

# Meeting Report

UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR)



## Recommendations

# Scientific Working Group on Dengue

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# SCIENTIFIC WORKING GROUP ON DENGUE

## Executive Summary

In recent decades, dengue has grown dramatically as a health, environmental and economic problem. However, the resources needed to cope - material, human and research - have not kept pace. In the coming 10 years, the environmental and social determinants of dengue transmission risks will continue to expand: another billion people will be added to the world population, the process of urbanization will intensify, and changes in global climate and local weather patterns are expected. In order to deal with the increasing threat of dengue, the Scientific Working Group (SWG) recommended that a multi-pronged approach be adopted which takes into account these changing social and environmental conditions.

## Recommendations

**Specifically, the SWG recommended that efforts be focused on reducing the mortality and morbidity caused by dengue haemorrhagic fever (DHF). This can be done by:**

- **Improving case management** using well-established clinical interventions.
- **Developing a whole new class of early prognostic/diagnostic tests**, particularly through research on the pathogenesis of vascular permeability and altered haemostasis.
- **Preventing viral transmission.** Currently, the only way to prevent dengue transmission is by **controlling the mosquito vector, *Aedes aegypti***. This will require the development and evaluation of new tools to reduce mosquito populations, including source reduction. Major efforts will be required to increase evidence-based vector control programmes and to support state-of-the-art research on human behaviour and behaviour change in relation to mosquito breeding.
- **Focusing dengue vaccine research** on early evaluation in children and **accelerating marketing** by setting standards for vaccine efficacy and safety.
- **Research capacity strengthening.** In both industrialized and disease endemic countries, severe shortages in research capacity and capability have been noted, reflected in a lack of vector control entomologists, field capable research scientists, clinical epidemiologists who can perform studies on improving DHF/dengue shock syndrome (DSS) case management, basic flavivirologists and cellular and humoral immunologists. In fact, dengue biology requires a balance between field capable scientists and molecular and genetic researchers. TDR should make a critical appraisal of resource needs in dengue, then design and follow a strategic plan to address them.

- ▶ **Fund raising.** TDR needs to help raise dengue to a new level of recognition as part of a major effort to attract new funds to support basic and applied research and to implement new methods for dengue control, whether vaccines, vector control, or ideally, both.



# SCIENTIFIC WORKING GROUP ON DENGUE

## Introduction

During the 20<sup>th</sup> century, the distribution and density of the mosquito vector, *Aedes aegypti*, expanded dramatically in tropical areas, beginning in large cities then spreading to the countryside. This was followed by global circulation of the four dengue viruses, a virus group closely related to yellow fever. Due to complex phenomena related to the circulation of multiple serotypes, a new yellow fever-like viral hemorrhagic fever emerged – dengue haemorrhagic fever (DHF). As TDR faces a new millennium, dengue will be one of the great emerging health challenges. DHF is unique in human medicine in that a first infection sensitizes so that approximately 2% of second (different type) infections go on to develop DHF. Dengue has been recognized in over 100 countries and territories and causes an estimated 50-100 million infections annually among the more than 2.5 billion people at risk. In 1998, 1.2 million cases of dengue and DHF were reported to WHO, including 3442 deaths. DHF has unique political resonance due to the panic created by the mix of an explosive disease attracting newspaper headlines and the requirement for life-saving intensive care.

In the past, WHO organized and supported vector control units in Bangkok and Jakarta. These contributed usefully to knowledge of the biology, ecology and control of *Aedes aegypti*. More than two decades ago, due to budgetary constraints, these units were phased out. In 1984, WHO initiated a programme for vaccine development that included a steering committee on dengue and Japanese encephalitis vaccines. This activity continues with modest funding. More recently, the WHO South East Asia Regional Office (SEARO) funded the development of a live-attenuated dengue vaccine. Authoritative technical guides for the diagnosis, management and control of dengue haemorrhagic fever have been published by WHO headquarters, SEARO and the Pan American Health Organization (PAHO). WHO regions and headquarters have supported operations research, meetings and workshops, and provided consultants to address various aspects of the diagnosis, control and case management of dengue and DHF.

The described WHO activities do not begin to address the challenging issues that lie ahead for dengue research, product development and disease control. Based on the global and expanding nature of the problem and obvious need, the Joint Coordinating Board of TDR voted in 1999 to add dengue to their disease portfolio.

The coming decade will see the world population expand by another 1 billion people. The process of urbanization (a major driving force in the dengue pandemic) will go on; already more than half of the world population lives in urban areas. If local authorities fail to provide basic services in urban areas, the dengue problem may increase. If the predicted global climate trends occur, dengue transmission may occur at higher altitudes and latitudes than now.

The following sections discuss the SWG's recommendations regarding research considered of high priority for reducing disease burden. Research that might logically be the responsibility of TDR is discussed separately from research that might be tasked to other partners.

### SWG Prioritization of needed research on dengue

	Activities most appropriate for other partners	Research for which TDR has a comparative advantage
<b>High priority for dengue prevention and control*</b>	<ul style="list-style-type: none"> <li>• <b>Dengue case management:</b> Assess efficacy and cost effectiveness of DHF treatment modalities in controlled trials, e.g. fluid and colloid management, anti-haemorrhage therapies. Identify and remove barriers to high-quality case management of dengue fever (DF)/DHF.</li> <li>• <b>Improve clinical-epidemiological diagnosis of dengue fever:</b> Evaluate predictive value of leukopenia and tourniquet test.</li> <li>• <b>Pathogenesis:</b> Develop appropriate animal models of DHF/DSS. Study target cells in severe or unusual dengue infections. Study host factors, e.g. genetic susceptibility, nutritional status and underlying conditions.</li> <li>• <b>Vector control:</b> <ul style="list-style-type: none"> <li>- Research to develop new and innovative vector control methods and evaluate novel and existing methods for efficacy and cost-effectiveness.</li> <li>- Appoint a task force on incorporation of vector control into urban planning and management.</li> <li>- Plan, conduct and evaluate feasibility studies of public-private vector control partnerships.</li> </ul> </li> <li>• <b>Surveillance:</b> <ul style="list-style-type: none"> <li>- Design studies to improve early warning, especially on borders of new epidemics and/or in annual flare-ups in endemic areas</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Diagnostics:</b> Develop improved methods for early specific detection of antibody, antigen and RNA.</li> <li>• <b>Treatment:</b> develop antivirals directed at protease or other poorly studied enzymes; develop anti-mediators directed at causes of increased vascular permeability or altered haemostasis.</li> <li>• <b>Pathogenesis:</b> study the mechanism of immune enhancement, neutralization escape, T-cell responses, viral virulence determinants by serotype and genotype, molecular basis of viral interference and mediators of plasma leakage and altered haemostasis.</li> <li>• <b>Dengue vaccines:</b> accelerate development by creating a product development group to work on current candidate live-attenuated vaccines and appoint a working committee to establish dengue vaccine safety guidelines.</li> <li>• <b>Vector control:</b> <ul style="list-style-type: none"> <li>Support multicentre studies: <ul style="list-style-type: none"> <li>- in vector biology that contribute to improved control and modelling of dengue transmission.</li> <li>- to develop and evaluate community-based mosquito control strategies,</li> <li>- to develop and evaluate (including cost-effectiveness) novel <i>Aedes aegypti</i> control methods.</li> </ul> </li> <li>• <b>Surveillance:</b> support the global and regional use of <i>Dengue-Net</i> including reporting viral isolates by serotype and genotype.</li> </ul> </li> </ul>
<b>Medium priority for dengue prevention and control</b>	<ul style="list-style-type: none"> <li>• <b>Vaccine research:</b> <ul style="list-style-type: none"> <li>Support research on additional technologies for producing dengue vaccines (e.g. through IVR).</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Basic social, economic and behavioural research:</b> <ul style="list-style-type: none"> <li>support studies to identify barriers to and opportunities for: <ul style="list-style-type: none"> <li>- scale-up of successful pilot community-based interventions</li> <li>- effective, sustainable behaviour change with regard to mosquito control.</li> </ul> </li> <li>• <b>Demonstration projects:</b> <ul style="list-style-type: none"> <li>- multicentre studies to evaluate integrated community-based vector control programmes.</li> </ul> </li> </ul> </li> </ul>

\* These are all important research areas that require funding and are not listed in order of priority

## RESEARCH FOR WHICH TDR HAS A COMPARATIVE ADVANTAGE

### Basic and Strategic Research (STR)

The SWG recommended opening the relevant TDR steering committees (on pathogenesis and functional genomics) to dengue applications. Pathogenesis research requires the possibility to study humoral and cell-mediated immune response caused by dengue viruses that differ by serotype and genotype. Special emphasis needs to be given to early infection factors that might have etiologic and prognostic (successfully predict imminent onset of vascular permeability) value. Research should include studies on the mechanisms of dengue virus neutralization by antibody, viral infection interference, viral virulence, steps in dengue virus entry into cells, and viral tropism. Although research on animal models is to be encouraged, it is expected that much pathogenesis research will be conducted in dengue endemic countries in diseased humans. Anti-viral research may require a commitment to strategic research on the functions of the proteins that are specified by the dengue genome. Similarly, anti-mediator research will derive from the results of fundamental studies on mechanisms of pathogenesis.

Strategic research is needed to generate fundamental observations related to the longevity and density of adult *Aedes aegypti*. Such research should be planned by experts convened by TDR then carried out in diverse ecological and geographical habitats so as to constitute a reasonably global survey. The derived data can be incorporated usefully into vector control programmes and into mathematical models of dengue virus transmission. To verify these models, more complex studies may be required in which the transmission of four dengue viruses among partially immune humans by diverse populations of vector mosquitoes is observed. TDR should consider expanding molecular entomology research to include research on innovative molecular/genetic methods to reduce vector populations and/or reduce vectoral capacity (e.g. anti-sense RNA). Such methods, if successful, should be subjected to cost-effectiveness analysis.

### Strategic Social, Economic and Behavioural Research (SEB) and Intervention Development and Evaluation (IDE)\*

There is an urgent need to develop and implement sustainable *Aedes aegypti* control to prevent dengue transmission. The SWG recommended that TDR support multicentre studies to develop and evaluate community-based *Aedes aegypti* control strategies that would include:

- strategies for ensuring effective, sustainable community participation (including feedback mechanisms for surveillance data)
- appropriate entomological indicators
- appropriate behaviour change indicators.

Although scale-up and follow-on social, economic and behavioural research was considered of medium rather than high priority (lower right quadrant of Table 1), it was agreed that such research is an integral part of community-based research strategies.

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\* now renamed Intervention Development and Implementation Research

## Product Research and Development (PRD)

High priority research includes the development of tests to detect primary or secondary dengue infections early in the course of infection so that dengue infected children can be triaged for more intensive observation. Responsibility for this research may be shared between the WHO Vaccines and Biologicals (VAB) department and TDR Diagnostics Discovery. In the clinical setting, early specific diagnosis of a dengue infection will save human resources, time and money. In the future, if potent, safe and affordable antivirals or anti-mediators (e.g. cytokines) become available, they could be administered to avoid severe illness. PRD research on diagnostic tests will benefit from strategic research on the mediators of vascular permeability and altered haemostasis or prognostic markers that are surrogates of other evanescent clinically relevant markers.

- Task force on live-attenuated vaccines

The SWG agreed that the appointment of this task force was urgent and high-priority. Each of the two groups working on live-attenuated tetravalent vaccines should be approached to discover their interest. It was felt that the existence of a dispassionate and scientifically competent task force might be useful to the design and conduct of Phase I–III clinical trials.

- Development of guidelines for the safety of dengue vaccines

This activity is complementary to, and may logically benefit from, the experiences of the task force. As new strategic research findings emerge from studies on pathogenesis or viral virulence, their implications for the safe administration of dengue vaccines will need to be reviewed and written into guidelines. This function should be assigned to an appropriate group without delay.

## Research Capacity Strengthening (RCS)

Research capacity strengthening is needed for all areas of research discussed above. Research applications from developing countries are to be encouraged. These may profit from targeted capacity strengthening awards.

## RESEARCH AND ACTIVITIES APPROPRIATE FOR OTHER PARTNERS

### Case management

Much important work needs to be done in dengue endemic countries to improve the management of DHF and, therefore, the survival of affected children. Much of the effort entails a commitment to training. Controlled trials are required to assess optimal treatment of dengue bleeding phenomena and loss of fluid and protein from vascular spaces. Ultrasound and other new diagnostic modalities need to be evaluated as tools for rapid diagnosis of DHF and monitoring of treatment.

### Improved clinical diagnosis

Accurate diagnosis of DHF first requires recognition that an individual is suffering from a dengue viral infection. An inexpensive, simple, clinically relevant tool is needed. A prospective multicentre trial should be conducted in which children with laboratory-confirmed dengue and other acute viral illnesses are enrolled. The purpose of the trial would be to measure the predictive value for acute dengue infection of the following: leukopenia, positive tourniquet test and an inverse ratio of mature:juvenile forms of polymorphonuclear leukocytes.

### Pathogenesis research

Continued efforts should be made to identify virus infected target cells in patients with severe or unusual dengue illnesses. Additional research is needed on host factors, such as genetic susceptibility or resistance to dengue infection. Studies in Africa are important to determine if the *Aedes aegypti* found in West Africa are genetically incapable of transmitting urban dengue viruses or whether dengue is so mild in Africans that reports of clinical disease are rare. The role of nutrition in ameliorating DHF should be studied.

### Vector control

#### ***Task force on incorporation of vector control into urban planning and management***

The SWG felt that the Communicable Diseases Control, Prevention and Eradication department of the Communicable Diseases cluster (CDS/CPE) of WHO should initiate this important effort to build a coalition among agencies that have responsibility, direct or indirect, for much of the vector control around the world, e.g. municipal and other local governments, ministries of environment, public agencies and private corporations responsible for drinking water supply and waste management, legal agencies, architectural firms, and NGOs involved in social housing projects. WHO should contribute to the organization of regional as well as global meetings to discuss shared problems and options for synergies in research activities in urban planning and management, and in developing policies for mosquito abatement in large urban areas. A social marketing component will be important. An essential partner may be the UN Centre for Human Settlements (HABITAT), which has its headquarters in Nairobi.

***Pilot study on public-private cooperation for vector control***

The SWG considered it important to encourage one or more dengue endemic countries to design a pilot project, involving a pest abatement company, on the control of *Aedes aegypti* and pest mosquitoes. The project should be designed for a defined area and time. Such a project will be particularly useful as participating public agencies will be required to define the terms of reference for mosquito control contracts and to develop methods for monitoring performance. The mosquito abatement districts in California constitute a public-private partnership that has provided sustained mosquito abatement for more than 60 years, and may serve as a useful model.

***Surveillance***

The SWG strongly endorses the establishment of DENGUE-NET (a web-based surveillance initiative within the CDS Communicable Disease Surveillance and Response - CSR - department) and encourages the exchange of information of dengue viral serotypes and genotypes. These data should be monitored for utility as an epidemic prediction tool. Special attention needs to be paid to surveillance efforts along national borders.

***Insecticide resistance***

The SWG considered it essential for member countries to continue to monitor insecticide resistance, particularly against newer insecticides. Monitoring of existing insecticides should be carried out as a routine public health programme, but should be complemented by a research programme on the mechanisms of insecticide resistance with appropriate attention paid to associated environmental and health risks.

***New and innovative mosquito control***

Research on new and innovative methods of mosquito control (e.g. permethrin impregnated cloth, copepods) is essential and requires support. WHO headquarters and regional offices should encourage and support well-designed evaluations of new and innovative vector control methods to include cost-effectiveness. Guidelines for cost-effective analysis of vector control programmes are available from WHO, but more research is needed. WHO can host regional and global meetings for the results of such studies to be reported.

## Annex

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