The problem with dengue

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1. The burden of disease

During the second half of the twentieth century, dengue became the most widespread vector-borne viral disease of humans, with current estimates of between 50 and 100 million cases of dengue fever per annum worldwide. Of these cases, 500,000 develop into the severe forms of the disease: dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Guzman and Kouri, 2002). Moreover, the frequency of epidemics involving more than one serotype (hyperendemicity) has increased. This situation was probably initiated by the economic disruption and human population migration during and immediately after the Second World War, which spread the main mosquito vector of dengue (Aedes aegypti) beyond its usual geographical locations, and also resulted in the reintroduction of disease into some areas (Gubler, 1997).

The spread of dengue was further enhanced during the following decades by the rapid increase in air travel, further population dislocations, uncontrolled urbanization and population growth, substandard housing and continual poor public health measures in many endemic countries.

Reports in both the scientific and the popular press indicated that 2001 saw the highest level of dengue activity ever recorded, with the disease being reported in over 100 countries, giving dengue a global distribution akin to that of malaria (Halstead, 2002). In 2001 alone epidemics occurred in Brazil, Cambodia, Colombia, Cuba, Ecuador, Laos, Malaysia, Myanmar, Peru, Thailand, Venezuela and Viet Nam. Moreover, no outbreak had been reported in Cuba for 20 years, due to effective vector control, and that in Hawaii was the first since the Second World War, sending a clear warning that dengue can readily return to countries from which it has been eradicated. The most dramatic increase in dengue activity has been in the Americas. In 1970 only dengue virus type 2 was present there, and even then in just a few countries, but now epidemics involving all four serotypes have been reported in most states. In 2001 the number of cases reported was more than double that seen in 1995, and in 2002 over 30 Latin countries reported more than a million cases of dengue fever, with over 17,000 cases of DHF in 20 countries.

Dengue fever is a severe public health problem in tropical countries, with attack rates among susceptible populations frequently ranging from 40 to 50%, or as high as 80–90% in some cases. Of the 500,000 cases of DHF that require hospitalization every year, death rates between 2.5 and 5% are recorded, but they can be as high as 20% in very young children if the appropriate treatment is not administered rapidly (Halstead, 1999). However, fatalities can fall to well below 1% with modern supportive therapy.

Dengue fever is characterized by an abrupt onset of high fever, accompanied by headache and myalgia. These symptoms can be debilitating: hence the nickname "breakbone fever". The more severe disease form, DHF, is graded according to four levels. Symptoms for grades I–III include spontaneous bleeding from the skin, nose and gums and circulatory failure or hypotension. Patients with grade IV disease are moribund, with no detectable pulse or blood pressure. References to DSS refer to patients with grade III or IV disease (McBride and Bielefeldt-Ohmann, 2000). However, because of difficulties in applying the current clinical case definitions, a...
series of alternatives has been proposed (Rigau-Perez and Bonilla, 1999).

2. Current treatments and control measures

There are no specific therapies or licensed vaccines for dengue. However, careful case management, centred on the maintenance of circulating body fluids, saves many lives. Disease control has concentrated on reducing vector populations, and routine measures usually include the application of larvicides to potential breeding sites such as water storage vessels and areas of open standing water (Putnam and Scott, 1995). During disease outbreaks, emergency control measures may also be initiated. These can include the spraying of adult insecticides from hand-held devices, vehiclemounted machines or aircraft, but in the last few decades ultra-low-volume space spraying has been increasingly used, a technique that can be ineffective against Aedes species if applied at the wrong time and using the wrong strategy. Thus, effective killing is transient and may not penetrate to indoor microhabitats. It is also costly and operationally demanding, and it requires regular monitoring of insect susceptibility to the insecticides.

3. Characteristics of virus and vector that enhance disease morbidity

In addition to the societal factors mentioned above, several characteristics of the virus, its vector and the immune response it elicits militate against the control of all forms of dengue. Dengue virus is a member of the Flaviviridae virus family and therefore contains a single-stranded, positivesense RNA genome. Mutation rates in viruses with RNA genomes can be six orders of magnitude greater than agents with DNA genomes, as no proof-reading enzymes are available for RNA-dependent RNA polymerases. Consequently, antigenic variants arise rapidly, live attenuated vaccines can in some circumstances revert to a virulent phenotype comparatively easily, and inter-virus genetic recombination can occur (Holmes and Twiddy, 2003; Seligman and Gould, 2004). In addition, there are four virus serotypes, and immunity to any one serotype does not protect against infection by the others, and in certain circumstances may enhance disease severity.

The behaviour of the main urban mosquito vector A. aegypti also contributes significantly to the spread of disease (Putnam and Scott, 1995). This vector has now spread throughout the tropics, and infected females are capable of transmitting the virus throughout their lives and by transovarial transmission to their offspring. Each mosquito can be infected by several virus subtypes without any direct pathogenic effects on the vector or effects on virus yield. Its feeding is easily interrupted, and as viraemia in humans can last up to 7 days, probing of several hosts can result in the spread of virus to a number of individuals. In tropical areas, transmission can occur throughout the year, although it is increased during the rainy season. The preferred vertebrate hosts for the mosquito vectors of dengue are humans, but in Africa, Southeast Asia and perhaps India there is evidence that the virus can be maintained in enzootic and epizootic sylvan cycles in non-human primates (Gubler, 1997). Recently, transmission of dengue by A. albopictus has also been demonstrated, increasing the potential geographic spread of these viruses.

4. The role of the immune response in DHF and DSS

Case series studied by Halstead and colleagues reported that DHF/DSS is 15–80 times higher in secondary infections than in primary infections and positively associated with pre-existing dengue-virus-specific antibodies (Halstead, 1982).

The many factors influencing antibody-dependent enhancement of infection (ADE) in vitro have been reviewed elsewhere (Halstead, 2003). A crucial component in this phenomenon is the presence of Fcγ receptors on the surface of a permissive cell, usually a member of the mononuclear phagocytic lineage. Complexes containing virus-specific antibody and the Fcγ receptor together appear to act as co-receptors, enhancing the efficiency of virus binding and increasing the number of infected cells. Thus, it could be hypothesized that in the infected patient pre-existing antibody could result in higher viral load, shortened incubation time and increased disease severity. Moreover, as many components of the cell-mediated immune system display Fcγ receptors on their cell surface, ADE could result in the destruction of these cells and further compromise recovery from disease.

ADE has been well documented in vitro, but despite several clinical studies, evidence for the role of ADE in human disease remains circumscribed. Consequently, many other hypotheses explain-
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The rapid rise in dengue and continue to do so. Moreover, the nature of the virus, its mosquito vectors and the immune response it generates all contribute to difficulties in controlling dengue. Although no vaccine is currently available, there are several candidates progressing through formal evaluation protocols. This progress should be enhanced by the announcement in 2001 of the Paediatric Dengue Vaccine Initiative, which should provide a network of phase 3 clinical trials to evaluate vaccine candidates (Almond et al., 2002). However, a licensed vaccine is several years away and there is still considerable development work to be done, while dengue is an escalating global problem now. Fatalities can be dramatically reduced by the rapid application of appropriate clinical care, and this must be made widely available. A dramatic improvement in the application of fundamental public health measures is also urgently needed, as well as better planning and strategic application of vector control measures.

5. Vaccine development

Although no licensed vaccine is available to combat dengue, a substantial amount of research has been undertaken over many years and in several countries. As a result, a number of conventional and novel vaccines are being developed and several are undergoing clinical trials (Jacobs and Young, 2003). Two classical live attenuated tetravalent dengue vaccines have been developed by repeated passage in cell culture. A vaccine developed at Mahidol University in Bangkok has been licensed to Aventis Pasteur, and another, developed at the Walter Reed Army Institute for Research in the USA, has been licensed to GlaxoSmithKline. Initial clinical trials of these vaccines have shown that both are capable of inducing an immune response to all four dengue serotypes. In addition, genetic manipulation techniques have produced infectious virus clones, which form the basis of several novel vaccine candidates. All these potential novel vaccines use an attenuated virus (either the 17D yellow fever vaccine virus or an attenuated dengue virus) as a backbone. Potential vaccines have been created by inserting the preM and E genes of one or more serotypes into the structural gene regions of the parent virus. These vaccine candidates have been shown to produce an immune response in mice, non-human primates or human volunteers. In addition to these chimeric viruses, dengue genes have been inserted into plasmids, vaccinia virus and defective adenoviruses by several research groups, with varying degrees of success. Most of the current vaccine candidates have relied on the E protein to produce an immune response. However, it is a relatively poor stimulator of cell-mediated immune reactions and could induce disease-enhancing antibodies. Consequently, several groups have produced vaccine candidates that rely on the NS5 protein, and many of these products have been shown to induce virus-specific immunity (Timofeev et al., 2004). The NS3 protein could also be a useful additional vaccine component, as it does not induce neutralizing antibodies but is the most potent stimulator of cell-mediated immunity.

6. Conclusions

Increased human activity, societal disruption and unplanned urban growth have contributed to the

References


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