Surveillance for Dengue and Dengue-Associated Neurologic Syndromes in the United States

Stephen H. Waterman,* Harold S. Margolis, and James J. Sejvar

United States–Mexico Unit, Division of Global Migration and Quarantine, US Centers for Disease Control and Prevention, San Diego, California;
Dengue Branch, Division of Vector-Borne Diseases, US Centers for Disease Control and Prevention, San Juan, Puerto Rico;
Division of High-Consequence Pathogens and Pathology, US Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract. Autochthonous dengue virus transmission has occurred in the continental United States with increased frequency during the last decade; the principal vector, *Aedes aegypti*, has expanded its geographic distribution in the southern United States. Dengue, a potentially fatal arboviral disease, is underreported, and US clinicians encountering patients with acute febrile illness consistent with dengue are likely to not be fully familiar with dengue diagnosis and management. Recently, investigators suggested that an outbreak of dengue likely occurred in Houston during 2003 based on retrospective laboratory testing of hospitalized cases with encephalitis and aseptic meningitis. Although certain aspects of the Houston testing results and argument for local transmission are doubtful, the report highlights the importance of prospective surveillance for dengue in *Aedes*-infested areas of the United States, the need for clinical training on dengue and its severe manifestations, and the need for laboratory testing in domestic patients presenting with febrile neurologic illness in these regions to include dengue.

Dengue is an arboviral disease of major public health significance caused by four serologically related flaviviruses, dengue viruses (DENVs 1–4), with an expanding worldwide distribution.¹ Although many DENV infections are asymptomatic, classic clinical dengue manifests as an acute febrile illness, with symptoms that include headache, retro-orbital pain, myalgia, arthralgia, and rash. Clinical dengue is usually a self-limited illness of about 1 week's duration, but severe illness can occur in both healthy persons and those with other underlying diseases. A relatively small percentage (approximately 10%) of persons with clinical dengue progresses to severe disease because of plasma leakage, which can lead to decompensated shock and death if not carefully managed with appropriate fluid therapy. Most patients requiring hospitalization for dengue have severe disease or complications related to underlying comorbid disease. DENVs seem to be less neurotropic than other flaviviruses, such as West Nile virus, St. Louis encephalitis virus, and Japanese encephalitis virus. DENV-associated neurologic disease, including neuroinvasive disease, has been rarely documented by isolation of virus and detection of DENV-specific immunoglobulin M (IgM) antibody in cerebrospinal fluid (CSF) or brain tissue. In Viet Nam, about 1% of patient hospitalizations with suspected dengue had encephalitis or aseptic meningitis syndromes.² Another study in Viet Nam found that 0.5% of children admitted for dengue hemorrhagic fever (DHF), which is a subset of severe dengue, had serologically confirmed DENV infection with encephalopathy, although rates of dengue-associated neurologic diseases as high as 21% have been reported.^{3,4}

The most efficient vector for DENV is *Aedes aegypti*, which is present in limited areas of the southern United States, but its current geographic distribution is not well-documented.⁵ *Ae. albopictus* is a less efficient transmitter of DENV, and it is known to have a wider distribution in the southern United States. Dengue outbreaks were non-existent in the continental United States from the end of World War II through the 1970s. Since the 1980s, occasional small outbreaks have been

detected and documented in south Texas; however, long-term epidemiologic studies have not been conducted to determine whether this region represents an endemic focus.⁶ Recently, small outbreaks have also taken place in Florida.⁷ Imported dengue cases among US travelers returning from endemic regions of the world are documented each year and can serve as the source of DENV transmission where the competent vector is present.⁸

Diagnostic testing for dengue has improved considerably over the past decade and no longer requires paired acute and convalescent specimens to determine DENV antibody seroconversion. The availability of reverse transcriptase polymerase chain reaction (RT-PCR) assays to detect viremia combined with IgM anti-DENV detection by IgM antibody capture–enzyme-linked immunosorbent assay (ELISA) allows for the accurate diagnosis of dengue with a single serum specimen obtained during the first 5–7 days of the illness. In the United States, Food and Drug Administration (FDA)-approved diagnostic tests for both analytes have been available since 2012.^{9,10}

A recent highly publicized report by Murray and others¹¹ describes a retrospective 2009 study looking for evidence of DENV infection in 3,768 serum and CSF specimens from patients in Houston, Texas who were hospitalized during 2003–2005.^{11–13} This report raises important issues regarding clinical dengue surveillance in the United States and the likelihood of detecting dengue, severe dengue, or dengue with unusual manifestations, such as neurologic syndromes. In this retrospective study, most of the patients had aseptic meningitis or encephalitis symptoms, and they had been previously tested serologically and ruled out as having arboviral disease caused by West Nile virus or St. Louis encephalitis virus. Murray and others¹¹ identified 47 (1.2%) patients with IgM anti-DENV using the PanBio (Brisbane, Queensland, Australia) ELISA, including 2 patients who were also positive for DENV-2 RNA in serum by nested RT-PCR. Because travel history from review of medical records and/or telephone interviews in 19 individuals with serologic evidence of recent DENV infection did not reveal travel to an endemic area, Murray and others¹¹ concluded that local DENV transmission occurred in Houston during 2003–2005.

Although the data are intriguing, the case by Murray and others¹¹ for local transmission of DENV in Houston, Texas during 2003–2005 (with an outbreak in 2003) is not fully convincing and illustrates the pitfalls of retrospective identification

*Address correspondence to Stephen H. Waterman, United States–Mexico Unit, Division of Global Migration and Quarantine, US Centers for Disease Control and Prevention, 3851 Rosecrans Street, San Diego, CA 92110. E-mail: shw2@cdc.gov

of dengue and the limits of dengue diagnostic testing in areas with low endemicity of DENV infection.

Several considerations undercut the argument that Houston, Texas experienced a local outbreak of DENV infections in 2003. First, the travel histories obtained over the phone were done 4–6 years after the acute illnesses, with ample opportunity for poor recall, and travel histories from retrospective medical record review are notoriously incomplete. Murray and others¹¹ do not specify the number of histories obtained in each manner. Second, Murray and others¹¹ fail to qualify the predictive value of a positive IgM anti-DENV test in such a low-prevalence situation. The referenced study of the PanBio assay describes a sensitivity of 96.8% and specificity of 99.4%,¹⁴ although this test was shown to have a lower specificity (approximately 85%) in a large multicenter study of dengue diagnostic tests.¹⁵ However, both of these studies were conducted with evaluation panels weighted toward what would be found in dengue-endemic populations. The predictive value of positive tests always drops when the prevalence of true infection is low. Assuming a true infection rate of 1% in this patient population and calculating with 97% sensitivity and 99% specificity, the predictive value of a positive IgM anti-DENV ELISA would be 50%, whereas using a 99% sensitivity and the specificity of 85% found in the larger study, the predictive value of a positive test is only 7% (93% false positives). Thus, one-half or more of the IgM-positive patients in this study may have been falsely positive for dengue. Third, 731 of the serum specimens and 641 of the CSF specimens included in the work by Murray and others¹¹ were tested at the Centers for Disease Control and Prevention (CDC) Dengue Branch using the CDC Real-Time DENV 1–4 PCR, and all were found to be negative. A partial explanation may be diminished antigen caused by multiple freeze–thaw cycles and uncertain dates for days post-onset of specimens being sent to the CDC Laboratory in Puerto Rico, but these results also cast doubt on the Texas results. Fourth, the geographic and race/ethnic distributions of laboratory positives seem random, an unlikely epidemiologic finding in that dengue usually disproportionately affects households of lower socioeconomic status. Studies in south Texas have documented higher rates of outbreak-associated dengue in households lacking air conditioning.^{16,17} Fifth, as mentioned, DENV infections presenting with neurologic manifestations are uncommon relative to the overall burden of dengue-associated illness, and the largest, best designed studies have suggested that neurologic manifestations occur in 1% or less of hospitalized suspected dengue cases.^{2,3} That the Houston medical community and public health system, less than 2 years after heightened concern about bioterrorism from the fall 2001 anthrax attacks and subsequent federal funding to states for surveillance and preparedness (<http://www.bt.cdc.gov/publications/feb08phprep/pdf/feb08phpkeyfindings.pdf>), would not detect an outbreak of hundreds of cases of febrile hospitalized illness, many likely with hemorrhagic manifestations and shock and likely to be managed in intensive care units, seems unlikely.

Although the retrospective study of stored laboratory specimens by Murray and others¹¹ likely overstates the case for a local outbreak of dengue in Houston during 2003, clearly, dengue is an expanding public health problem worldwide. Imported dengue from Mexico, the Caribbean, and other endemic regions has occurred and continues to occur in Houston and other cities in the United States, and secondary

cases in households or nearby neighbors are possible in regions where *Ae. aegypti* are present. Investigations of recent outbreaks in the United States suggest that dengue is underdiagnosed and underreported. Enhanced prospective surveillance for acute febrile illnesses in areas potentially at risk for DENV introduction is necessary to determine definitively whether local transmission is taking place and the magnitude of such transmission, if present. We fully concur with the recommendation that physicians and other primary care providers, particularly in Texas, Florida, and other *Aedes*-infested parts of the United States, familiarize themselves with dengue diagnosis and management to minimize morbidity and mortality from severe illness.

The identification of putative hospitalized dengue cases with neurologic manifestations in Houston merits additional comment. Little doubt exists that the two PCR-positive patients identified in the study had DENV infections; both had classic dengue fever symptoms by chart review. US clinicians in *Aedes*-infested regions are most likely to encounter suspect dengue cases presenting with undifferentiated acute febrile illness during the summer and fall. Although the proportion of infections manifesting with severe disease varies between outbreaks and with previous DENV exposure, viral serotype, and strain, surveillance studies suggest that up to 60% of patients requiring hospitalization may develop signs of DHF.¹⁸ Physicians should maintain a high index of suspicion in such patients for signs of increased vascular permeability, a phenomenon that occurs around the time of defervescence and thus, requires careful patient counseling, monitoring, and follow-up. The Houston study, although problematic, underscores that the laboratory workup of patients with aseptic meningitis, encephalitis syndromes, and perhaps, other neurologic syndromes with febrile prodromes, such as Guillain–Barre syndrome and other post-infectious neurologic illnesses, in such settings reasonably should include dengue diagnostic testing as well as testing for West Nile virus and other arboviruses known to occur in a given region.¹⁹ Such testing may help us to gain a better understanding of the true burden of dengue-associated neurologic illness, information that is, to date, limited. Although the proportion of febrile neurologic disease caused by dengue in dengue-endemic areas has been reported to be anywhere between 5% and 47%, the assessment of dengue-associated neurologic illness has also been hampered by unclear and differing case definitions, differences in confirmation of dengue infection, and lack of differentiation of various neurological entities (e.g., encephalopathy versus encephalitis), resulting in this considerable variability.^{20,21}

We encourage medical institutions and organizations in these regions to ensure ongoing availability of medical education training on vector-borne diseases of major public health importance, such as arboviral and rickettsial disease. Such trainings should cover natural history and epidemiology, clinical spectrum of illness, differential diagnosis, laboratory diagnosis, clinical management essentials, and disease reporting responsibilities. Although CNS involvement is now listed as one of the criteria for severe dengue in the World Health Organization case classification,²² standardized criteria currently do not exist for neurological manifestations of dengue. Input from subject matter experts from a variety of dengue-related fields in an international forum will be important to formulate such standardized criteria for dengue-associated neurologic illness. Detailed epidemiologic and clinical studies

are needed to accurately assess the incidence, prevalence, and overall burden of neurologic illness associated with dengue and further define the spectrum of neurologic illness associated with DENV infection. Public health departments in these *Aedes*-infested regions can partner with clinicians and hospitals in such efforts to enhance surveillance with readily available and sufficient laboratory testing of suspect cases for early warning of disease transmission and evaluation of disease burden, including important but currently unclear questions, such as the overall burden of dengue neurologic illness. Such a partnership will make possible reduced morbidity and mortality through optimal clinical management, early initiation of community-wide vector control, and the scientific basis for dengue vaccine recommendations as vaccine availability appears on the horizon.²³

Received January 7, 2014. Accepted for publication September 21, 2014.

Published online November 4, 2014.

Acknowledgments: We thank Dr. Tyler Sharp of the CDC Dengue Branch for his assistance with the manuscript.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Authors' addresses: Stephen H. Waterman, United States–Mexico Unit, Division of Global Migration and Quarantine, US Centers for Disease Control and Prevention, San Diego, CA, E-mail: shw2@cdc.gov. Harold Margolis, Dengue Branch, Division of Vector-Borne Diseases, US Centers for Disease Control and Prevention, San Juan, Puerto Rico, E-mail: hsm1@cdc.gov. James J. Sejvar, Division of High-Consequence Pathogens and Pathology, US Centers for Disease Control and Prevention, Atlanta, GA, E-mail: zea3@cdc.gov.

REFERENCES

- Gubler DJ, 1998. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev* 11: 480–496.
- Solomon T, Minh Dung N, Vaughn D, Kneen R, Thao LTT, Raengsakulrach B, Loan HT, Day NPJ, Farrar J, Myint KSA, Warrell MJ, James WS, Nisalak A, White NJ, 2000. Neurologic manifestations of dengue infection. *Lancet* 355: 1053–1059.
- Cam BV, Fonsmark L, Hue NB, Phuong NT, Poulsen A, Heegaard ED, 2001. Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. *Am J Trop Med Hyg* 65: 848–851.
- Domingues RB, Kuster GW, Onuki-Castro FL, Souza VA, Levi JE, Pannuti CS, 2008. Involvement of the central nervous system in patients with dengue virus infection. *J Neurol Sci* 267: 36–40.
- Eisen L, Moore CG, 2013. *Aedes (Stegomyia) aegypti* in the Continental United States: a vector at the cool margin of its geographic range. *J Med Entomol* 50: 467–478.
- Clark GG, 2008. Dengue and dengue hemorrhagic fever in northern Mexico and south Texas: do they really respect the border? *Am J Trop Med Hyg* 78: 361–362.
- Centers for Disease Control and Prevention, 2010. Locally acquired dengue – Key West, Florida, 2009–2010. *MMWR Morb Mortal Wkly Rep* 59: 577–581.
- Centers for Disease Control and Prevention, 2010. Travel-associated dengue surveillance – United States, 2006–8. *MMWR Morb Mortal Wkly Rep* 59: 715–719.
- Wright WF, Pritt BS, 2012. Update: the diagnosis and management of dengue virus infection in North America. *Diagn Microbiol Infect Dis* 73: 215–220.
- Santiago GA, Vergne E, Quiles Y, Cosme J, Vazquez J, Medina JF, Medina F, Colón C, Margolis H, Muñoz-Jordán JL, 2013. Analytical and clinical performance of the CDC real time RT-PCR assay for detection and typing of dengue virus. *PLoS Negl Trop Dis* 7: e2311.
- Murray KO, Rodriguez LF, Herrington E, Kharat V, Vasilakis N, Walker C, Turner C, Khuwaja S, Arafat R, Weaver SC, Martinez D, Kilborn C, Bueno R, Reyna M, 2013. Identification of dengue fever cases in Houston, Texas, with evidence of autochthonous transmission between 2003 and 2005. *Vector Borne Zoonotic Dis* 13: 835–845.
- Ackerman T, October 9, 2013. Dengue virus identified in Houston: potentially lethal disease carried by mosquitoes found in city. *Houston Chronicle*. Available at: <http://www.chron.com/news/health/article/Dengue-virus-identified-in-Houston-4883103.php>.
- Gustafson TA, 2013. *Houston, We Have Dengue Fever*. Available at: <http://www.npr.org/blogs/health/2013/10/16/235628882/houston-we-have-dengue-fever>. Accessed April 4, 2014.
- Vazquez S, Hafner G, Ruiz D, Calzada N, Guzman MG, 2007. Evaluation of immunoglobulin M and G capture enzyme-linked immunosorbent assay Panbio kits for diagnostic dengue infections. *J Clin Virol* 39: 194–198.
- Hunsperger EA, Yoksan S, Buchy P, Nguyen VC, Sekaran SD, Enria DA, Pelegriño JL, Vazquez S, Artsob H, Drebot M, Gubler DJ, Halstead SB, Guzman MG, Margolis H, Nathanson CM, Rizzo Lic NR, Bessoff KE, Kliks S, Peeling RW, 2009. Evaluation of commercially available anti-dengue virus immunoglobulin M tests. *Emerg Infect Dis* 15: 436–440.
- Reiter P, Lathrop S, Bunning M, Biggerstaff BJ, Singer D, Tiwari T, Baber L, Amador M, Thirion J, Hayes J, Seca C, Mendez J, Ramirez B, Robinson J, Rawlings J, Vorndam V, Waterman S, Gubler D, Clark G, Hayes E, 2003. Texas life-style limits transmission of dengue virus. *Emerg Infect Dis* 9: 86–89.
- Ramos MM, Mohammed H, Zielinski-Gutierrez E, Hayden MH, Robles Lopez JL, Fournier M, Rodriguez Trujillo A, Burton R, Brunkard JM, Anaya-Lopez L, Abell Banicki A, Kuri Morales P, Smith B, Muñoz JL, Waterman SH; The Dengue Serosurvey Working Group, 2008. Epidemic dengue and dengue hemorrhagic fever at the Texas-Mexico border: results of a household-based seroepidemiologic survey, December 2005. *Am J Trop Med Hyg* 78: 364–369.
- Centers for Disease Control and Prevention, 2007. Dengue hemorrhagic fever – U.S. – Mexico Border, 2005. *MMWR Morb Mortal Wkly Rep* 56: 785–789.
- Kanade T, Shah I, 2011. Dengue encephalopathy. *J Vector Borne Dis* 48: 180–181.
- Lum LC, Lam SK, Choy YS, George R, Harun F, 1996. Dengue encephalitis: a true entity? *Am J Trop Med Hyg* 54: 256–259.
- Carod-Artal FJ, Wichmann O, Farrar J, Gascón J, 2013. Neurologic complications of dengue virus infection. *Lancet Neurol* 12: 906–919.
- World Health Organization, 2009. *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control*, 3rd Ed. Geneva: World Health Organization.
- Halstead SB, 2012. Dengue vaccine development: a 75% solution? *Lancet* 380: 1535–1536.