DISEASE WATCH | IN THE NEWS

WHO/TBP/Arnold

World TB Day

The 2004 Global TB Control report — launched at the second Stop TB Partners' Forum on World TB Day, March 24th — contained encouraging news on the progress that has been made in TB detection and treatment over the past 2 years. However, WHO Director-General Lee Jong-wook cautioned that there was still a lot of work to do to meet the targets set for 2005. If current trends continue, the case detection rate in 2005 is expected to be 50%, some way short of the target of 70%. The 2005 targets are an important milestone towards achieving the Millennium Development Goal of halving the global burden of TB by 2015. Progress is being made however — 3 million individuals are now enrolled in DOTS (directly observed treatment, short course) programmes worldwide, an increase of 1 million compared with 2001. **WHO**

Outbreak news

Since 20th December 2003, >15,000 cases of cholera have been recorded in Mozambique and at least 90 people have died.

An emergency mass vaccination campaign is under way in Liberia in an attempt to stop an outbreak of yellow fever before the rainy season starts in April.

The latest cycle of dengue fever in Indonesia has so far caused >400 deaths and led to >23,000 people being hospitalized since January. All four of the viral serotypes have been detected. Intensive insecticide spraying is being used in an effort to control the mosquitoes that transmit this disease.

A nipah-like virus has been detected in association with an outbreak of encephalitis in Bangladesh, which so far has caused 17 deaths.

DISEASE WATCH | FOCUS

Dengue

BACKGROUND

Causative agent. Dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) are progressively more severe clinical manifestations of dengue infection caused by four, single-strand RNA flaviviruses known as DEN-1–4. Virus transmission occurs through the infective bite of *Aedes aegypti*, a mosquito with high biting frequencies and readily interrupted feeding behaviour. The virus replicates in lymph nodes, spleen, liver and mononuclear phagocytic cells in other tissue systems.

Current global status. Dengue is the most important arboviral disease of humans. An estimated 50 million dengue infections and 500,000 DHF cases occur annually, particularly in south-east Asia, the western Pacific and the Americas[1] (FIG. 1).

RECENT DEVELOPMENTS

New basic knowledge. Dengue viruses encode three structural proteins — capsid (C), membrane (M) and envelope (E) proteins — and seven non-structural (NS) proteins.

In the Americas, the transition from DF to DHF and DSS occurred in Cuba in 1981, when an Asian genotype virus (DEN-2) was introduced into a DEN-1-immune population[2]. By contrast, when the American genotype DEN-2 infected a DEN-1-immune population in Iquitos, Peru, only mild disease resulted[3,4]. Differences in the outcome of secondary infection seem to be due to the high level of cross-neutralization between DEN-1 antibodies and the DEN-2 virus[5]. It is hypothesized that Asian dengue strains that successfully circulate in highly dengue-immune populations have lost cross-reactive epitopes, as a mechanism of immune escape. Important for the development of DHF/DSS is enhanced viral replication during the early stage of infection[6], which is apparently mediated by non-neutralizing antibodies that are residual from an earlier dengue infection and is known as antibody-dependent enhancement (ADE)[7]. So, early infection, the time interval between first and second infection[8], virus strain and host genetic factors are involved in severity of the disease outcome. Plasma leakage, the main patho-physiological feature of DHF, seems to be particularly correlated with blood concentrations of cytokines (such as IFN-γ, IL-2 and TNF-α) and infected cell lysis, owing to dengue-specific T lymphocytes[9]. The ultimate causes of haemorrhage due to vasculopathy, platelet reduction or dysfunction and prothrombin-complex deficiency are even less clear, although platelet-activating factors and, potentially, platelet-destroying mechanisms have been described[10,11].

New tools and intervention methods. An effective dengue vaccine should protect against the four serotypes and should be long-lasting to avoid antibody titres dropping to sub-neutralizing levels. Six live attenuated vaccines are in various stages of development[12]. Two live attenuated vaccines have reached Phase II evaluation, and 3–4-year follow-up data for one vaccine show protection against disease and no increase in severe dengue. In preparation for Phase III trials, there is still considerable need for field site development and epidemiological characterization of study populations. A dengue vaccine could be highly cost-effective, as the cost

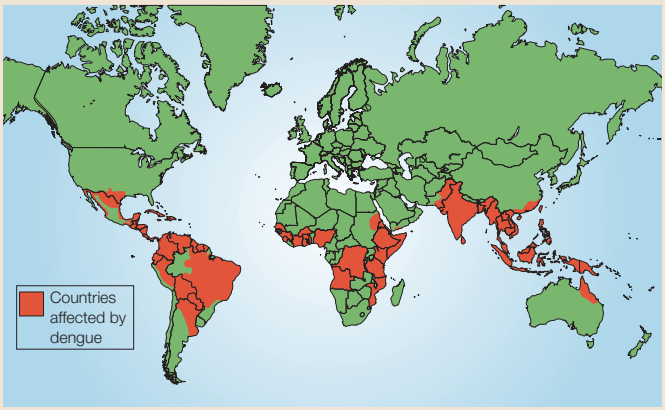
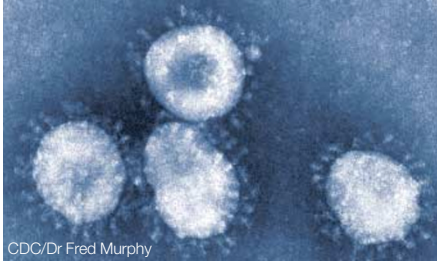


Figure 1 | Areas where there is a risk of dengue transmission



CDC/Dr Fred Murphy

The origins of SARS

In a paper published in the February issue of *Emerging Infectious Diseases*, a special issue of this CDC journal focusing on severe acute respiratory syndrome (SARS), a team of researchers from China report that a SARS-like virus was circulating in Hong Kong 2 years before the start of the 2003 outbreak. Circulating antibodies to human SARS coronavirus (SARS-CoV) and/or animal SARS CoV-like virus were detected in 17 serum samples collected from 938 healthy adults in 2001. The authors speculate that the viruses circulating in 2001 are antigenically closer to the animal SARS CoV-like virus than the human SARS Co-V and failed to adapt successfully to a human host. **CDC**

Infectious risk from bushmeat

A report in *The Lancet* has provided the first confirmation of the transmission of a retrovirus from non-human primates to humans in a natural setting. Nathan Wolfe and colleagues investigated the transmission of simian foamy virus (SFV) from animals to humans in rural villages in Cameroon. Of the 1,800 participants in the study, 1,099 (61%) were regularly exposed to the blood and body fluids of non-human primates through the hunting and butchering of these animals. SFV antibodies were detected in 1% of this group. This study demonstrates that retroviruses are actively being transmitted to humans in natural settings and has lent weight to calls for a ban on the trading of bushmeat. **The Lancet**

Fluoroquinolone ban upheld

A US Food and Drug Administration (FDA) judge has upheld a ban on the use of the fluoroquinolone Baytril in poultry. Baytril, which is manufactured by Bayer, was banned as part of the October 2000 FDA ruling that outlawed the use of fluoroquinolones in poultry feed, in response to growing concern that the intensive use of antibiotics in livestock contributes to the spread of antibiotic resistance in bacteria. The judge cited 'serious questions about the safety of Baytril use in poultry'. Bayer plan to lodge a final appeal with the FDA commissioner. If the commissioner also backs the decision, Baytril could be banned by June.

In the News was compiled with the assistance of David Ojcius, University of California, Merced, USA.

per disability-adjusted life year has been estimated as US $50 (REF. 13). In addition, both the WHO-based Initiative for Vaccine Research (IVR) and the Paediatric Dengue Vaccine Initiative (PDVI) are working to facilitate vaccine development.

Current dengue diagnostic tools include anti-dengue immunoglobulin M (IgM) detection, which indicates a recent infection, and the use of PCR, which allows detection of the dengue virus genome in serum, mosquitoes and tissues. Improved tests that allow early diagnosis, including clinical prognosis, are urgently needed; one such test which targets the NS1 protein is currently under development.

Discovery of a drug that reduces viral load in dengue patients has been initiated at the Novartis Institute for Tropical Diseases in Singapore. A library of more than 1 million compounds is being tested against a cloned fraction of the NS3 viral enzyme so that a candidate lead molecule can be identified. A rapid-acting compound with minimal side effects might also be effective as a chemoprophylactic component, potentially preventing the occurrence of large outbreaks. However, successful antiviral therapy will depend on rapid early diagnosis.

At present, the only methods for reducing dengue transmission are reduction of human–vector contact and control of the mosquito populations. New tools are under development, such as insecticide-treated curtains and improved formulations of larvicides that are safe for use in drinking water.

In addition, implementation of DengueNet — a global system for standardized epidemiological and virological surveillance — will allow a continually updated database to be maintained for timely control measures and epidemiological research.

New strategies, policies and partnerships. New vector-control measures and new partnerships with, for example, municipal authorities are needed. Given that mosquito habitat management or treatment methods rely on the involvement of individuals, communities and governments, a manual using the COMBI approach (Communication for Behavioural Impact) has been developed to assist programme planners in developing sustained community action plans for dengue prevention and control[14]. Transgenic technology to interupt pathogen transmission has been developed for *A. aegypti*[15], using the introduction of exogenous DNA into the germ line. Completion of the *A. aegypti* genome sequence will facilitate the research process.

CONCLUSIONS AND FUTURE OUTLOOK

The pipeline of vaccine candidates looks promising, but their use for disease control will require careful safety follow-up to assure that no sensitization to severe disease occurs. An improved understanding of the molecular mechanisms of pathogenesis of severe disease will help to overcome this threat. Monitoring the molecular structure of circulating virus exposed to selective pressure from vaccine-induced immunity will be important. Vector control will also be needed. Capacity building will be essential for the sustained delivery of vector control measures to protect high-risk populations and respond to epidemics or the threat of epidemics.

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TDR Reference Group on Dengue: A. Castro, D. Focks, D. Gubler, L. Lloyd, M. Guzman, S. Halstead, S. Kalayanarooj, J. San Martin, S. Vasudevan. TDR/WHO, 20 Avenue Appia, CH-1211 Geneva, Switzerland.

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Online links

FURTHER INFORMATION

TDR: http://www.who.int/tdr/

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