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 disease 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.[1] 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.[2] 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.[3] 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.[4] The safety of paracetamol has been under considerable debate,[1] but a review[5] 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[6] has reopened the issue of the actual safety of therapeutic doses of paracetamol.[2]

Watkins and colleagues[6] 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

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in the paracetamol-treated groups had concentrations of alanine aminotransferase that were more than three times the upper limit of normal (suggesting liver injury), whereas none of 39 participants given placebo had an increase to this level (p<0·001). In 27% of participants given therapeutic doses of paracetamol, increased alanine aminotransferase concentrations (to more than eight times the upper limit of normal) were recorded.

Three other studies[7–9] lend support to the idea that therapeutic doses of paracetamol might be associated with liver injury in some patients. For patients with severe acute viral hepatitis, recent ingestion of therapeutic doses of paracetamol was associated with higher serum transaminases and greater prolongation of prothrombin time compared with patients that did not have additional paracetamol.[10,11] In a preliminary study from France,[12] 52% of patients with biochemical and clinical evidence of acute liver injury while on antitubercular drugs had a history of recent paracetamol ingestion. Thus, at clinical onset of acute liver disease, use of paracetamol might be associated with exaggerated liver injury in some individuals. For patients who present with acute liver injury, markedly elevated serum alanine aminotransferase, and who have a history of recent paracetamol ingestion, physicians should consider paracetamol hepatotoxicity as a cause and consider treatment with acetylcysteine.[13]

Although the provocative data from Watkins and colleagues[6] need to be strengthened by other studies—particularly of patients on long-term continuous treatment with paracetamol—they raise many questions about the safety of commonly recommended doses of paracetamol. Review of the recommendations about how paracetamol is sold in the future might be appropriate. However, Watkins and colleagues' findings should not be taken out of context because unnecessary anxiety may encourage patients to switch to potentially more toxic alternatives.

Doctors, health workers, pharmacists, and patients need to be made aware that administration of paracetamol in doses that are thought traditionally to be safe might lead to raised transaminases, suggesting some degree of liver injury. Such awareness is particularly important for people who are likely to be at high risk of unintentional paracetamol hepatotoxicity—eg, those who are dependent on alcohol, are severely malnourished, consume paracetamol chronically, smoke tobacco, have acute liver disease, or who receive treatment with inducers of liver enzymes.

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