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Update on the global spread of dengue

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ABSTRACT

The global spread of dengue fever within and beyond the usual tropical boundaries threatens a large percentage of the world's population, as human and environmental conditions for persistence and even spread are present in all continents. The disease causes great human suffering, a sizable mortality from dengue haemorrhagic fever and its complications, and major costs. This situation has worsened in the recent past and may continue to do so in the future. Efforts to decrease transmission by vector control have failed, and no effective antiviral treatment is available or foreseeable on the immediate horizon. A safe and effective vaccine protective against all serotypes of dengue viruses is sorely needed.

1. Introduction

Dengue fever (DF) causes enormous suffering to mankind. DF is a mosquito-borne disease caused by any one of four dengue fever virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) belonging to the genus Flavivirus, family Flaviviridae. They are spherical, lipid-enveloped, 40–50-mm single-stranded RNA particles that share structural and pathogenic features but have distinct genetic and serological characteristics. The relationships between the serotypes and transmission efficiency or disease expression are uncertain, but DENV-2 and DENV-3 are likely to contribute the most to disease severity and mortality.

The detection of dengue antibodies in the sera of non-human primates in forest or scarcely populated settings in Asia and Africa suggests that these animals are involved in DF virus enzootic transmission, but the relationship of this phenomenon to human infection is unknown [1]. Several species of non-human primate have been experimentally infected since 1914. These animals are susceptible in terms of viraemia and development of an antibody response, but they do not exhibit detectable clinical signs of DF [2]. Humans can be infected from non-human primates under certain laboratory conditions [3,4].

Dengue fever viruses are overwhelmingly transmitted between persons by female *Aedes* mosquitoes. *Aedes aegypti* and *Aedes albopictus* are highly competent, efficient and adaptable species that remain closely associated with humans, water and domestic/peridomestic environments. Mosquitoes breed outdoors but take shelter indoors and commonly feed in either surroundings flexibly around sunrise and sunset. Transmission occurs subsequent to mosquitoes feeding on an infected individual during the period of viraemia and following an arthropod phase of extrinsic incubation; henceforth the mosquito probably remains infectious for life. Transfusion, transplant and transplacental transmission are quite rare.

After human inoculation the incubation period varies between 2 days and 2 weeks. Clinical variability ranges from asymptomatic seroconversion to devastating and even lethal disease. Children commonly experience undifferentiated fever; adults typically have fever and chills, headache (often retro-orbital), severe malaise and musculoskeletal pain. Exanthema, leukopenia and thrombocytopenia are common, as are transaminase elevations. The widespread use of imaging procedures has uncovered the otherwise unapparent but frequent occurrence of pleural, pericardial or peritoneal effusions. Haemorrhagic manifestations may be unapparent, barely detectable or extremely severe and may be the cause of death. Capillary leak and hypovolaemia are characteristic of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) [5,6].

Although the three clinical presentations most commonly observed are undifferentiated febrile illness, DF (also termed classical dengue) and DHF (complicated or not by DSS), atypical forms such as severe hepatitis, myocarditis and encephalopathy, among others, are being seen more often in endemic areas. A very long homotypic immunity notwithstanding, heterotypic neutralizing immunity is short-lived, and inoculated individuals can be infected by other serotypes and become ill after a few months. A subsequent infection by a different serotype may be responsible for amplification of the infection by antibodies, resulting in greater viraemia and severity of the clinical manifestations – the antibody-dependent enhancement mechanism [7,8].

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2. History

Human dengue fever is possibly as old as humanity [9]. The first available records suggesting potential cases of dengue fever are found in a Chinese medical encyclopaedia from the Jin Dynasty for the years AD 265–420. The writings describe the disease, with an epidemiological insight, as 'poison water' associated with flying insects. Some two thousand years later, the first outbreaks of an illness compatible with classical dengue fever took place in the Caribbean in 1635 and 1699, long before the reported simultaneous epidemics of 1779 and 1780 that came about in Asia, Africa and North America. These reports strongly suggest that 200 years ago the distribution of vectors was widespread [10]. In 1789 Benjamin Rush reported the first definitive case of the disease and coined the term 'breakbone fever'. Since then, major outbreaks have been recognized worldwide every 20–40 years. The absence of epidemic dengue from 1946 to 1963 can be attributed to the partial success of the *Aedes aegypti* eradication programmes designed to prevent urban yellow fever [11,12]. Since then the region has been widely reinfested and dengue has re-emerged.

World War II caused significant ecological and demographic changes that facilitated the transmission and spread of dengue in the Asia–Pacific region, including high mobility of civilians and soldiers and increased numbers of susceptible individuals in endemic areas. Transport of cargo, economic expansion and continuous urbanization facilitated the movement and breeding of adult vectors, and propagation of the viruses [13,14].

3. Current situation

Dengue is endemic to tropical and subtropical countries and is the arboviral disease that has spread most rapidly among the tropical and subtropical regions of the planet. It also behaves in an epidemic fashion when appropriate conditions exist. The occurrence of conditions that favour endemicity and epidemicity, namely the presence of large territories with *Aedes* mosquito infestation, sizeable susceptible human groups and the continuous introduction and/or circulation of one or more serotypes are factors responsible for endemic and epidemic DF and DHF [15]. Environmental parameters such as temperature and precipitation affect the demography and behaviour of *Aedes* vectors, therefore climate, the disordered increase in the global population, international travel, poverty and lack of sustained programmes at various levels [13] are assumed to be contributing factors. However, the specific contribution of each factor is difficult to measure. For example, it has recently been noted that there is no consistent or unequivocal association between DF epidemiology and the El Niño Southern Oscillation climate pattern [16].

DF transmission occurs in more than 100 countries in the Asia–Pacific region, the Americas, the Middle East and Africa, and numbers of cases continue to rise [17,18]. It is estimated that about 2.5 billion individuals, a staggering 40% of the world population, inhabit areas where there is a risk of transmission of DF [19] and that the disease burden has increased at least fourfold in the last three decades. Modelling also suggests that approximately 50–100 million human infections occur annually, of which about 500 000 are DHF. WHO estimates 22 000 deaths per year, chiefly in paediatric patients. Further, in endemic regions, the probable DF disease load in disability-adjusted life years is high – 0.42×1000 population. In South East Asia and the Western Pacific region the attack rate can reach $6400 \times 100\,000$ population, but a steep rise has been reported in the Americas during the last decade.

3.1. The Americas

The epidemiology of dengue in the Americas has recently been reviewed. Although transmission follows a seasonal pattern, a 4.6-fold increase in reported cases has been observed consistently over the last three decades [20]. In an analysis of Pan American Health Organization information, the total dengue cases reported increased dramatically from 1 033 417 (16.4/100 000) during the 1980s, to 2 725 405 (35.9/100 000) during the 1990s and 4 759 007 (71.5/100 000) during 2000–7. Similarly, the number of DHF cases increased from 13 398 during the 1980s, to 58 419 during the 1990s and 111 724 during 2000–7, a worrisome 8.3-fold increase. Brazil reported the most dengue cases (54.5%) during the 27-year study period but ranked sixth in total DHF cases. Venezuela reported the highest number of DHF cases (35.1%) during the same period [20].

Molecular epidemiology data strongly suggest that the situation is extremely variable. DENV-3, for example, has been introduced into Brazil at least twice and into Paraguay from Brazil at least three times [21]. Multiple lineages have circulated in Puerto Rico since 1980 [22], and the invasion and maintenance of DENV-2 and DENV-4 in a clear geographic structure supports diversity between outbreaks [23]. Available data imply that the most frequent serotypes in Latin America in the last three decades have been DENV-1, DENV-2 and DENV-3. Most DF patients have been adolescents and young adults, but in Venezuela DHF incidence has been higher among infants.

Recent outbreaks in the region include large and densely populated areas such as Rio de Janeiro in 2002 and 2008, Bolivia in early 2009 and, most recently, in the northern provinces of Argentina. The disease has spread as far as Buenos Aires [24,25].

In the USA, imported DF cases have been reported in the 48 continental states among travellers and immigrants. Secondary transmission seems to be a rare phenomenon. Outbreaks have taken place in Hawaii in 2001 and Texas in 2005. Puerto Rico reports most cases in US citizens [26].

3.2. Asia

Dengue emerged as a public health problem in South East Asia during World War II. The urbanization that began after the end of the war continues, and the resulting population growth has facilitated the continuing epidemic of virus in the region.

The Philippines recorded its first epidemic of dengue haemorrhagic fever in 1953/1954, followed by another in 1958, and Thailand reported an outbreak in Bangkok in the 1950s. Since then the cyclical epidemics have continued, becoming greater in magnitude. Asian countries with the highest number of dengue cases are Vietnam, Thailand and the Philippines. In all these countries there is movement of the four serotypes of the virus. Reports from the Queen Sirikit Institute of Child Health in Bangkok confirm the presence of all four serotypes with a variable dominance. These reports have been able to differentiate cases of primary infection from reinfection, showing that 87% of cases in Thailand are reinfections and only 13% are primary infections. This observation allows us to understand the degree of hyperendemic transmission in the region [27,28].

Twenty percent of the world's population, some 1 300 000 people, live in China. One-fifth of the country falls within tropical latitudes and therefore has an increased risk of transmission of dengue. Various reports of outbreaks of dengue came from China in the 1980s and 1990s but since 2003 the WHO has not received any reports of dengue in China, making it impossible to determine the real situation in the country [29].

India, the second most populous country in the world, has reported outbreaks of dengue fever and dengue haemorrhagic fever since 1945. Reports from Delhi and other cities have increased in

recent years, with additional evidence of movement of the four serotypes. Additionally, there is evidence of active transmission not only in cities but also in rural areas [30].

3.3. Africa

It is known that the dengue virus has circulated in the African continent since the early 20th century. Despite the lack of epidemiological surveillance, reports from different African countries (Seychelles, Kenya, Mozambique, Sudan, Djibouti, Somalia, Comoros, Nigeria, Senegal, Burkina Faso) have revealed that outbreaks of the four serotypes have increased dramatically since 1980, although they are still rare when compared with South East Asia and the Americas [31].

3.4. Europe

In Europe, imported DF is the most common cause of fever in returning travellers [32]. Data from the European Network on Imported Infectious Disease Surveillance (TropNetEurop), which assesses approximately 12% of European patients with imported infectious diseases, suggest that the number of imported dengue cases in Europe increased from 64 in 1999 to a maximum of 224 in 2002 and has since remained at 100–170. In 2008, 116 cases were reported, mostly in European travellers; 43% had travelled to Europe from South East Asia, 14% from Latin America, 12% from the Indian subcontinent, 11% from the Caribbean and 4% from Africa, reflecting worldwide dengue activity and travel preferences.

Since established homogeneous populations of *Aedes albopictus* have been identified in European countries, and data exist suggesting that most of Europe will become favourable for *Aedes albopictus* establishment, its spread to Europe is anticipated [33,34].

4. Conclusion

Cumulatively, DF and DHF have had a major negative impact on the lives of billions of people in all tropical and subtropical regions. Mortality is appreciable and economic losses incalculable. The incidence of the disease in South America and the Caribbean has risen dramatically in recent decades. The burden of the disease continues to be very high in the Asiatic continent, particularly in South East Asia, and cases continue to be found in Africa and even Australia. In North America and Europe, the established populations of *Aedes* vectors and continuing travel and migration provide an opportunity for large and severe outbreaks in a massive susceptible population.

Given the above facts, the reality that community-driven mosquito control measures have failed and the absence of an effective vaccine, more suffering can be anticipated. The ongoing development of a chimaeric tetravalent immunogen does, however, represent a hope for current and future generations.

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