# Editorial: Towards a global dengue research agenda

**J. Farrar**[1], **D. Focks**[2], **D. Gubler**[3], **R. Barrera**[4], **M. G. Guzman**[5], **C. Simmons**[1], **S. Kalayanarooj**[6], **L. Lum**[7], **P. J. McCall**[8], **L. Lloyd**[9], **O. Horstick**[10], **R. Dayal-Drager**[11], **M. B. Nathan**[11], and **A. Kroeger**[10] **on behalf of the WHO/TDR Dengue Scientific Working Group**

[1]Hospital for Tropical Diseases, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam [2]Infectious Disease Analysis, Gainesville, GA, USA [3]Asia-Pacific Institute of Tropical Medicine and Infectious Diseases, John A. Burns School of Medicine, Honolulu, USA [4]Dengue Branch, Centers for Disease Control and Prevention, San Juan, Puerto Rico [5]Instituto de Medicina Tropical "Pedro Kouri", Ciudad de la Habana, Cuba [6]Queen Sirikit National Institute of Child Health, Bangkok, Thailand [7]Department of Paediatrics, University of Malaya, Kuala Lumpur, Malaysia [8]Vector Research Group, Liverpool School of Tropical Medicine, Liverpool, UK [9]Consultant, San Diego, CA USA [10]UNICEF/UNDP/WORLD BANK/WHO Special Program for Research and Training in Tropical Diseases, Geneva, Switzerland [11]World Health Organization, Geneva, Switzerland

## Keywords

dengue research; dengue burden; dengue vectors; dengue clinical management

## Epidemiological challenge and international response

Dengue is the most rapidly advancing vector-borne disease with an estimated 50 million dengue infections occurring annually (Figures 1 and 2). As a result of major demographic changes, rapid urbanization on a massive scale, global travel and environmental change, the world – particularly the tropical world – faces enormous challenges from emerging infectious diseases. Dengue epitomizes these challenges. In the early years of the 21st century, we are collectively failing to meet the threat posed by dengue as the disease spreads unabated and almost 40% of the world's population now live at risk of contracting it. Because of the rapidly increasing public health importance of dengue, the 2002 World Health Assembly Resolution (WHA55.17) urged greater commitment among Member States and WHO to dengue control; of particular significance is the 2005 Revision of the International Health Regulations (WHA58.3), which includes dengue fever as an example of a disease that may constitute an international public health emergency.

Dengue was incorporated in 1999 into the portfolio of the Special Programme for Research and Training in Tropical Diseases (TDR/WHO), leading to new and disease-endemic

**Corresponding Authors: Axel Kroeger and M. Nathan,** UNICEF/UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (Axel Kroeger), and Department of Neglected Tropical Diseases, NTD/WHO (Michael Nathan), 1211 Geneva, Switzerland. kroegera@who.int and nathanm@who.int.

country (DEC) led research initiatives. Dengue vaccine discovery/development was taken up by the Initiative for Vaccine Research (IVR), another WHO-based department. New partners appeared on the scene: the Pediatric Dengue Vaccine Initiative (PDVI) and the Innovative Vector Control Consortium (IVCC), both financed by the Bill and Melinda Gates Foundation, and the Rockefeller Foundation. DENCO and DENFRAME, international consortia supported by the European Commission, were created to study dengue pathogenesis, clinical management and discovery of new diagnostics, and vector control. Concurrently, a TDR/PDVI international laboratory network is evaluating available and new dengue diagnostics, whereas TDR-supported multicentre studies on targeted vector interventions are exploring ways for more cost-effective vector control strategies (TDR 2005; Focks & Alexander 2006). IVR works with PDVI on standardized tools for vaccine evaluation. Industry has a renewed interest in product development in the areas of dengue vaccines, drugs, diagnostics and insecticide formulations for vector control. The *Aedes* genome has been sequenced and laboratory experiments with genetically transformed vectors are under way. Ecosystem-based interventions against the dengue vector are being analysed by TDR/IDRC-(International Development Research Centre, Canada) coordinated multicountry studies and clinical/pathophysiological studies are being conducted in Vietnam, Malaysia, Philippines and Thailand with support from the Wellcome Trust, UK, and the Armed Forces Research Institute of Medical Science (AFRIMS), Bangkok.

These are examples of major research initiatives which are complemented by internally or externally financed studies and training activities in many dengue-endemic countries. At the same time, an Asian–Pacific Dengue Partnership is evolving; Mekong Delta countries are receiving support for dengue activities from the Asian Development Bank and the WHO Regional Office for the Western Pacific; and a new Strategy for Integrated Dengue Management in the American Region is being promoted. Guidelines for planning social mobilization and communication (Parks & Lloyd 2004) and clinical management (Kalayanarooj & Nimmannitya 2004; WHO 2006a), as well as dengue CD ROMs (Wellcome/TDR 2005; WHO 2006b) and other training materials have been published. Dengue Net, a web-based information system, has been established by WHO. Internationally renowned training courses are the biennial course in Cuba (10th anniversary in 2007) and the clinical management course in the Bangkok Children's Hospital.

## Dengue Scientific Working Group 2006

It was against this background that the Dengue Scientific Working Group of 60 experts from 20 countries including WHO staff from four Regions and headquarters met in Geneva in October 2006 to review existing knowledge on dengue and to establish priorities for future dengue research aimed at improving dengue treatment, prevention and control. The goal of the Scientific Working Group was to outline a research agenda by identifying potentially fruitful directions as well as key bottlenecks and making detailed and specific research recommendations. The SWG wanted to identify areas of research that could lead to tangible benefits for people in disease-endemic countries in the coming years as well as outline a strategic vision for applied and basic research from which benefits would be felt in the medium to long term.

It was noted that there is currently no specific clinically useful diagnostic test, no drugs, no available vaccine, and that we have failed to widely or effectively implement existing vector control and clinical management measures that we know would help to reduce the disease transmission and case fatality rate. Yet, there has never been a more optimistic time to be involved in dengue and dengue research, and interest in the disease has attracted a new generation of talented and committed clinicians and scientists. Modern science, from clinical medicine to basic research on pathophysiology, drug and vaccine discovery, through to the social and behavioural sciences and vector biology and control, offers a unique opportunity to make a tangible and substantial impact on dengue over the next decade. But, in order to achieve what is possible, the dengue research community needs to: push for much greater implementation of existing knowledge to reduce severe morbidity and case fatality, extend basic and clinical research to understand the underlying pathophysiology, aid diagnostic and drug discovery and further improve clinical outcome, speed up the development of vaccine candidates including moving as quickly as possible to efficacy trials, and gather the evidence for implementing best practices for controlling the major vectors.

All of this is possible in the next 10 years. But to achieve it, dengue control needs a much stronger voice within dengue-endemic countries and within the global public health community to persuade society, funding agencies and policy-makers of the importance of the disease. We are at a critical epidemiological juncture in infectious, particularly viral, emerging diseases at the start of the 21st century, and in many ways dengue serves as a model for how we might meet that challenge. The lessons learned from dengue will have implications for a number of other diseases and our approach to their control. The implementation of the best of existing knowledge and practice supplemented by future research applied in an integrated, holistic fashion can be expected to significantly change the lives of individuals living in dengue-endemic countries in the coming years.

## Global dengue research agenda

The priority dengue research areas are organized along four major research streams which will provide evidence and information for policy-makers and control programmes and lead to more cost-effective strategies which will reverse the epidemiological trend.

## Stream 1: Research related to reducing disease severity and case fatality

### Optimization of clinical management

We need an efficient outpatient system; clinical and laboratory indicators of early dengue, plasma leakage and shock need to be identified as well as effective and safe methods of managing severe haemorrhage, dengue in pregnancy, and patients with co-morbidity. These indicators and methods must be validated in order to scale up improved and standardized treatment guidelines. We propose research in

- new methods and guidelines for triage and outpatient care of dengue patients, plus validations of their feasibility and results at different levels;

- the validity, role and accessibility of available and new diagnostics for dengue;

- the predictive value of prognostic markers (host/viral early warning signs) of disease severity, and validation procedures for early recognition and treatment of plasma leakage and shock;

- standardized approaches to determining clinical signs of shock in children and adults, including the role and techniques of measuring blood pressure in shock patients, and of diagnosing severe dengue through ultrasound, other non-invasive technology, and laboratory markers (albumin, cholesterol);

- alternative ways for effective and safe management of haemorrhage, infected pregnant women, co-morbidities such as obesity, diabetes mellitus, hypertension and chronic heart diseases, and of severe dengue using oral re-hydration therapy;

- the causes of dengue deaths (including treatment failures) in order to learn from negative outcomes.

## Process and impact evaluation of staff training

Implementation of training programmes in case management can lead to an immediate reduction of case fatality, as has been shown in many countries. However, training has to be standardized and adapted to the prevailing local health care system. A review of dengue morbidity and mortality targeted at resolving the major problems in case management could include reorganization and reallocation of resources. The process and impact of existing/future training programmes to determine how best we can implement improved dengue case management in different health care systems and achieve greatest impact should be investigated.

## Understanding host genetics and other critical issues in dengue pathogenesis

A better understanding of dengue pathogenesis will be the foundation for rational future clinical interventions. In particular, we require further research of

- the molecular and pathophysiological changes underlying endothelial permeability in plasma leakage syndrome;

- dengue virus diversity (which may account for heterogeneity in virus biology including virulence and epidemic potential);

- mechanisms of antibody-mediated enhancement and protection (the immune response to dengue viruses may paradoxically pre-dispose individuals to severe disease);

- mechanisms of virus entry and cellular/tissue tropism;

- T and B cell responses and their relation to immunopathology in primary and secondary infections.

## Stream 2: Research related to transmission control through improved vector management

### Development and evaluation of vector control tools and strategies

Although powerful vector control tools are available, in practice, their effectiveness has been compromised by issues of delivery, coverage and acceptability. We need to evaluate

- the efficacy of new vector control tools and strategies in different contexts;

- the effectiveness, cost, community acceptance and feasibility of combinations of new and/or existing tools, including integrated vector management and ecosystems interventions, with a range of partners in different contexts;

- optimal scaling-up of pilot projects to state or national level in order to identify and disseminate best practices.

### Surveillance and response

Disease and vector surveillance are fundamental to effective programme management. To improve decision-making, surveillance systems must be strengthened by developing and validating reliable risk indicators and making use of information technology. Studies should address

- improved methods such as pupal demographic surveys and their application in operational contexts as indicators of risk for outbreak and for informing targeted intervention;

- development and use of early warning and response systems;

- triggers (factors and information) of effective responses to incipient epidemics;

- the contribution of information technology (e.g., GIS, bioinformatics, Dengue Net, mathematical models) to decision-making.

## Stream 3: Research related to primary and secondary prevention

### Vaccines

Vaccines offer the greatest hope for dengue prevention and there are several candidates in clinical development. The challenge has been to identify vaccine components and immunization strategies that are suitably safe, but broadly immunogenic. The identification of immune correlates of protection should accelerate successful vaccine development and regulatory approval. Research should focus on

- discovery and pre-clinical research of vaccines, new vaccine candidates, adjuvants, and vaccination strategies;

- correlates of protective immunity for use as an endpoint in vaccine trials;

- immune responses in vaccine trials and natural infections;

- development of further field sites, including sites free of non-dengue flaviviruses, and the prospects for Phase 3 and 4 vaccine evaluation;

- future vaccine use and coverage through vaccine implementation research.

## Drugs

Anti-dengue drugs may have prophylactic (e.g. outbreak prevention) and therapeutic (e.g. prevention of severe disease) uses, with an ensuing impact on disease incidence and severity. Anti-viral drug discovery for dengue has accelerated in recent years along with our knowledge of 'drugable' targets in the virus. Hence, we need further elucidation of

- the structure of viral encoded proteins to aid rational drug, diagnostics and vaccine design;

- new (including natural) products or existing licensed drugs with good safety profiles and to foster drug discovery efforts.

## Stream 4: Health policy research contributing to adequate public health response

There is a contradiction between the high priority afforded at political level to dengue and the low allocation of resources to dengue prevention and control. Health policy research in the areas listed below will facilitate a redress of this imbalance:

- issues and events that will, through adequate dissemination of information [including of burden of disease (DALYS) and costs of illness], elevate dengue to a high priority at national and international levels;

- case studies of national programmes to identify factors leading to success or failure of dengue prevention and control programmes in order to develop a set of best practices;

- decision-making that results in a declaration of state of emergency to allow more timely and effective political response, identification of the data triggers used in this process;

- the burden of dengue in less studied regions, particularly Africa, and its role as a contributor to 'fevers of unknown origin'.

## Conclusion

The Scientific Working Group hopes this research agenda will help provide a strategic plan for how we might collectively achieve the aims of reducing dengue morbidity and mortality and its negative socio-economic impact. Donors and the research community are encouraged to take part in this major programme and to contribute through timely information to the database. WHO/TDR is establishing for keeping track of research activities and relevant findings.

## Acknowledgements

Wellcome Trust and was followed by a meeting about updating the global dengue guidelines organized by the Department of Neglected Tropical Diseases (NTD/WHO).

## References

DengueNet. [accessed 7 November 2006] http://www.who.int/csr/disease/dengue/denguenet/en/index.html

Focks, DA.; Alexander, N. Multicountry study of Aedes aegypti pupal productivity survey methodology: findings and recommendations (TDR/IRM/DEN/06.1). Special Programme for Research and Training in Tropical Diseases (TDR); Geneva: 2006. http://www.who.int/tdr/publications/publications/pdf/aedes_aegypti.pdf [accessed 7 November 2006]

Kalayanarooj, S.; Nimmannitya, S. Guidelines for Dengue Hemorrhagic Fever Case Management. Queen Sirikit National Institute of Child Health; Bangkok, Thailand: 2004.

Parks, W.; Lloyd, L. Tunis, World Health Organization Mediterranean Centre for Vulnerability Reduction. 2004. Planning Social Mobilization and Communication for Dengue Fever Prevention and Control. WHO/CDS/WMC/2004.2, TDR/STR/SEB/DEN/04.1

TDR. Dengue Diagnostics: Proceedings of an International Workshop; 2005. TDR/IRM/DIAG/DEN/05.1

Wellcome Trust – TDR. Topics in International Health: Dengue. CD Rom, CABI Publishing; Wallingford, Oxford, UK: 2005.

World Health Assembly. [accessed 7 November 2006] Dengue fever and dengue haemorrhagic fever prevention and control (WHA 55.17). http://www.who.int/gb/ebwha/pdf_files/WHA55/ewha5517.pdf

World Health Assembly. [accessed 7 November 2006] Revision of the International Health Regulations (WHA 58.3). http://www.who.int/gb/ebwha/pdf_files/WHA58/WHA58_3-en.pdf

WHO. Pocket Book of Hospital Care for Children. Guidelines for the Management of Common Illnesses with Limited Resources. World Health Organization; Geneva: 2006a. Dengue; p. 166-171.

WHO. An Audiovisual Guide for Health Care Workers Responding to Outbreaks. 2006b. Dengue Haemorrhagic Fever: Early Recognition, Diagnosis and Hospital Management. WHO/CDS/EPR/2006.4
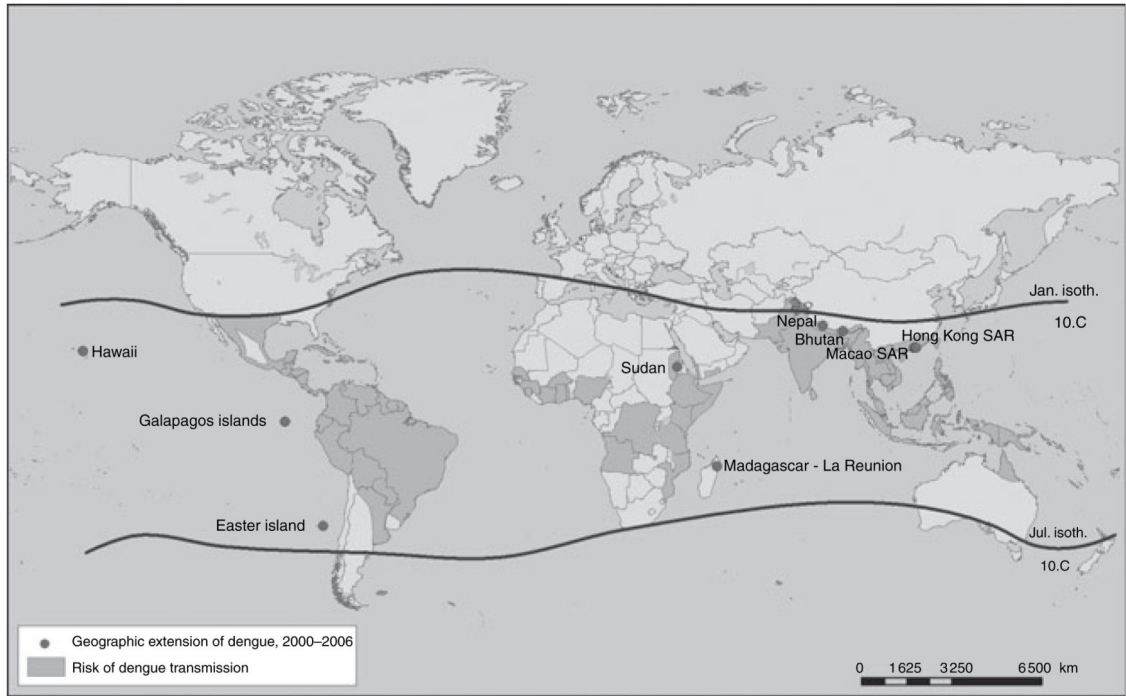
**Figure 1. Countries or areas at risk of dengue transmission, 2006.**
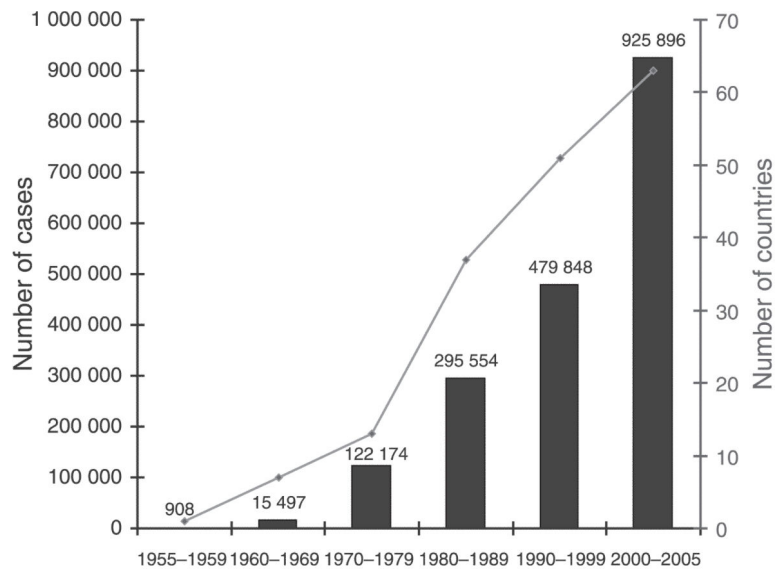
**Figure 2. Average annual number of DF/DHF cases reported to WHO and of countries reporting dengue.**