

Dengue and Hemorrhagic Fever

A Potential Threat to Public Health in the United States

David M. Morens, MD

Anthony S. Fauci, MD

MOST INDIVIDUALS IN THE UNITED STATES ARE AS little concerned about dengue fever as they were a decade ago about West Nile fever. That situation could change if dengue continues its expansion as one of the world's most aggressive reemerging infections. After decades of absence in the United States, the sometimes deadly disease is again striking US individuals, causing an epidemic in Hawaii in 2001,¹ appearing with increasing frequency along the Texas-Mexico border,² returning with unprecedented severity in US tropical territories and commonwealths such as Puerto Rico,³ and striking overseas travelers.^{4,5}

Widespread appearance of dengue in the continental United States is a real possibility. The range of *Aedes albopictus* ("Asian tiger mosquito"), a secondary dengue vector related to the classical vector, *Aedes aegypti*, has been expanding globally at an alarming rate, perhaps aided by global warming.⁶ Since its introduction into the United States in 1985, *Aedes albopictus* has spread to 36 states, bringing with it an increased risk of dengue outbreaks.⁷ Moreover, as dengue has reemerged throughout South and Central America and the Caribbean, its fatal form, dengue hemorrhagic fever (DHF),⁸ has appeared in many countries as well as in Puerto Rico.³ Between January 1, 2007, and November 30, 2007, the Pan American Health Organization received reports of 760 846 cases of dengue and 19 976 cases of DHF in the Americas.⁹ Globally, dengue and DHF case counts have been increasing steadily for more than 50 years. In the mid-1950s, annual case reports to the World Health Organization (WHO) totaled only approximately 900; by 2005, annual case reports had increased to nearly a million, submitted by more than 60 nations.¹⁰

Worldwide, dengue is among the most important reemerging infectious diseases with an estimated 50 million to 100 million annual cases, 500 000 hospitalizations (often requiring intensive care), and, by WHO estimates, 22 000 deaths, mostly in children.¹⁰ Fortunately, standardized therapy coupled with intensive education in many coun-

tries, most notably in Thailand, has greatly reduced case-fatality rates.¹¹ The economic and social effects of dengue are also enormous because the disease tends to occur in explosive epidemics that paralyze communities and sometimes entire nations.¹²

An explanation for why a group of viruses so well adapted to humans, having caused debilitating but nonfatal influenza-like illnesses for centuries, should suddenly expand geographically into new areas, and also turn more deadly, has proved elusive. The formidable challenges of understanding dengue pathogenesis and of developing effective therapies and vaccines must be met to effectively fight this important reemerging disease.

Dengue Viruses and Their Mosquito Vectors

Dengue is caused by any of 4 related flaviviruses, the viral family of yellow fever virus, West Nile virus, and Japanese encephalitis virus. Dengue viruses are maintained in continuous urban cycles of human-mosquito-human transmission. The classical vector, *Aedes aegypti*, is also the vector of yellow fever and the unrelated alphavirus chikungunya. Apparently dispersed from its ancestral African home by shipping and the slave trade,¹³ *Aedes aegypti* became established 400 or more years ago in tropical and subtropical settings worldwide, uniquely adapting to human peridomestic environments, supporting the subsequent global dispersion of dengue viruses. Today, *Aedes aegypti* is well established in much of the tropical and subtropical world. The alternative dengue vector, *Aedes albopictus*, appears to be continuing its geographic expansion into temperate climates, potentially worsening the global dengue situation.⁷

Dengue and DHF/Dengue Shock Syndrome

Although asymptomatic and mild cases are common, classic dengue fever is clinically similar to influenza, but with a variable and generally unimpressive maculopapular exanthem.¹⁴ Dengue hemorrhagic fever and its severe or fatal form, dengue shock syndrome (DSS), are complications defined by the WHO.^{15,16} The terminology is confusing, how-

Author Affiliations: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

Corresponding Author: David M. Morens, MD, National Institute of Allergy and Infectious Diseases, Bldg 31, Room 7A-03, National Institutes of Health, Bethesda, MD 20892 (dmorens@niaid.nih.gov).

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ever, because certain hemorrhagic signs (thrombocytopenia, epistaxis, petechiae) are also present in approximately 10% of uncomplicated dengue cases and are not by themselves predictive of disease severity, progression, or hypotension. Dengue-related shock results not from hemorrhage but from capillary leakage of intravascular fluids, electrolytes, and small proteins into perivascular tissues, leading to pleural and pericardial effusions, decreasing blood pressure, low tissue perfusion, and oliguria.¹⁵ Imminent development of shock, which can be predicted by a gradually increasing hematocrit over a period of several hours with normal hydration, requires cautious therapy with intravenous replacement solutions to expand intravascular volume without causing fluid overload. Such therapy generally produces dramatic clinical responses. Nevertheless, patients still die because of delayed treatment or uncommon complications.

Controversy Over the Pathogenesis of DHF and DSS

Increasing evidence suggests that the pathogenesis of DHF may result from a dynamic interplay between human population immunity and dengue virus evolution. Underlying factors associated with the post–World War II appearance of epidemic DHF included rapid urbanization and severe crowding in southeast Asia, providing a facilitative environment for co-circulation of multiple dengue serotypes. An important discovery in the 1960s was that DHF and DSS occurred predominantly in association with second dengue infections, and uncommonly in association with first, third, or fourth dengue infections,^{17,18} an observation since confirmed in many dengue epidemics. Moreover, DHF risk appears to depend on the sequence of infection with different virus serotypes (eg, in 1 study the dengue-1/dengue-2 sequence was most frequently pathogenic, followed by the dengue-3/dengue-2 sequence).¹⁹

In infants, however, DHF reveals an entirely different and highly unusual pattern in its association with first, as opposed to second, dengue infections, and in its confinement largely to the middle infant months (5–8 months²⁰). Among those common denominators shared by infant DHF cases associated with first dengue infections, and DHF cases in older children associated with second infections, is anti-dengue IgG antibody at low titer. In the first instance, such antibody is acquired transplacentally and in the second instance it is acquired naturally from an individual's first dengue infection. In the 1970s, this realization led to the still controversial hypothesis that antibody-dependent viral infection enhancement—a well-documented phenomenon associated with other virus families¹⁸—is involved in DHF pathogenesis.²¹ As predicted by *in vitro* studies,²² however, the pathogenesis of DHF and DSS may reflect a more complex interplay between viral phenotype, viral virulence, and host immunity.

A working hypothesis for disease severity posits that dengue viruses facing the pressures of high population immunity in hyperendemic areas are selected for survival in an immunological milieu of nonneutralizing cross-reactive antibodies elicited by prior infections with other dengue serotypes. Selected viruses are those most readily captured and bound to cell surfaces by nonneutralizing dengue antibodies via Fc-FcR interaction (antibody-dependent infection enhancement), thereby up-regulating infection.¹⁸ However, the possible roles of other antibody-associated phenomena have not been ruled out (eg, antibody-dependent cellular cytotoxicity or antibody pruning of the viral quasi-species to eliminate less pathogenic, in favor of more pathogenic, viruses). In any case, there is little understanding of how such viral or immunological phenomena might cause the capillary leak syndrome of DSS. Studies have suggested a pathogenic role for cytokines, including tumor necrosis factor α , IL-2, CCL2 (chemokine [C-C motif], ligand 2), and macrophage inhibitory factor, among others¹⁷; however, clear pictures of DHF and DSS pathogenesis have not resulted.

Dengue Vaccine Conundrums

The question of dengue pathogenesis is important in its own right, but more so because promising dengue vaccines are now under development, some already in phase 2 safety and efficacy testing.¹⁶ These include inactivated, live attenuated, chimeric, subunit, and DNA vaccines. If naturally and maternally acquired dengue antibody can precipitate severe disease on subsequent infection, will vaccine-induced antibody do the same? What are the indicators and correlates of safety and risk? How can vaccine safety be ensured? None of these questions can be adequately answered at present. A degree of comfort is provided by evidence that dengue disease severity seems to be unaffected by prior vaccination with other flavivirus vaccines (yellow fever and Japanese encephalitis vaccines).

Vaccines currently under development follow the strategy of attempting to elicit antibodies to each of the 4 dengue virus serotypes (they are intended to be quadrivalent vaccines containing critical protective epitopes from each serotype). Although this seems logical, it is not the strategy taken by nature—protection from DHF in natural settings apparently results from anamnestic antibody responses to noncritical epitopes shared by sequentially infecting serotypes, not by development of serotype-specific immunity to each of them.¹⁸ Regardless of the vaccine strategy pursued, a key remaining question is whether vaccines will elicit antibodies that decline over time to the point at which they no longer protect from but may enhance infection. This conundrum has implications for vaccination strategy, including whether only individuals with monotypic antibody patterns (evidence of a single, past dengue infection) should be recommended for vaccination.

Treatment, Control, and Prevention

There are no drugs for specific dengue treatment and no drug candidates in late-stage development.²³ Fluid and electrolyte therapy to treat the capillary leak syndrome of DSS and blood/blood product administration for hemorrhage are effective¹¹ but are not universally available in remote locales. Use of aspirin should be avoided. There are no data establishing the efficacy of glucocorticoids. Passive immunotherapy with convalescent plasma or monoclonal antibodies would be difficult because virus disappears by the time the shock syndrome begins, and because of the theoretical risk of antibody-mediated immunopathogenesis.

Vector control also has proven to be a difficult challenge.¹⁴ Following the banning of DDT, abandonment of *Aedes* eradication campaigns allowed mosquito populations to quickly rebound. Vector adulticiding with other agents proved to be less effective, and larval control and source reduction have been difficult to sustain in developing countries.¹⁴ Aggressive health education in Southeast Asia has informed citizens about dengue symptoms, treatment, and vector control and has undoubtedly saved lives but has not prevented epidemics. Mosquito bioengineering is being attempted by several research groups,²⁴ but its development appears to be at an early stage.

Conclusions

Dengue is among the most important globally reemerging infectious diseases. It already has reemerged in US tropical and subtropical locales and threatens temperate zones of the continental United States where mosquito vectors continue to expand in geographic range. In recent decades, dengue disease has followed vector expansion; DHF, a deadly but poorly understood complication, has tended to follow as well. The combined effects of global urbanization and increasing air travel are expected to make dengue a growing international health problem for the foreseeable future. Global deaths from DHF already rank with yellow fever in exceeding combined deaths from all other viral hemorrhagic fevers, including Ebola, Marburg, Lassa, Korean, and Crimean-Congo. Without specific therapy or fully effective vector control options, development of dengue vaccines protective against all 4 serotypes remains a top priority, but is complicated by technical challenges, lack of animal models, the need to raise protective immunity against antigens from 4 different viruses administered simultaneously, and safety concerns surrounding the possibility of vaccine-induced immune enhancement contributing to heightened pathogenesis.

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