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Dengue in children

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Summary Dengue is a mosquito-borne viral disease of expanding geographical range and increasing incidence. The vast majority of dengue cases are children less than 15 years of age. Dengue causes a spectrum of illness from mild fever to severe disease with plasma leakage and shock. Infants and children with secondary heterologous dengue infections are most at risk for severe dengue disease. Laboratory diagnosis of dengue can be established within five days of disease onset by direct detection of viral components in serum. After day five, serologic diagnosis provides indirect evidence of dengue. Currently, no effective antiviral agents are available to treat dengue infection. Therefore, treatment remains supportive, with emphasis on close hematological monitoring, recognition of warning signs of severe disease and fluid-replacement therapy and/or blood transfusions when required. Development of a dengue vaccine is considered a high public health priority. A safe and efficacious dengue vaccine would also be important for travelers. This review highlights the current understanding of dengue in children, including its clinical manifestations, pathogenesis, diagnostic tests, management and prevention.
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Introduction

Dengue has emerged as an increasing public health problem over the past 50 years, particularly in southeast Asia and Central and South America.[1] It has been suggested that there is also a substantial level of dengue transmission in Africa.[2] The vast majority of dengue cases, nearly 95 percent, are children less than 15 years of age.[3] Dengue virus belongs to the family *Flaviviridae*, genus *Flavivirus*. It is a vector-borne disease transmitted to humans by *Aedes* mosquitos, mainly *Aedes aegypti*. This is a day-biting mosquito that preferentially feeds on humans, taking multiple blood meals from one or several human hosts. They breed in containers and are closely associated with human dwellings, thus transmitting virus at higher rates in urban settings. The geographical range of a secondary dengue vector, *Aedes albopictus*, has expanded substantially over the past 30 years. However, this is a less efficient vector and is currently not seen as a major contributor to dengue transmission.[4] The term 'dengue virus' refers to a group of

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four genetically and antigenically related viruses that are known as serotypes (DENV-1 to DENV-4).

Global distribution and burden of dengue

The urban-adapted *A. aegypti* mosquito is widely distributed across tropical and subtropical regions. Emerging from Africa during the slave trade, dengue spread into Asia through commercial exchanges in the 18th and 19th centuries, and the virus has spread globally with an increase in travel and migration in the past 50 years.[5] Rapid population growth and urbanization have resulted in a higher availability of vector breeding sites. Efforts to control dengue benefited from an elimination campaign in the mid 20th century. In 1947, the Pan American Health Organization (PAHO) adopted a proposal by Brazil for an eradication program to remove the *A. aegypti* vector. The aim of this campaign was eradication of urban yellow fever, which shares the same vector as dengue. The successful elimination of *A. aegypti* from nineteen South and Central American countries resulted in the Americas being an almost dengue-free zone from 1952 to 1965. Unfortunately, this campaign reversed to a strategy of control because of reduced political will and insufficient financing and the first reports of dengue disease occurred soon after in 1968.[6] Since its re-emergence in South and Central America, dengue has spread rapidly throughout the region and children have become increasingly affected with severe disease.[7] In Asia, an elimination goal for dengue or its vector has never been proposed.[8] National surveillance data from Asian countries show that infants under 1 year of age and children aged 4—9 years have consistently been at the highest risk for severe dengue disease.[9,10]

While the historical expansion of dengue disease is well documented, the current morbidity burden attributable to dengue is poorly defined. A map of the current distribution of dengue virus transmission that quantifies dengue virus transmission based on available global evidence is presented in Fig. 1.[2] Global estimates of dengue virus infections based on an assumed constant annual infection rate among a crude approximation of the population at risk have yielded figures of 50—100 million infections per year. This number is widely cited and currently used by the World Health Organization (WHO).[1] However, profound search for known records of dengue worldwide by Bhatt et al. estimated that 390 million dengue infections occur per year: 96 million manifesting as clinically apparent and 294 million manifesting inapparently.[11] This number is more than three times the dengue burden estimate of the WHO.[1]

Children with mild dengue infection do not generally require hospitalization and mild or asymptomatic dengue infections are often not detected by the public health surveillance system. However, the presence of this potential reservoir of infection has profound implications for: (1) correctly enumerating economic impact and triangulating with independent assessments of disability adjusted life years (DALYs),[12] (2) elucidating the population dynamics of dengue viruses,[13] and (3) making hypotheses about population effects of future vaccine programs[14], as outlined by Bhatt et al.[11]

Clinical manifestations of dengue disease

Dengue virus infection is often inapparent,[11,15] but can lead to a wide range of clinical manifestations, from mild fever to plasma leakage and the potentially fatal dengue shock syndrome.[1] The clinical manifestations of dengue in infants differ, with a greater frequency of plasma leakage and shock compared with dengue in older children.[16,17] Dengue disease was originally classified by the WHO into dengue fever, dengue hemorrhagic fever and dengue shock syndrome.[18] However, as dengue spread worldwide, it became evident that this classification was not universally applicable for clinical management.[19] In 2009, the WHO issued a revised classification which distinguishes between severe and non-severe dengue.[1] Severe dengue is also known as

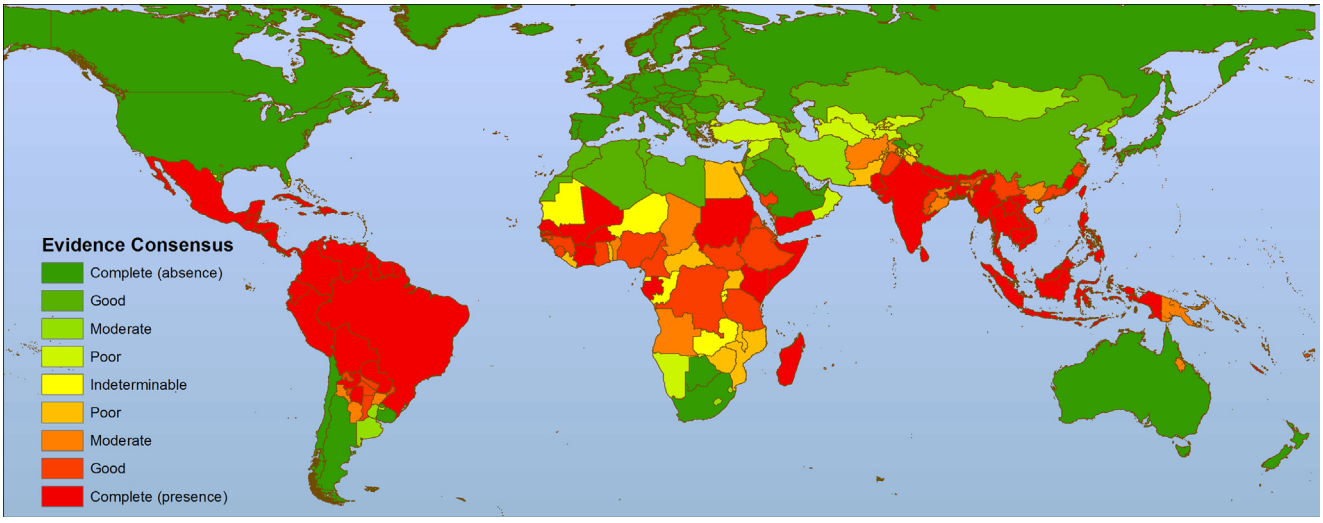

Figure 1 National and subnational evidence consensus on complete absence (green) through to complete presence (red) of dengue, from Brady et al.[2]

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