Working Group for priority research in the coming years were structured into four streams. The first stream is aimed at reducing disease severity and case fatality by enhanced case management. Research is needed to develop better diagnostics, to identify warning signs for severe disease, to develop evidence-based criteria for standardisation of treatment procedures, and for recognition of comorbidity (mainly chronic diseases) and of dengue in pregnancy. Training programmes for inexperienced health staff need to be validated.

The second stream of research is aimed at reducing virus transmission and avoiding epidemics. This requires further development and evaluation of promising vector-control methods (eg, insecticide-treated window curtains and water-container covers, and controlled-release insect-growth regulators) and approaches (eg, interventions targeting the most productive water-containers), and analysis of the cost-effectiveness of participatory interventions and partnership models. Experience of scaling-up vector control at all programme

Figure: Average yearly number of dengue cases reported to WHO (columns) and number of countries reporting dengue (line)

Data were obtained by Michael Nathan and Renu Dayal-Drager (WHO) using information from DengueNet—a WHO-established web-based information system (http://www.who.int/csr/disease/dengue/denguenet/en/index.html).
levels (from local to national and international) and of successful and unsuccessful disease and vector surveillance systems needs to be recorded to allow adoption of best practices in other places.

The third stream relates to primary prevention through dengue vaccines and to secondary prevention through drugs. This aim requires better understanding of viral and host factors. Immune responses in natural infections and vaccine trials need to be better characterised, correlates of protective immunity must be identified as endpoint measures in vaccine trials, new vaccine candidates and adjuvants have to be tested, and alternative vaccination strategies need to be assessed. Better descriptions of viral-encoded proteins will accelerate drug design and testing of existing licensed drugs and natural or other products.

Finally, the fourth stream of research is aimed at enhancing the public-health response at national and international levels through health-policy research. Research is ongoing into the burden caused by dengue to societies and families, and there are scattered analyses of country dengue programmes that can help identify factors leading to success and failure. Health-policy research should also be extended to less studied regions, such as Africa, where dengue is especially neglected. In summary, with good synergy between research, policy, and prevention and control, there are real prospects for reversal of the upward trend of the global dengue pandemic.

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Paracetamol: are therapeutic doses entirely safe?

Paracetamol (acetaminophen in the USA) is thought to be safe in recommended doses, up to 4 g a day in adults. In most countries, paracetamol can be purchased in retail stores as an over-the-counter preparation, and it is currently the most widely used analgesic and antipyretic drug worldwide.

Paracetamol is hepatotoxic and nephrotoxic at doses of more than 4 g a day in adults. Over the past 15 years, especially in Europe and in the USA, paracetamol has become the most important cause of acute liver failure—a devastating disorder in which more than 85% of patients with a poor prognosis who do not have transplantation die. Of particular concern is that in recent years, unintentional overdoses, rather than those that are intentional, have been the main cause of paracetamol-induced acute liver failure in the USA; the actual dose taken can be as low as 7 g a day. The safety of paracetamol has been under considerable debate, but a review by the US Food and Drug Administration Office of Drug Safety concluded that no change was needed in how the drug is sold. However, a recent study by Paul Watkins and colleagues did a participant-blinded diet-controlled study in 145 selected healthy volunteers. The study was designed to determine why abnormal liver-function tests had been recorded during early clinical development of a new combination of an opioid (hydrocodone) and paracetamol. Participants were randomly assigned placebo, paracetamol (4 g a day), or a combination of this dose of paracetamol with one of three opioids, with an intended duration of treatment of 14 days. Although trough paracetamol concentrations in any group did not exceed therapeutic limits, 31–44% of participants...