Return of Epidemic Dengue in the United States: Implications for the Public Health Practitioner

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ABSTRACT

Conditions that facilitate sustained dengue transmission exist in the United States, and outbreaks have occurred during the past decade in Texas, Hawaii, and Florida. More outbreaks can also be expected in years to come. To combat dengue, medical and public health practitioners in areas with mosquito vectors that are competent to transmit the virus must be aware of the threat of reemergent dengue, and the need for early reporting and control to reduce the impact of dengue outbreaks. Comprehensive dengue control includes human and vector surveillance, vector management programs, and community engagement efforts. Public health, medical, and vector-control communities must collaborate to prevent and control disease spread. Policy makers should understand the role of mosquito abatement and community engagement in the prevention and control of the disease.

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Dengue has traditionally been characterized as a neglected tropical disease that primarily affects populations in developing countries.¹ In recent decades, however, this disease has gained a new foothold in developed countries around the world, particularly those with subtropical regions, and now threatens the United States.² During the last 20 years, dengue outbreaks have occurred in Texas,³ Hawaii,⁴ and now in southern Florida.⁵ These outbreaks have reaffirmed that the U.S. has the conditions for autochthonous (i.e., locally acquired) transmission of the dengue virus. Therefore, public health practitioners and clinicians should be alerted to possible cases among returning travelers and the threat of dengue reemerging in the U.S. in years to come.⁵

The reestablishment of dengue as a transmissible disease in the U.S. has significant implications for public health. We outline several public health imperatives for preventing, mitigating, and responding to dengue outbreaks. Specifically, our review highlights the unique aspects of recent dengue outbreaks in the U.S.; the role of vector management programs and their impact on controlling dengue spread; the principal signs, symptoms, and methods for diagnosis and confirmation of dengue illness; and the public health tools to help prevent and control dengue transmission.

BACKGROUND

Dengue is the most common and fastest-spreading mosquito-borne virus in the world. In fact, there has been a 30-fold global increase in the incidence of dengue in the past 50 years,⁶ with an estimated 50 million dengue infections now occurring each year.⁷ The World Health Organization estimates that approximately two-fifths of the global population (about 2.5 billion people) live in areas where the natural and social environment support dengue transmission, and where competent mosquito vectors are present.^{8,9}

Dengue is a *Flavivirus* that is associated with a spectrum of illnesses. There are four dengue virus serotypes—DEN-1, DEN-2, DEN-3, and DEN-4—the first three of which have been involved in recent outbreaks in the U.S. Notably, certain Asian genotypic strains within the DEN-2 serotype appear to be associated with more severe outbreaks and more severe disease, in terms of clinical symptoms and viremia, than are seen with other serotypes.^{10,11} Human infection with one serotype conveys serotype-specific lifetime protective immunity. However, individuals infected subsequently with another serotype are at risk for more severe disease manifestations, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

These complications presumably result from virus interaction with preexisting dengue antibodies from an antecedent infection.^{8,12} *Aedes* mosquito vectors are known to transmit the dengue virus, principally *Aedes aegypti* (*Ae. aegypti*) and *Aedes albopictus* (*Ae. albopictus*). *Ae. aegypti* is considered to be the more efficient vector for dengue.¹³ In the U.S., *Ae. aegypti* is present in significant numbers in the southern states and along the Eastern Seaboard.¹⁴ *Ae. albopictus* has a larger range in the U.S., which spans the South, the East Coast, and the Mississippi River Delta (Figure 1).^{15,16}

DENGUE IN THE AMERICAS: BRIEF HISTORY AND THE ROLE OF *AE. AEGYPTI* ERADICATION

Dengue pre-1850

Although dengue virus was not isolated until 1945,¹⁷ epidemiologic and clinical reports are consistent with the occurrence of dengue epidemics in larger U.S. cities, as far back as Colonial times. In 1780, a dengue-like outbreak was reported in Philadelphia, Pennsylvania, and in the 1820s, dengue outbreaks also occurred in Pensacola, Florida; Charleston, South Carolina; Savannah, Georgia; and New Orleans, Louisiana.¹⁸

Dengue: 1850–1945

During this period, dengue epidemics—some with tens of thousands of reported cases—occurred every few years in the southern U.S. In the late 1800s, the mosquito vector theory of disease showed that mosquitoes transmitted infections such as filariasis, malaria, and yellow fever. Mosquito-control programs, which began early in the 1900s in Havana, Cuba, and the Panama Canal Zone and later extended to most of Latin America, led to the virtual elimination of endemic yellow fever. These programs focused on reducing breeding habitats and killing larvae in containers, installing adequate sewage systems, fumigating via pesticides to kill adult mosquitoes, and clinical screening for the disease. In addition to these methods, later programs also successfully incorporated the use of dichlorodiphenyltrichloroethane (DDT). Successes in controlling yellow fever through mosquito-control programs led to a marked decrease in the incidence of dengue.^{19,20}

Dengue following World War II

The *Ae. aegypti* eradication program established by the Pan American Health Organization in the 1940s and 1950s to combat yellow fever was one of the most important factors in suppressing dengue in the U.S. through the 1970s.^{19,20} A reemergence of dengue infections in the Americas was evident in the 1980s with the occurrence of major epidemics of dengue in

Figure 1. Dengue vector populations (2009) and locally acquired disease in the United States (1980–2010)^a

^aAreas marked in black indicate counties where mosquito surveillance has shown the presence of *Ae. albopictus* and/or *Ae. aegypti*. These areas are vulnerable to dengue outbreaks. Unmarked areas do not necessarily indicate the absence of the vector, as, in some areas, this may be the result of limited surveillance. Information on mosquito populations used for this map is from the Centers for Disease Control and Prevention's ArboNet and Exotic Vectors database data, as compiled for 2009 by Dr. Chet Moore, Colorado State University. Reference: Moore C. Reported distribution of exotic vectors in the U.S., 2009. Fort Collins (CO): Colorado State University; 2010.

Ae. aegypti = *Aedes aegypti*

Ae. albopictus = *Aedes albopictus*

DEN = dengue

CDC = Centers for Disease Control and Prevention

countries that had been dengue-free for 35 years or longer.^{13,21,22} Several factors were associated with the expanded presence of dengue in the Americas at that time. First, the rapid increase in urban population density and vector breeding habitats provided ideal conditions for more widespread virus transmission. Second, support for mosquito-control programs waned, DDT use was banned, and mosquito control shifted to less effective methods, such as space spraying. Finally, increased globalization and travel led to the global movement of different dengue serotypes, and increased the opportunity for dengue to be introduced into susceptible areas.^{13,21–23} Dengue outbreaks have occurred throughout the Americas since the 1980s; however, the U.S. has only seen sporadic outbreaks, primarily along the U.S.-Mexico border.

Recent epidemics in the U.S.

In the past 60 years, the majority of cases reported in the U.S. have been imported, travel-associated infections in individuals returning from foreign endemic areas.²⁴ Case reports suggest that there are approximately 100 imported cases to the U.S. each year. Continually increasing international travel in recent decades, particularly to dengue-endemic areas, has increased the threat of dengue to the U.S.²⁵ In addition to travel-associated cases, a few notable dengue outbreaks involving autochthonous transmission have occurred in the U.S., while mosquito-control efforts have decreased in many parts of the country.

Hawaii, 2001–2002. In September 2001, the Hawaii Department of Health was notified of a suspect case

of autochthonous transmission, which was later confirmed by laboratory diagnosis. During the course of the outbreak investigation, 1,644 suspected cases were evaluated, and 122 cases of dengue were confirmed. While this outbreak was relatively small, the epidemic is notable for three reasons: (1) the 2001–2002 dengue epidemic was the first known occurrence of autochthonous transmission in Hawaii since 1944; (2) the vector responsible for the outbreak was *Ae. albopictus*, demonstrating this vector's competence in sustaining an epidemic in the absence of *Ae. aegypti*; and (3) it highlighted the vulnerability to dengue reintroduction of a susceptible population, in the setting of increasing circulation of the virus in the Pacific Basin region.⁴ In the spring of 2011, the Hawaii State Department of Health began investigating two confirmed and two suspected cases of autochthonous transmission.²⁶

Brownsville, Texas, 2005. Dengue activity in southern Texas demonstrates the significance of both imported cases from adjacent Mexico and the risk of rapid establishment of local transmission after importation of the virus. Limited outbreaks of locally acquired dengue have occurred sporadically in Texas along the border with Mexico since 1980.²⁷

In summer 2005, the city of Brownsville, Texas, confirmed three cases of autochthonous dengue and 24 cases of dengue in people who had traveled to Mexico. It was part of a much larger epidemic that included 1,251 cases of dengue in the bordering Mexican city of Matamoros. What was most significant about this outbreak was the number of severe cases of dengue (DHF) that occurred in Matamoros, where 17.8% of the 1,251 confirmed cases were DHF. However, during the preceding four years, only 3.7% of dengue cases in that region of Mexico had been classified as DHF.³ Reasons for the differences in the severity of disease between Brownsville and Matamoros are speculative but may be due to the introduction of a more virulent genotype of DEN-2.²⁸ Residents of both cities cross the border frequently, and the mosquito burden in the two locations is similar. However, living and working conditions differ between the two cities.²⁹

Dengue remains an ongoing threat to southern Texas; prevalence of immunoglobulin (IgG) antibody to dengue was 38% in a randomly selected cohort of 800 adults in Cameron County on the Texas-Mexico border. People born in Mexico had statistically significantly higher antibody prevalence compared with those born in the U.S.³⁰

South Florida, 2009–2010. In 2009 and 2010, Florida experienced its first documented cases of autochtho-

nous dengue since 1946. The first case, recognized in a woman who had traveled to Monroe County, Florida, was identified in September 2009. Subsequent investigation led to recognition of an outbreak in the Key West area of Monroe County. In 2009, 29 cases of locally acquired dengue were confirmed in Key West, and a serosurvey revealed that approximately 5% of Key West residents had been recently infected with dengue.⁵ During 2010, 67 cases of locally acquired dengue had been reported: 65 cases were in Key West, and one case each occurred in Broward County and in Miami-Dade County.³¹ As of the end of 2011, there were two locally acquired cases each in Miami-Dade and Palm Beach counties, and one case each in Hillsborough and Martin counties.³²

EVALUATION, DIAGNOSIS, CONFIRMATION, AND TREATMENT OF DENGUE ILLNESS

In 2010, dengue was added to the list of Nationally Notifiable Infectious Conditions,³³ signaling national concern about this public health threat and recognition by CDC of the need for increased surveillance and reporting. State reporting of dengue to CDC is voluntary. The presence of a non-travel-associated case of dengue should alert local public health authorities to the possible existence of an outbreak. Health-care providers also need to be alerted to this possibility. They should understand the spectrum of dengue illness, the importance of obtaining confirmatory specimens, and the process for reporting suspect cases of dengue.

Signs and symptoms of dengue illness

Of those experiencing their first dengue infection, children are more likely to be asymptomatic, and adults are more likely to be symptomatic. Most people with symptomatic illness will have uncomplicated dengue infection, presenting as undifferentiated fever or dengue fever. Severe dengue, seen in few infected people, manifests as DHF or DSS.

Classic dengue fever. People with classic dengue fever typically begin experiencing influenza-like symptoms about four to seven days after the infecting mosquito bite. Symptoms include joint pain, prostration, musculoskeletal pain, nausea, vomiting, and rash. Approximately three to four days into symptomatic illness, fever dissipates but may recur, giving the illness a biphasic or “saddleback” fever pattern. Hepatitis may also complicate the illness.³⁴ Current treatment for those with dengue fever is supportive care. Hemorrhagic manifestations, such as petechiae or gum bleeding, may also be seen in some patients.

Figure 2. Case classification for potential dengue cases^a

Disease case classification	Definition
Suspect	A clinically compatible case of dengue illness that is epidemiologically linked to a confirmed case
Probable	A clinically compatible case of dengue illness with laboratory results indicative of presumptive infection
Confirmed	A clinically compatible case of dengue illness with confirmatory laboratory results

^aAdapted from the Council of State and Territorial Epidemiologists' resource on Dengue Virus Infections in the Nationally Notifiable Conditions List, which is available from: URL: <http://www.cste.org/ps2009/09-ID-19.pdf>

Severe dengue: DHF and DSS. Severe dengue is mostly seen in people who are infected with a second dengue serotype, after having experienced a different dengue serotype infection at some time in the past. Infants with maternal antibodies to dengue are also at risk.³⁵ Patients with DHF experience the same symptoms as those with classic dengue fever, but at defervescence exhibit hemorrhagic manifestations and evidence of plasma leakage shown by hemoconcentration and pleural effusions. Approximately 20%–30% of patients with DHF will progress to DSS, the most severe form of the disease, with shock and severe swelling due to capillary leakage.³⁶ The early course of illness for both DHF and DSS is indistinguishable from classic dengue fever, and both DHF and DSS manifest following resolution of fever.³⁴ Vigorous supportive treatment, including strict attention to fluid and electrolyte balance, is the only available treatment and can reduce mortality to as low as 1% (Figure 2).⁸

Confirmatory diagnosis of dengue

When dengue fever is suspected, laboratory confirmation of illness is necessary to provide a diagnosis and prognosis, and to allow for public health reporting. As shown in Figure 3, several relatively simple steps are necessary to confirm diagnosis.³⁷

Three approved and commonly used clinical diagnostic tests are available in the U.S. for dengue: real-time polymerase chain reaction (RT-PCR), immunoglobulin M (IgM) antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), and IgG ELISA. Culture of the virus has largely been supplanted by RT-PCR methods. However, due to the natural history of dengue infection, many patients come to medical attention after the viremic phase of illness (i.e., the first five days of illness) when PCR may be negative,

leaving serologic assays as the chief means of diagnosis. The standards for serological analysis, IgM and IgG ELISA testing of blood, are the preferred and highly sensitive means of diagnosis.³⁴ As shown in Figure 4, ELISA testing can require up to three days for completion and should be performed after six days of illness have passed.³⁸

Role of early recognition

Early detection and knowledge of illness, timely reporting, confirmation, and rapid response are vital in dengue control.^{39,40} Because no specific antiviral treatment or vaccine is available, management of dengue outbreaks relies primarily on vector control. Health departments will require time to scale up vector-control activities, and the more lead time they have, the more efficacious the measures will be. Finally, early recognition allows for more timely communication with the public, which is important.

PROPOSED PUBLIC HEALTH TOOLS FOR MITIGATION OF DENGUE

Public health practitioners should have capabilities in place to recognize and respond to dengue outbreaks, control of which largely depends on disease surveillance, clinician awareness, and mosquito vector control. After identification of an outbreak, the following interventions are needed.

Figure 3. Testing^a for dengue infection in suspect patients

- Step 1: Obtain blood specimens from suspect patient to confirm infection.
 - First 5 days of illness: First blood sample.
 - 14–21 days after onset of illness: Second blood sample.
 - Note: If a patient is seen more than five days after onset of illness, only a single sample is needed.
- Step 2: Test of blood specimens for antibodies to dengue or the presence of the virus nucleic acid signatures by PCR.
 - ≤5 days after onset of illness: PCR is likely to be positive (definitive diagnosis).
 - >5 days after beginning of symptoms: IgM antibodies that indicate recent exposure will be present (presumptive diagnosis).
- Step 3: Notify local health authorities.

^aTests may be offered by a hospital or reference laboratory (e.g., Quest, LabCorp, Mayo Clinic, or a university), a local/state health department, or the Centers for Disease Control and Prevention. The processing of samples for serologic diagnosis takes approximately one week, and for PCR results, approximately three days. For information as to where specimens should be sent, providers should contact state or local health departments.

PCR = polymerase chain reaction

IgM = immunoglobulin M

Figure 4. Time course of dengue infection

IgM = immunoglobulin M

IgG = immunoglobulin G

D = day

Mo = month

Vector control and surveillance

Mitigation efforts have played significant roles in controlling dengue outbreaks and will continue to do so even when a vaccine becomes available. Mosquito-control programs for dengue and other mosquito-borne diseases exist in a variety of forms in the U.S. Some mosquito-control programs are stand-alone programs without government funding, while others may be part of state or local public health, animal control, or environmental health departments. CDC provides additional expertise and guidance for state and local vector-control programs.

Successful control of dengue vectors is difficult to achieve and even more challenging to maintain. Vector-control programs work to control mosquito populations through pesticide spraying to kill adult mosquitoes, elimination of breeding habitats, and water management; the use of larvicides to kill mosquitoes in the larval stage; and the provision of biological controls, such as mosquito-eating fish.⁴¹ Mosquito-control programs use surveillance and sampling to determine the extent of mosquito populations and to measure the impact of mosquito-reduction campaigns.¹⁹

Community engagement

Community engagement in areas that are vulnerable to dengue is a vital part of vector control, surveillance, reporting, and response to an outbreak. Community engagement is especially important to reduce mosquito

breeding on privately owned property and to sustain a long-term program.²² Communication campaigns and outreach may be necessary to improve public understanding of why they should support mosquito control, the dangers of dengue, and the consequences of allowing mosquitoes to breed around their homes. Without this public-private partnership in the control of dengue vectors, mosquito-control programs are unlikely to successfully prevent or control dengue outbreaks.

Engagement of the clinical community in areas that are susceptible to dengue is critically important. Clinicians should be educated and informed about the status of the disease in their area, so that they will be aware and more likely to diagnose cases of dengue. Public health authorities can help inform clinicians by providing a case definition and frequent updates about any dengue activity in their jurisdiction.

Candidate vaccines

The U.S. Food and Drug Administration has not licensed a dengue vaccine. However, three promising candidate vaccines are currently in clinical trials. All candidate vaccines are live attenuated tetravalent formulations that are being developed separately by Sanofi Pasteur, GlaxoSmithKline, and the National Institutes of Health. Dengue vaccines have been difficult to develop because of concerns about the occurrence of DHF/DSS in individuals who may be exposed to a dengue virus after being vaccinated but before

the tetravalent virus immunity is achieved following immunization.⁴² Although current vaccine development efforts are aimed at endemic area populations outside the U.S., if licensure were sought in the U.S., a tetravalent dengue vaccine would likely be recommended for all travelers to endemic areas. Domestic use of such a vaccine would likely be reserved for locations where endemic transmission was identified (Figure 5).

CONCLUSIONS

Dengue has traditionally been categorized as a neglected tropical disease not frequently associated with the U.S. However, recent dengue activity in the U.S. demonstrates that areas of the country are at risk of experiencing outbreaks. Practitioners in areas with dengue mosquito vector species should be aware of the risk of imported dengue resulting in an outbreak. The risk for dengue outbreaks is steadily increasing as the result of changing demographics and increases in international travel to dengue endemic regions.

Figure 5. Key messages for U.S. public health practitioners regarding dengue infection

- Increasingly frequent introductions of dengue are occurring in the U.S. in areas with *Aedes albopictus* and/or *Aedes aegypti* mosquitoes, thus heightening the possibility of local epidemics and endemic foci. Public health practitioners in areas where these vectors are present should be aware of the dengue threat.
- In areas vulnerable to dengue, patients and health-care providers should be educated about the signs and symptoms of dengue. Medical providers should be encouraged to obtain specimens and report cases.
- The presence of multiple serotypes and newly introduced genotypes of dengue is a cause for concern and may lead to increased incidence of severe dengue (dengue hemorrhagic fever and dengue shock syndrome) in the U.S.
- Policy makers should understand the critical role of vector control and allocate funds for this activity according to the risks they face for dengue outbreaks.
- States that are at risk for dengue and those that have had outbreaks should strengthen disease surveillance for dengue, including both human disease surveillance and vector surveillance.
- Health departments in areas at risk for dengue should strengthen collaboration with mosquito-abatement districts to identify risks to local communities and to exchange information and data.
- Travelers from dengue endemic areas with fever within two weeks of return should have dengue considered in the diagnosis.
- Public health departments and mosquito-control agencies should prioritize public communication and community engagement for reducing mosquito populations and recognizing and reporting possible cases.

To prevent and mitigate the impacts of dengue, early investments are needed to detect outbreaks and limit spread. Public health practitioners must be alerted to the possible occurrence of dengue in the population and engage with the public to increase awareness about dengue. Clinicians must be aware of dengue as a possible diagnosis for patients with a febrile illness during the summer and autumn, when mosquitoes are most prevalent. Vector-control agencies should increase their investments in mosquito control to prevent and respond to dengue and other mosquito-borne diseases.

Dengue has the potential to reemerge as a public health threat in many areas of the U.S., and dengue outbreaks could have severe health and economic consequences. Many vulnerable communities are not aware of the risk, which is why public health practitioners play a key role in raising community awareness and also establishing robust prevention, mitigation, and response efforts for this threat.

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