

Global Situation of Dengue and Dengue Haemorrhagic Fever

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Dengue, and the severe complications, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), are the most important arbovirus diseases in the world today. Indeed, there is a global pandemic of these diseases in progress throughout the tropical and sub-tropical regions of the world. Over the past several decades, there has been a dramatic increase in both the geographic distribution and the incidence of these diseases. As an example, for the 25 year period 1956 to 1980, the average number of DHF cases per year was less than 30,000. During the following five year period, this rate increased nearly five-fold, to almost 150,000 cases per year, and in the next five year period, 1986 to 1990, the number of cases increased an additional two-fold.

The reasons for this increase in dengue and DHF may be found in four societal changes: increased urbanization leading to more densely populated areas; increased air travel, leading to rapid dissemination of new serotypes of dengue virus into susceptible populations; changes in lifestyle that have led to increase availability of vector mosquito breeding sites; and human population growth resulting in an increase in the susceptible population. These changes have been most dramatic in southeast Asia since the end of World War II, and the increases in dengue and DHF have been most dramatic there as well. These societal changes have been accompanied by entomological changes during the past 20 years that have resulted in increases in the density of the primary dengue vector mosquito, *Aedes aegypti*, and a reinfestation of the Americas by this species, following the aborted attempt at its eradication from the hemisphere.

Dengue and DHF/DSS have followed a progression in southeast Asia, first with the initial appearance of DHF/DSS, followed by sporadic cases leading to an endemic situation with cases seen every year, and in certain areas with all four dengue serotypes present most or all of the time. This pattern has progressed from a few countries affected in the Region in the 1950's and 1960's, to most countries from India to southern China now affected.

The pattern of expansion of dengue and DHF/DSS seen in southeast Asia is being repeated today in the Americas. The similarities in events leading to endemic DHF are apparent, with the Americas experiencing a dramatic increase in *Ae. aegypti* distribution and density, increased dengue transmission, the introduction of multiple dengue serotypes, fre-

quent dengue epidemics, the first appearance of DHF, and finally epidemics of DHF. The cornerstone to the introduction and evolution of dengue and DHF in the Americas has been the dramatic reinfestation of the Americas by *Ae. aegypti*. At the termination of the *Ae. aegypti* eradication campaign, this species was found in only a few countries of northern South America, the Caribbean, and the southeastern United States. Over the following 20 years, virtually every locality where the mosquito had been eliminated during the eradication campaign was reinfested. Today, both the distribution and density of *Ae. aegypti* is as great, or even greater, than it was prior to the eradication campaign. This abundance of a competent mosquito vector, coupled with the societal changes already mentioned, has resulted in to a situation in the Americas similar to that experienced in southeast Asia 20 years or so ago.

It is likely that similar events are unfolding in much of tropical and subtropical Africa; however, data is limited on the existence of dengue and DHF there, although some major outbreaks have been reported recently.

Clearly the challenges of this global pandemic of dengue and DHF/DSS demand immediate and coordinate action. Three approaches are now being pursued by WHO to address this emergency. These are improved, sustainable vector control, increased training, and vaccine development.

The key to sustainable control of *Ae. aegypti* rests with community involvement, since this mosquito species is highly adapted to life in close association with humans. It breeds in water holding containers in and around the home, and readily enters houses to feed and rest. Consequently, control efforts must rely to a large extent in convincing people that they must personally eliminate vector breeding around their homes by control of potential mosquito breeding sites. These efforts should be integrated with other vector control resources, such as entomological surveillance, insecticide applications and personal protective measures, especially during outbreak situations. Clearly active entomological surveillance efforts are required to monitor vector population densities and organize effective interventions if outbreaks are to be prevented.

Training plays a critical part in dengue prevention and control programmes. Workshops for health care providers that focus on the appropriate treatment of DHF/DSS patients have clearly been shown to save lives. Clinicians who are familiar with the clinical course of DHF/DSS are much better prepared to effectively treat these patients as compared to those without past experience or appropriate training. Likewise, parents must be made aware of the critical warning signs of DHF/DSS, so that they will bring their sick children to the hospital at the first sign of shock. Finally, public educational campaigns are needed to ensure that the population at risk understands how the disease is spread, its clinical characteristics, and preventive measures. These efforts, when coupled with improved laboratory diagnostic capabilities and effective surveillance of disease and vectors, can

significantly reduces the risk of dengue and DHF/DSS.

As reagents are not commercially available for the laboratory diagnosis of dengue and DHF/DSS, WHO is attempting to develop regional sources for routine use. Efforts at regional self sufficiency in dengue reagents will require assistance from the network of WHO Collaborating Centres for Virus Reference and Research.

Although a protective vaccine is not yet available for dengue, good progress has been made, and vaccination may play a role in the future prevention of dengue. The problem of vaccine development for dengue and DHF/DSS is complicated by the fact that four distinct viruses may cause dengue and DHF/DSS, there is not protective cross protection between these different serotypes, and the risk of severe DHF/DSS is substantially greater among those suffering a second of subsequent infection with dengue. Consequently, any vaccine must protect against all four dengue serotypes.

Candidate live, attenuated vaccines to all four dengue virus serotypes have been developed by Dr Natth Bhamarapravati and his colleagues at Mahidol University in Thailand with the support of WHO and others. Preliminary results indicate that these vaccines are safe and immunogenic, eliciting good neutralizing antibody responses when administered to humans. Serological follow-up of individuals receiving candidate vaccines indicates that neutralizing antibodies persist for at least five years following inoculation, the current length of follow-up. While efficacy tests have not been attempted, it is generally believed that neutralizing antibodies are a good indication of protection. Experiments to determine the stability of candidate vaccines in vector mosquitoes, *Ae. aegypti*, found that a high titer of vaccine virus was required to infect feeding mosquitoes, generally higher than that seen among vaccinated persons. In addition, the candidate vaccine viruses failed to replicate well in vector mosquitoes, and when examined following growth in mosquitoes, it was determined that the candidate vaccines retained their attenuated characteristics. Commercial production of these candidate dengue vaccines is under development, with formal efficacy testing planned for the near future.

In addition to the efforts of the team at Mahidol University, the WHO Global Programme on Vaccines has for several years supported an effort to develop vaccines to dengue and Japanese encephalitis (JE) using molecular technology. At present, the most promising approaches have been expression of virus-like particles from engineered vaccinia constructs that contain a portion of the Pre-M and E genes of dengue and JE viruses. Other approaches have included expression of structural and non-structural components in baculovirus expression systems, development of chimeric viruses, and purification of subunit particles. Only the expression of virus-like particles by recombinant vaccinia has reached the stage of human testing.

In summary, dengue and DHF/DSS are of growing importance throughout the tropics and subtropics. Their increase is due to societal changes and dramatic increases in both the distribution and density of the primary vector mosquito of dengue, *Ae. aegypti*. To combat this threat, the WHO is focusing on sustained vector control, expanded training opportunities, enhance surveillance and laboratory capabilities, and vaccine development efforts. These programmes will require active participation, not only by members of the health care professions, but also by the community members themselves.