Strategic Direction for Research

Dengue

Disease burden and epidemiological trends

The global burden of dengue has grown dramatically in recent decades, and it is currently classified as an emerging or re-emerging infectious disease. Dengue fever (DF) and dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) occur in over 100 countries, with more than 2.5 billion people at risk and an estimated 50 million infections per year. The disease is endemic in all WHO Regions except the European Region (EUR). The major disease burden is found in south-east Asia and the western Pacific, with increased reporting of DF/DHF in the Americas. Globally, the number of cases increased more than 4 fold between 1970-95, and an unprecedented 1.3 million cases of cases of dengue fever and dengue haemorrhagic fever were reported to WHO in 1998, including over 3600 deaths. The pandemic largely affected the WHO Regions of the Americas (AMR), South-East Asia (SEAR) and Western Pacific (WPR). More than 55% of the cases, mostly of dengue fever, and only 2% of the deaths, were reported from AMR. However, in this region, dengue fever and dengue haemorrhagic fever are reported separately, whereas in SEAR and WPR the data are aggregated and the great majority of reported cases are hospitalized cases of dengue haemorrhagic fever. The burden of severe disease remains proportionately much greater in the affected Asian and Pacific countries. Typical of post-epidemic periods, dengue activity was much lower in the year after the pandemic, but the number of reported cases increased again in 2000, to over 500 000. Preliminary data for the year 2001, up to September, for two of the three regions (AMR and SEAR), show a further, large increase in reported cases (>525 913 cases), with nearly 500 deaths. These data suggest a level of activity comparable in magnitude with that of 1998.

Table: Cases of dengue fever and dengue haemorrhagic fever reported to WHO 1998-2001*

WHO Region	1998		1999		2000		2001*	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Western Pacific	356 554	1470	64 066	112	45 603	167	NA	NA
South-East Asia	218 859	2075	55 405	471	57 997	542	119 707	452
Americas (DF)	708 146	0	317 040	0	394 847	0	400 875	0
Americas (DHF)	12 426	83	5216	98	5667	92	5331	44
Americas (total)	720 572	83	322 256	98	400 514	92	406 206	44
Eastern Mediterranean	*No dengue cases reported to WHO (several countries are affected, including Pakistan, Somalia, Sudan)*							
African	*No dengue cases reported to WHO*							
World	**1 295 985**	**3628**	**441 727**	**681**	**504 114**	**801**	**525 913**	**496**

* Provisional data to September 2001 NA: data not available DF: dengue fever DHF: dengue haemorrhagic fever
Only the Americas countries report DF and DHF separately.

Several recent studies have provided estimates of the costs of DF/DHF epidemic outbreaks, in terms of both US$ per case and DALYs lost to dengue. For example, estimates for the cost per treated case were: Cuba, US$ 299; Nicaragua, US$ 44; Peurto Rico, US$ 28; and Thailand, US$ 118. A recent analysis of the impact of dengue in Puerto Rico using DALYs demonstrated that the loss of DALYs/year/million population to DF/DHF is much greater than previous estimates which considered the impact of DHF alone (658 for DF/DHF versus 2 for

DHF). Related studies show that the number of DALYs lost to dengue in Latin America and the Caribbean region is similar to those values attributed to meningitis, hepatitis, malaria, the childhood cluster of diseases or TB. In a recent study by Shepard et. al. on DF/DHF in Asia, DALYs lost were estimated to be 1156 per million population, approximately 1/6 those reported for TB or malaria in Asia**.** Additional studies are required to estimate the figures for US$/case/DALY/death averted.

Current control strategy

The WHO Global Strategy for Prevention and Control of Dengue Fever/DHF, as established in 1995, comprises five major elements:

- **Selective vector control, with community and intersectoral participation** – control activities are directed towards geographic areas with highest risk of transmission, integrating all appropriate methods.
- **Active disease surveillance based on a strong health information system** – involves clinical and laboratory-based dengue surveillance for early detection of epidemics, and vector surveillance for monitoring and evaluation of control programmes.
- **Emergency preparedness** – requires the development of emergency and contingency plans, including education of the medical community, hospitalization plans, case management and emergency vector control.
- **Capacity building and training** – for surveillance, laboratory diagnosis, case management and vector control at professional, supervisory, technical and field levels.
- **Vector control research** – including studies on vector biology and control, disease relationships, design and management of control programmes (including social and economic approaches) and cost benefit analyses. The relative impact of the components of integrated vector control require further elucidation.

Major problems and challenges for disease control

The reasons for the persistence/global emergence of DF/DHF as a major public health problem are complex and not fully understood. In the Americas, where vector control measures had succeeded in eliminating the mosquito vector from most of Latin America, re-infestation of tropical regions with the vector *Aedes aegypti* now puts over 300 million urban dwellers at risk, and resulting epidemics provide the opportunity for the four dengue serotypes to move between countries and sub-regions. Globally, effective mosquito control is the exception rather than the rule in dengue-endemic countries. Major global demographic changes have occurred, especially uncontrolled population growth, mobility and unplanned urbanization. Among many other man-made items, good larval habitats are provided by household water storage containers, discarded solid waste items, such as plastics, glass containers and used automobile tyres. Increased travel by humans serves to spread dengue viruses between population centres of the tropics. And finally, decentralized and often weak public health infrastructures now place emphasis on implementing emergency control methods in response to epidemics as opposed to developing programmes to prevent epidemic transmission. In the face of poor surveillance, epidemics often reach or pass peak transmission before they are detected. Epidemics can be averted by timely and intensive vector control but the cost-effectiveness of such measures is not well defined.

Research needed to address these constraints

It is imperative that a global effort be implemented to support research on new and improved mosquito control and transmission interruption technologies including insecticide-treated materials, space spray techniques, visual and olfactory

adult collection devices, and research on the development of effective prevention strategies, including first and second generation dengue vaccines (no good animal models exist). All countries in dengue-endemic areas need to develop and implement new emergency control strategies for epidemic DF/DHF (adequately trained staff, with simple equipment and standard intravenous infusion supplies can often reduce the DHF case fatality rate from 5-10% to less than 1%). Standardized and clear case definitions for DF and DHF need to be tracked and reported separately. Active, effective laboratory-based dengue surveillance (with regional reference centres) would allow most national programmes to detect epidemics sufficiently early to allow for appropriate decisions and timely deployment of control measures. The *DengueNet* initiative addresses these issues. Source reduction, larviciding and personal protection measures (when used in a timely manner) are considered to be important elements of an emergency response. However, the impact of these interventions on transmission remains unclear. Indicators need to be developed which allow the householders themselves to monitor the status of dengue and its control in the community. Indeed, the monitoring, assessment and evaluation of behaviours related to dengue needs to be addressed and better understood. All of these activities involve the identification and building of partnerships among donors, the public sector, NGOs, and the private and commercial sectors.

Ongoing research on dengue

Currently the main focus of public sector funding for dengue research (estimated to be US$ 15 million in 2001) is on molecular epidemiology, immune pathophysiology, second generation vaccine discovery research, and new or improved approaches to vector control (TDR has US$ 160 000 to date). Many dengue-endemic countries support modest research programmes, mainly in the field of vector control and identification of epidemiological/viral risk factors for DHF epidemics. Several companies (Aventis Pasteur; Acambis; GlaxoSmithKline [GSK]; Novartis; Bavarian Biotech; MaxyGen; PanBio) have invested in dengue vaccine and diagnostics R&D (estimated to be around US$ 2-4 million in 2000). Several candidate vaccines (live attenuated and second generation infectious clones/chimeric versions) are in clinical trial in USA and Thailand. In December 2001, a major meeting on Accelerating the Development and Introduction of a Dengue Vaccine was convened in Ho Chi Minh City, Viet Nam by Rockefeller and International Vaccine Institute, and co-sponsored by Aventis, GSK and WHO/TDR. The meeting was very successful in bringing together vaccine researchers/developers and potential stakeholders. Several rapid immuno-chromatographic diagnostic tests are on the market, but are expensive (US$ 2-4) and remain to be tested in head-to-head comparisons and their cost-effectiveness determined. No commercial chemotherapy R&D activities appear to be under way.

TDR's comparative advantages

The Dengue Research Scientific Working Group (SWG) identified the following *high priority* research topics for which TDR has a comparative advantage (not in order of priority):

- **Diagnostics** - develop improved methods for early specific detection of antibody, antigen and RNA.
- **Treatment** - evaluate feasibility to develop antivirals directed at protease or other poorly studied enzymes; develop anti-mediators directed at causes of increased vascular permeability or altered haemostasis.
- **Pathogenesis** - study the mechanism of immune enhancement, neutralization escape, T-cell responses, viral virulence determinants by serotype/genotype, molecular basis of viral interference and mediators of plasma leakage/altered haemostasis.

- **Dengue vaccines** - accelerate development by creating a product development group on current candidate live-attenuated vaccines and appoint a working committee to establish dengue vaccine safety guidelines.
- **Vector control** - fund multicentre studies in vector biology that contribute to improved control and modelling of dengue transmission; develop and evaluate community-based mosquito control strategies; develop and evaluate (including cost-effectiveness) novel *Aedes aegypti* control methods.
- **Surveillance** - support the global and regional use of *Dengue Net*, including reporting viral isolates by serotype and genotype.

Medium priority topics include:

- **Basic social, economic and behavioural research** - studies to identify barriers to and opportunities for: (i) scale-up of successful pilot community-based interventions; (ii) effective, sustainable behaviour change with regard to mosquito control.
- **Demonstration projects** - multicentre studies to evaluate integrated community-based vector control programmes.

Strategic emphases for dengue research in TDR

TDR has identified the following strategic emphases for research on Dengue:

- **Diagnostics** – evaluation of currently available diagnostic tests.
- **Pathogenesis** – development of a dengue pathogenesis research portfolio (to be initiated).
- **Vaccine development** – WHO/IVR product development team and group on dengue vaccine safety, issued guidelines for testing dengue vaccines in endemic populations.
- **Treatment** – implementation research on case management strategies for epidemic DF/DHF.
- **Vector control** – capacity building to accelerate the development of effective community-based vector control strategies to be evaluated in multicentre studies on prevention and control; and development of novel vector control methods and tools for entomological monitoring and evaluation (to be initiated).
- **Epidemiology** – multi centre studies on the dynamics of virus transmission (to be initiated in collaboration with Mekong Basin Disease Surveillance [MBDS])
- **Surveillance** – capacity building to support the use of *Dengue Net* in Asia as a platform for developing multi centre research partnerships (ongoing in Thailand, Indonesia, Singapore and Viet Nam).
- **Basic social, economic and behavioural research** – develop instruments/ guidelines for promoting studies on community-based interventions and behaviour change with regard to mosquito control (ongoing as a collaboration between TDR and the WHO department for Communicable Disease Prevention, Control and Eradication).

The next Dengue SWG meeting is scheduled for 2004.

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