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The Challenge of Dengue – Desperately Seeking Solutions

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Dengue has acquired the dubious honour of being the world's most important mosquito-borne viral disease, rendering about 2.5 billion people in 100 countries at risk. An estimated 60 million cases occur annually, a significant fraction of whom require hospitalisation for haemorrhagic and hypotensive complications, culminating in 30,000 fatalities. Epidemics of dengue have been reported regularly, particularly in crowded urbanised areas in tropical and subtropical regions, including Southeast Asia. In 1996 alone, over 3,000, 14,000, 8,000 and 3,000 cases were reported in Singapore, Malaysia, Vietnam and Jakarta, respectively. Sobering statistics indeed. In addition to population expansion, urbanisation, poverty, lifestyle changes and widespread travel, changing climatic patterns have been blamed for the worldwide upsurge of dengue outbreaks[1]. Global warming, the decline in the quality of the world's ecosystems affect the distribution of water and encourage breeding of the dengue-virus-bearing Aedes mosquito vector. Higher temperatures associated with the El Nino weather phenomenon accelerate the growth of mosquitoes and increase the replication rate of dengue viruses[2]. For example, a simple mathematical model has projected a three-fold rise in dengue incidence in Indonesia by 2070. These factors have fuelled the relentless advance or reappearance of Aedes and dengue to areas such as Irian Jaya, North Queensland, Karachi, New Delhi and the Americas. In the face of this daunting onslaught, intensive research is buttressing our armamentarium via improved diagnostic techniques, better understanding of pathophysiology and ardent development of vaccines.

The majority of suspected dengue patients are most rapidly diagnosed by serology, the method of choice being IgM capture ELISA. User-friendly commercial kits are now available for detecting dengue-specific IgM antibodies which generally remain up to 90 days. As an adjunct technique, amplification of viral nucleic acid by the polymerase chain reaction (PCR) facilitates the early detection of dengue virus in the serum during viraemia which correlates with the febrile phase[3]. PCR is also useful as an epidemiological tool by distinguishing between the four distinct dengue virus types present in clinical serum and field-caught Aedes mosquito specimens[4]. Furthermore, genetic sequence analyses of the numerous geographically and temporally-separated strains of dengue viruses elucidate their molecular epidemiology and evolution.

There is convincing evidence that the risk of developing dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) is greater in individuals suffering from an anamnestic secondary dengue infection, particularly with dengue 2 virus. This immune enhancement event is mediated by circulating, cross-reactive but non-neutralising dengue viral antibodies. Dengue 2 virus binds to human platelets only in the presence of virus-specific antibody *in vitro*, thus supporting a role for immune-mediated clearance of platelets in the pathogenesis of thrombocytopaenia in DHF and DSS[5]. Serum levels of tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) cytokines are elevated in dengue patients[6]. Moreover, exposure to culture fluids from antibody-enhanced, dengue virus-infected peripheral blood monocytes triggers endothelial cell activation which can be abolished by treatment of monocyte culture fluids with anti-TNF-α antibody[7]. It is not inconceivable that anti-cytokine antibodies like TNF-α antibody could be recruited in therapeutic trials for the improved management of dengue complications. Of great significance is the new discovery that the cellular receptor utilised by dengue virus envelope protein to selectively bind to target cells is a highly sulphated type of heparan sulphate[8]. The polysulphated anti-parasitic compound suramin inhibits dengue viral attachment and infection *in vitro*. The downstream benefits of this breakthrough could include the design of pharmaceutical agents which inhibit target cell binding, and the production of novel vaccines by modification of the receptor-binding region of dengue virus.

In confronting this emergency of the global dengue pandemic, one of the key priorities of the World Health Organisation is supporting vaccine development. Monovalent and multivalent live, attenuated vaccines have been tested in human volunteers, with some candidate vaccines shown to be safe and immunogenic, eliciting good neutralising antibody responses which persist for at least five years. Besides natural mutation by serial passage for creating new vaccines, molecular genetic engineering is being exploited to generate recombinant subunit vaccines, virus-like particles

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and intertypic chimaeric viruses[1]. Recently, a nucleic acid vaccine in the form of expression plasmid constructs containing dengue viral pre-M and envelope genes was developed[9]. Mice inoculated with this vaccine mounted antibodies that neutralised dengue virus *in vitro*, the first promising demonstration of dengue DNA vaccination, which lacks the potential drawback of vaccine-induced illness.

Whilst awaiting the emergence of effective drugs and vaccines hopefully in the not too distant future, public education campaigns on the danger, spread and prevention of dengue; community participation and active entomological surveillance and control programmes should continue to play pivotal roles in the battle against dengue[10].

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