STATE-OF-THE-ART REVIEW

The Burden of Dengue and Chikungunya Worldwide: Implications for the Southern United States and California

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ABSTRACT

Background: Dengue virus (DENV) spreads to humans through the bite of an infected *Aedes aegypti* or *Aedes albopictus* mosquito and is a growing public health threat to both industrialized and developing nations worldwide. Outbreaks of autochthonous dengue in the United States occurred extensively in the past but over the past 3 decades have again taken place in Florida, Hawaii, and Texas as well as in American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and the US Virgin Islands. As the *Aedes* vectors spread worldwide it is anticipated that DENV as well as other viruses also transmitted by these vectors, such as Chikungunya virus (CHKV), will invade new areas of the world, including the United States.

Objectives: In this review, we describe the current burden of dengue disease worldwide and the potential introduction of DENV and CHKV into different areas of the United States. Of these areas, the state of California saw the arrival and spread of the *Aedes aegypti* vector beginning in 2013. This invasion presents a developing situation when considering the state's number of imported dengue cases and proximity to northern Mexico as well as the rising specter of chikungunya in the Western hemisphere.

Findings: In light of the recent arrival of *Aedes aegypti* mosquito vectors to California, there is now a small but appreciable risk for endemic transmission of dengue and chikungunya within the State. It is likely, however, that if DENV or CHKV were to become endemic that the public health situation would be similar to that currently found along the Texas-Mexico border. The distribution of *Aedes* vectors in California as well as a discussion of several factors contributing to the risk for dengue importation are discussed and evaluated.

Conclusions: Dengue and chikungunya viruses present real risks to states where the *Aedes* vector is now established. Scientists, physicians, and public health authorities should familiarize themselves with these risks and prepare appropriately.

Key Words: arbovirus, antiviral, California, chikungunya, dengue, flavivirus, vaccine

INTRODUCTION

In terms of the population size at risk and economic burden, dengue remains the most globally important mosquito-transmitted viral infection.[1] Dengue virus (DENV) is a vector-borne flavivirus, a genus that also includes the West Nile (WNV), yellow fever, and Japanese encephalitis viruses. Dengue virions are spherical, approximately 50 nm in diameter, and feature a host-derived lipid bilayer containing a single copy of the approximately 11,000 base pair positive-sense single-stranded RNA genome coding for 3 structural (PrM, C, and E) and 7 nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5).[2,3] There are 4 antigenically distinct DENV serotypes in circulation among humans, DENV-1 through DENV-4.[4-6] A potential fifth serotype, DENV-5, was recently isolated from a patient in Borneo; however, it remains unclear if this virus is capable of sustained transmission between humans.[7] Although infection with a particular serotype will confer lifelong immunity to that strain, this protection is generally weak and short-lived against the other DENV serotypes, lasting around 2 to 3 months at most.[3,4,8] Indeed, infection with a heterologous subtype is correlated with more severe disease, likely as a result of antibody-dependent enhancement (ADE).[9-11] By this mechanism, antibodies raised against the previously

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encountered serotype bind to the new virus type and promote their entry into leukocytes harboring the Fc receptor glycoprotein on their surface.[12,13]

The majority of DENV infections are asymptomatic and consequently difficult to detect. When disease does become apparent, symptoms are generally self-limiting and range from lethargy, fever, and rash to organ failure and hemorrhage. Dengue cases may be classified as either (typical) dengue or severe dengue, with the latter characterized by severe plasma leakage (leading to shock, known as dengue shock syndrome, or fluid accumulation and respiratory distress), bleeding, and/or significant organ impairment.[3,4] The case fatality ratio for severe dengue has ranged from 20% in some outbreaks to less than 1%.[3,14] Up to 90% of severe dengue cases are the result of a secondary heterotypic infection, with the remaining percentage resulting from primary infections of infants younger than age 1.[15] The incidence of severe dengue in infants may be due to the maternal transmission of non-neutralizing antibodies that facilitate antibody-mediated enhancement, a hypothesis that was recently supported by in vivo experiments in mice.[16,17] Several other risk factors for severe dengue have been described and include virus strain, host genetics, female sex, obesity, youth, chronic disease, ethnicity, and heterosubtypic infection.[3,4]

The clinical course of dengue begins after a 3- to 7-day incubation period and may last for ≥10 days. Once symptoms begin, the patient is capable of transmitting the disease to an *Aedes* spp. mosquito vector. The initial febrile phase may last for up to a week and is characterized by a high fever (>38.5°C), arthralgia, headache, vomiting, rash, and/or mild hemorrhagic symptoms such as petechiae or bruising. Although the majority of cases will spontaneously recover following the febrile stage, a small number of patients, primarily children or young adults, will progress to the critical phase that is characterized by increased vascular permeability and resultant hemorrhage (severe dengue/dengue hemorrhagic fever or shock), leading to death. The critical phase generally begins around defervescence and may last ≤4 days. At the end of this phase, patients will enter the final period of spontaneous recovery during which they experience a rapid improvement of their condition.[3,4] There is some evidence for a "post-dengue syndrome" in patients recovering from apparent disease that is characterized by persistent fatigue, arthralgia, myalgia, and malaise ≤2 years after their illness.[18]

DISTRIBUTION AND GLOBAL BURDEN OF DISEASE

Dengue is, at its core, a global disease. Around 2.5 billion people, or 35% of the global population, live in a region where dengue is endemic.[1] The speed with which dengue spreads worldwide to become a global health concern is alarming: Before 1970, only 9 countries had reported outbreaks of severe dengue. By 2014, this number had grown to include >100 countries in Africa, North and South America, southeast Asia, Europe, and the Pacific reporting severe dengue outbreaks.[19] The World Health Organization (WHO) estimates that 50 million to 100 million dengue infections occur each year, around 500,000 of which will proceed to severe dengue resulting in >20,000 deaths, primarily among pediatric cases[9,19] (Fig. 1). The WHO figure of 50 million to100 million cases of dengue each year was derived by extrapolating from ratios of dengue cases to severe dengue cases and deaths resulting from severe dengue cases.[20] A more sophisticated approach involving data from the literature and online resources reporting areas of dengue occurrence yielded an approximation of 96 million apparent DENV infections out of 390 million overall infections per year.[21] Of the apparent infections, 70% occurred in Asia, with half of those infections occurring in India alone. Despite these estimations, some have argued that dengue is widely and acutely underreported across the subcontinent.[22] Africa and the Americas bore around 14% of the global total each; however, it is widely thought that surveillance in Africa is inadequate largely due to underreporting and the difficulty of the differential diagnosis versus other endemic viral diseases on that continent. Within the WHO southeast Asia region, which includes around half of the 2.5 billion people living in dengue-endemic countries, costs associated with dengue treatment and vector control averaged $950 million 2010 USD^{2010} per year between 2001 and 2010.[23,24] The economic and societal costs of dengue in the Americas is even steeper at an estimated at $1billion to $4 billion USD^{2010} each year.[25] Approximations of annual aggregate direct medical care costs in individual countries are large (all values are in USD^{2010}): India spends $521 million, the Philippines $328 million, Puerto Rico $38.7 million, and Malaysia $57 million.[26-29] In Singapore alone, the economic burden of dengue is around $1 billion USD^{2010}, half of which is spent solely on vector-control efforts.[30] Worldwide, estimates are as high as $39 billion USD^{2010} per year on the costs of medical care, surveillance, vector control, and lost productivity.[31] The direct and indirect costs of dengue are substantial and are likely an enormous burden on the developing tropical nations where dengue is most often endemic.

HISTORY OF DENGUE VIRUS AND DENGUE HEMORRHAGIC FEVER

Ancestral dengue virus arose 1000 to 2000 years ago among monkeys in either Africa or Asia; DENV-1 and DENV-2 probably emerged much more recently, perhaps within the past 3 centuries.[32,33] Descriptions of the disease have existed in the medical literature for ≥130 years and reports of a dengue-like illness are found in Chinese