Recent Advances in Dengue: Relevance to Puerto Rico

David H. Noyd, BA*; Tyler M. Sharp, PhD†

Dengue represents an increasingly important public health challenge in Puerto Rico, with recent epidemics in 2007, 2010, and 2012–2013. Although recent advances in dengue vaccine development offer hope for primary prevention, the role of health professionals in the diagnosis and management of dengue patients is paramount. Case definitions for dengue, dengue with warning signs, and severe dengue provide a framework to guide clinical decision-making. Furthermore, the differentiation between dengue and other acute febrile illnesses, such as leptospirosis and chikungunya, is necessary for the appropriate diagnosis and management of cases. An understanding of dengue epidemiology and surveillance in Puerto Rico provides context for clinicians in epidemic and non-epidemic periods. This review aims to improve health professionals' ability to diagnose dengue, and as highlight the relevance of recent advances in dengue prevention and management in Puerto Rico. [*P R Health Sci J 2015;34:65-70*]

Key words: Dengue, Epidemiology, Public Health

Dengue represents an increasingly important global health challenge, as recent estimates suggest that nearly 2.5 billion people worldwide are at risk for infection (1) and 390 million infections occurred in 2010 (2). The 4 dengue virus-types (DENV-1–4) that cause dengue are single-stranded, positive-sense RNA viruses of the family *Flaviviridae*. *Aedes aegypti* and *Ae. albopictus* mosquitoes are endemic throughout the tropics and subtropics and serve as the primary vector for DENV transmission. DENV infection can result in a range of outcomes, from asymptomatic infection, to self-limited acute febrile illness (AFI), to potentially fatal severe dengue (1).

In 2009, the World Health Organization (WHO) revised the clinical classification of dengue, reclassifying dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) (3) as dengue, dengue with warning signs, and severe dengue (1). A major impetus for this change was the observation that many life-threatening dengue cases did not meet the definition of either DHF or DSS, and the identification of clinical signs and symptoms present in some dengue cases were positively associated with the development of more severe illness (4, 5). Dengue is characterized by fever, anorexia, rash, aches and pains, and leucopenia (1). Warning signs that signal development of severe dengue include abdominal pain, persistent vomiting, mucosal bleed, hepatomegaly greater than 2 centimeters, clinical fluid accumulation, lethargy or restlessness, and hemoconcentration concurrent with a rapid decrease in platelet count. Severe dengue is characterized by plasma leakage that may lead to shock, severe bleeding, severe organ impairment or any combination thereof.

In Puerto Rico, clinical suspicion of dengue should be followed by the collection of a serum specimen and completion of a Dengue Case Investigation Form (available at www.cdc.gov/dengue/resources/dengueCaseReports/DCIF_English.pdf or www.cdc.gov/dengue/resources/dengueCaseReports/DCIF_Spanish.pdf) to enable case reporting and diagnostic testing by either reverse transcriptase-polymerase chain reaction (RT-PCR) to directly detect viral genome and/or IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) to detect anti-DENV immunoglobulin M (IgM) antibodies. Although primary DENV infection confers lifelong immunity to the infecting DENV type, subsequent infection with another DENV type confers a slight but statistically significant increased risk of developing more severe illness (6).

Currently, no vaccine or anti-viral drug is available to prevent or treat dengue, although several vaccine candidates are in clinical trials (7, 8). The mainstay for treatment of dengue is therefore supportive care, which can reduce the case-fatality rate in hospitalized patients from approximately 10% to less than 0.5% (1, 9). The clinical management of patients depends on recognition of the 3 phases of dengue: the febrile phase, critical phase, and recovery phase. During the febrile phase, maintaining proper hydration and vigilance for the warning signs of severe dengue are important. Defervescence, typically 3–7 days after illness onset, defines the start of the critical phase, which typically lasts 24–48 hours. Hemoconcentration may also occur as a result of plasma leakage in the critical phase, in which case judicious use of intravenous fluids and close monitoring

*Oregon Health & Science University, Dengue Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, San Juan, PR; †Dengue Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, San Juan, PR

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Address correspondence to: Tyler M. Sharp, PhD, Centers for Disease Control and Prevention - Dengue Branch, 1324 Calle Cañada, San Juan, PR 00920. Email: tsharp@cdc.gov

of clinical status are needed to avert shock, organ impairment, and unnecessary morbidity. Corticosteroids, though once thought to benefit dengue patients, have not been shown to decrease mortality or morbidity due to dengue and in fact may result in increased morbidity due to immunosuppression and/or the increased risk of gastrointestinal bleeding (10, 11). The recovery phase reflects a return to normal capillary permeability, although continued monitoring of fluid status is important to avoid fluid overload. Detailed patient management protocols and best practice guidelines elaborate on the appropriate clinical management of patients suspected of having or with confirmed dengue (Figure 1) (1).

Dengue epidemiology

Outbreaks of dengue-like illnesses were first reported in the 1600s and have been consistently reported from various regions of the tropics for more than a century. Although the Americas experienced a reprieve from dengue in the 1950s and 1960s following an extensive *Aedes aegypti* elimination program by the Pan American Health Organization (PAHO) (12), the recent resurgence of dengue in the region reflects global trends (1, 13, 14) in urbanization and migration and demonstrates that current prevention measures are inadequate (15,16). The number of dengue cases reported to WHO nearly doubled between the 1990s and the early 2000s (17), and in 2010 an estimated 96 million dengue cases occurred worldwide (2). The need to evaluate the economic impact of dengue and novel prevention methods, such as vaccines, underscores the importance of maintaining disease surveillance to better understand changes in dengue epidemiology.

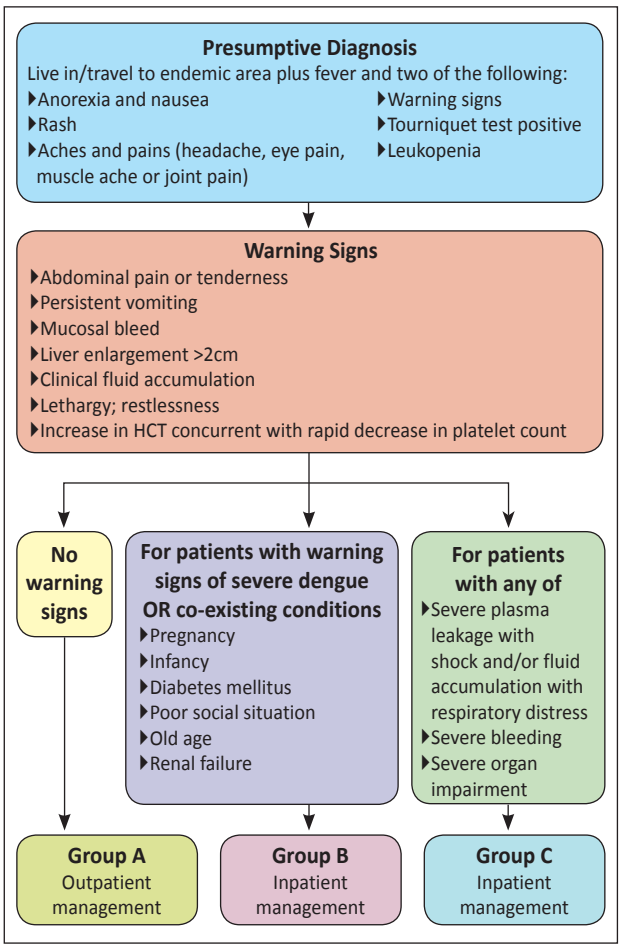

Figure 1. Schematic of World Health Organization guidelines (1) for clinical management of patients suspected of having dengue.

The seasonal and cyclical natures of dengue are due in part to environmental influences, in particular rainfall, temperature (18), and weather indices such as El Niño Southern Oscillation (19), all of which affect the proportion of individuals in the population that are susceptible to the DENV types in circulation. DENV transmission via the vector *Ae. aegypti* tends to increase as conditions favor the reproduction of mosquitos. Nevertheless, a recent review of the literature emphasizes the complex interactions between environment, the mosquito vector, and host factors in the propagation of DENV, cautioning that the current methods, which rely on environmental models to predict the spread of dengue, have limitations (20).

Dengue in Puerto Rico

The first reported dengue outbreak in Latin America occurred in the early 1600s on the Caribbean island of Martinique (21). Similar outbreaks of a dengue-like illness spread throughout Latin America over the subsequent 3 centuries (21). In Puerto Rico, outbreaks of a dengue-like illness were reported in 1918 (22) and in 1945 (23), DENV-2 was isolated during an outbreak in 1963–1964 and endemicity of dengue was documented soon after (24). The introduction of additional DENV types was documented in outbreaks in the 1970s and 1980s, and in 1998 an outbreak occurred in which all 4 DENV types were circulating (25). Dengue epidemics occurred most recently in Puerto Rico in 2007 (26), 2010 (27), and 2012–2013 (PRDH, unpublished data) (Figure 2).

Dengue epidemiology in Puerto Rico during epidemic and non-epidemic years consistently reveals a disproportionate burden of disease for individuals aged 10–19 years, followed by younger children and infants; nonetheless, adults consistently represent roughly one-half of all reported cases (25-27). There have been no consistent differences in the incidence of dengue by sex or race. In 2007, a total of 10,508 suspected cases and 44 deaths were reported; however, only one-third of the suspected cases and 11 of the fatal cases had laboratory evidence of DENV infection. Moreover, among all the laboratory-positive dengue cases identified, the percentage of individuals that had been previously infected with a DENV was greater than 75% (26). A separate investigation regarding the 11 lab-confirmed deaths revealed that less than half received a clinical diagnosis of dengue, more than half were given corticosteroids, and none were managed according to the WHO guidelines (28). Subsequently, the 2010 epidemic documented nearly 27,000 suspected cases and 128 fatal cases, of which half and one-third were laboratory confirmed, respectively (27). Similar to the

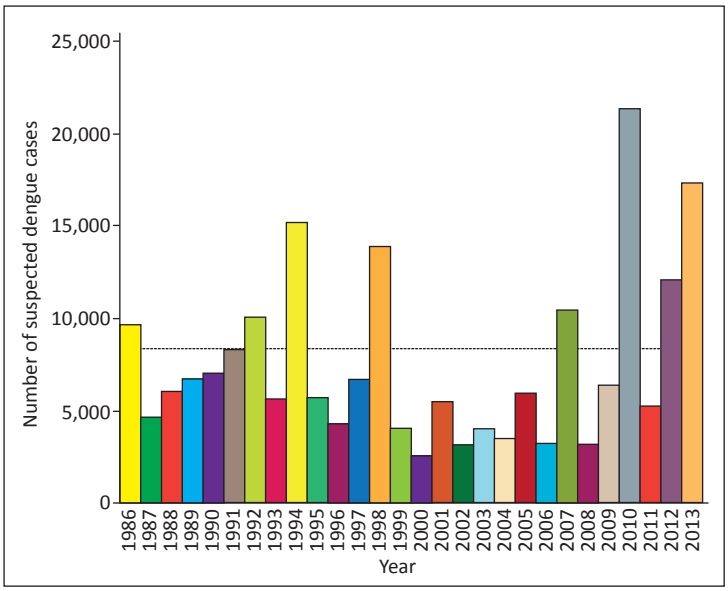

Figure 2. Suspected dengue cases reported to the passive dengue surveillance system during 1986-2013. The dotted horizontal line indicates the epidemic threshold.

2007 epidemic, approximately 80% of the dengue cases had been previously infected with a DENV. The 2007 and 2010 epidemics illustrated critical lessons about dengue epidemiology in Puerto Rico and revealed several aspects of dengue clinical case management in need of improvement (e.g., use of non-isotonic intravenous saline, frequency of vital sign monitoring, administration of corticosteroids).

Dengue surveillance in Puerto Rico

Dengue in Puerto Rico is monitored with the Passive Dengue Surveillance System (PDSS), which was established in the late 1960s (29). PDSS was, for several decades, a collaborative surveillance system co-operated by Puerto Rico Department of Health (PRDH) and the Centers for Disease Control and Prevention-Dengue Branch (CDC-DB) located in San Juan. However, since 2012, the PDSS has been operated primarily by PRDH. A general overview of PDSS spans from the initial interfacing of a patient with the health care system to the reporting of a suspected dengue case to the public health response (Figure 3). Overall goals of dengue surveillance1 include the early detection of increased incidence to enable early intervention, measurement of disease burden, evaluation of programs to prevent and control dengue, and facilitation of appropriate resource distribution.

An evaluation of PDSS from 2009–2011, guided by the 9 attributes of public health surveillance (30), identified strength in the utility, flexibility, and stability of the system; however, timeliness, sensitivity, and acceptability represented attributes to be improved (CDC-DB, unpublished data). Data quality, positive predictive value, and simplicity of the surveillance system were considered to be acceptable. The total times for specimens to be transported (Figure 4), processed, tested, and reported back to clinicians were 10 days in an epidemic period and 15 days during a non-epidemic period, thus reducing the clinical utility of diagnostic testing for health care providers. Nevertheless, the primary purpose of PDSS is to inform public health decision-making and not to produce diagnostic test results. The stability of PDSS over the past several decades contributes to its utility in monitoring dengue epidemiology and in directing public health action in Puerto Rico.

An inherent limitation of passive surveillance is the difficulty of measuring the true burden of disease. A meta-analysis of surveillance systems throughout Latin America and Southeast Asia revealed significant underreporting of dengue cases: from 3–9 symptomatic cases not being reported for each

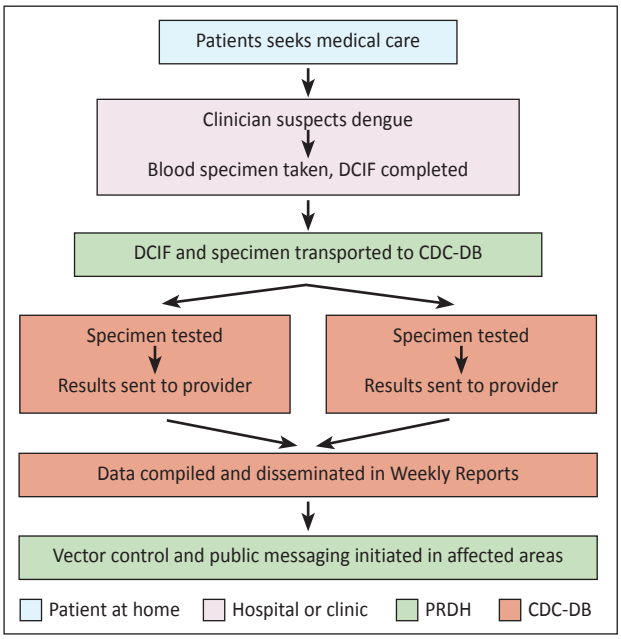

Figure 3. Schematic of how the passive dengue surveillance system (PDSS) operated until 2012. PDSS is initiated when a patient seeks medical care, following which the patient's medical provider suspects dengue as a cause of the patient's illness. When this occurs, the clinician orders a blood specimen be collected from the patient and the Dengue Case Investigation Form (DCIF) is completed; both the specimen and DCIF are transported by the Puerto Rico Department of Health (PRDH) to the Centers for Disease Control and Prevention, Dengue Branch (CDC-DB). Specimens are tested, and the patient information from the DCIF is entered into a database at the CDC-DB. Diagnostic test results are sent to the health care provider who reported the case, who then relays the results to the patient and, if necessary, requests that the patient return to provide a convalescent serum specimen. Patient demographic information is compiled into weekly reports that CDC-DB and PRDH disseminate to stakeholders and the public via weekly reports. PRDH uses data from these reports to direct response activities in the areas most affected by dengue. After 2012, all activities indicated as being conducted by CDC-DB began instead to be conducted by PRDH.

case that was reported (31). Studies in Puerto Rico in the 1990s estimated that for each case of dengue reported to the PDSS, 10–27 additional cases were not reported (32, 33). Although recent estimates of underreporting are needed, much anecdotal evidence suggests that PDSS is biased towards hospitalized cases (CDC-DB, unpublished data).

To improve surveillance, a pilot enhanced surveillance system was implemented in 2005 in Patillas to encourage health care providers to report suspected cases (34). In 2009, the WHO recommended the addition of sentinel surveillance systems to complement passive surveillance (1, 31). To meet this need, in 2012 CDC-DB established the Sentinel Enhanced Dengue Surveillance System (SEDSS) in Ponce, and later expanded it to sites in Guayama and Carolina (35). A major utility of the SEDSS sites includes the ability to determine baseline levels of dengue, which will be needed to evaluate the efficacy of a dengue vaccine and more accurately quantitate the burden of all clinically-apparent dengue cases. This will enable a better understanding and evaluation of interventions that are implemented to control dengue in Puerto Rico.

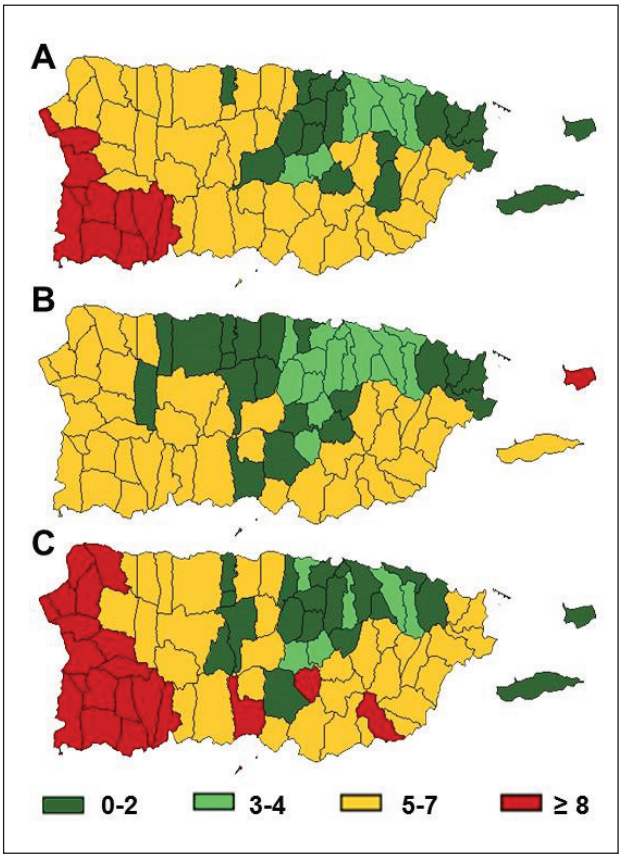

Figure 4. Median number of days needed for a specimen to arrive at Centers for Disease Control and Prevention, Dengue Branch (CDC-DB), according to a particular patient's municipality of residence in 2009 (A), 2010 (B) and 2011 (C). Light green, dark green, yellow, and red regions indicate municipalities with an average transport time of 0–2, 3–4, 5–7, and >8 days, respectively.

Dengue diagnosis

Dengue surveillance systems in Puerto Rico, both passive and enhanced, depend on accurate diagnostic testing to identify DENV-infected individuals; however, the time between specimen collection and laboratory confirmation frequently approaches 2 or more weeks due primarily to delays in specimen transport and in the subsequent receipt of reports containing diagnostic test results (CDC-DB, unpublished data). Consequently, surveillance-based diagnostic testing provides minimal clinical utility to the health care provider. Rapid diagnostic tests, in conjunction with a clinical diagnosis of probable dengue, promise greater utility in population-based surveillance for dengue, particularly in resource-poor settings in which instrument-independent laboratory diagnostics are necessary (36, 37). Despite this, rapid diagnostic tests have not yet been demonstrated to be sufficiently reliable to enable individual patient diagnosis and management. Alternatively, highly sensitive and specific laboratory-based diagnostic tests are now available that can accurately diagnose dengue patients using a single serum specimen. Both molecular (38) and serologic (39) diagnostic tests that have been approved by the FDA are available in Puerto Rico at PRDH and CDC-DB, and currently all submitted specimens are tested for evidence of DENV infection. However, until these or other tests are available at centralized locations in hospitals and clinics, the clinical diagnosis made by the health care provider will continue to be the primary method used to diagnose and, consequently, treat suspected dengue cases.

The clinical diagnosis of dengue in endemic areas is often complicated by the myriad of other endemic acute febrile illnesses (AFIs) and the dynamic epidemiologic trends of such diseases. Influenza, leptospirosis, an array of respiratory illnesses, and various other bacterial infections often muddle the picture of a non-differentiated AFI, which may be misdiagnosed as dengue during dengue epidemics (40). The aforementioned WHO criteria for dengue demonstrate considerable overlap of the non-specific symptoms with those of other AFIs. Furthermore, the recent emergence of chikungunya in Puerto Rico (41), which has a clinical presentation similar to that of dengue and is also transmitted by *Aedes* species mosquitos (42), further complicates the identification of dengue patients.

Historically, epidemiologic studies focus primarily on differentiating laboratory-positive dengue patients from dengue-negative patients in regions with endemic dengue. One systematic review (43) and studies in Puerto Rico (44) observed associations between dengue cases and decreased platelets and white blood cell count in addition to observing an increased proportion of patients with myalgia, rash, and hemorrhagic signs. Specific comparisons between patients with dengue or influenza revealed high proportions of rash, hemorrhagic signs, and positive tourniquet test, as well as pronounced thrombocytopenia and leukopenia, among dengue patients (45). The scientific literature regarding the clinical manifestations of dengue, though varied in the development of predictive models

and likely influenced by the circulation of different DENV types, provides a framework from which to evaluate the utility of clinical diagnoses and improve the timeliness of diagnosis.

Advances in dengue prevention

In 2003, the Pan American Health Organization (PAHO) developed the Integrated Management Strategy for Dengue Prevention and Control (*Patio Limpio*), and most countries in the region adopted this approach; however, the impact of this program has since been shown to be minimal (21). The lack of effective approaches in terms of the primary prevention of dengue (e.g., a dengue vaccine, sustainable and effective vector control methods) therefore demonstrates the importance of secondary prevention (e.g., disease surveillance, clinical diagnosis, patient management) in mitigating the morbidity and mortality associated with dengue.

An example of this is that after noting the sub-optimal management of fatal dengue cases during the 2007 epidemic in Puerto Rico (46), medical epidemiologists from CDC-DB utilized the 2009 WHO Dengue Guidelines (1) to design a 4-hour clinical training course for physicians, that outlined the recommended management of dengue patients. When the 2010 epidemic was growing in magnitude and fatal cases began to be reported, the Secretary of Health of Puerto Rico mandated that all clinicians who see dengue patients take the course, and more than 11,000 clinicians were ultimately trained. An evaluation of clinical practices in 2009 compared to 2011 demonstrated significant increases in adherence to the recommended clinical practices, such as the use of isotonic intravenous saline, frequency of monitoring vital signs, and avoidance of corticosteroid administration (CDC-DB, unpublished data). This course was subsequently developed into an online training (available at www.cdc.gov/dengue/training/cme.html) that clinicians can take to receive continuing medical education credit. Thus, although an effective and sustainable approach to the primary prevention of dengue is not yet available, improvements in the clinical management of hospitalized dengue patients can reduce the case-fatality rate to below 0.5% (9).

Despite the recognition of dengue as a neglected tropical disease, considerable attention by global, regional, and local stakeholders has produced invaluable resources to guide preventive efforts. The most recent initiative by the WHO focuses on diagnosis and case management, integrated surveillance and outbreak preparedness, sustainable vector control, future vaccine implementation, and basic operational and implementation research as key components to reduce dengue mortality by 50% and morbidity by 25% by 2020 (47).

Recent advances in dengue vaccine development offer hope for control and prevention. One vaccine candidate reported an overall efficacy of 56%, with an excellent safety profile from a phase III trial in Southeast Asia (48), though sub-optimal protection against illness due to infection with DENV-2 was consistent with previous studies (8). Nevertheless, the potential to prevent dengue, especially severe cases (49), with this vaccine and others (50) in development underscores the importance of accurate clinical diagnosis and surveillance to measure the impact of those vaccines. Therefore, until a vaccine or other sustainable and effective approach to dengue control becomes available, health professionals will continue to play the most critical role in the clinical management of individuals with dengue or other AFIs in Puerto Rico.

Resumen

Dengue representa un reto importante de salud pública en Puerto Rico con epidemias recientes en 2007, 2010 y 2012–2013. Aunque avances recientes en el desarrollo de vacunas contra el dengue ofrecen esperanza para la prevención primaria, el rol de profesionales de salud para diagnosticar y manejar pacientes de dengue es primordial. Las definiciones de caso para dengue, dengue con señales de alarma y dengue severo proveen un marco para guiar las decisiones clínicas. Además, la diferenciación entre el dengue y otras enfermedades febriles agudas, como leptospirosis y chikungunya, es necesaria para el diagnóstico y el manejo apropiado de casos. Un entendimiento de la epidemiología del dengue y la vigilancia en Puerto Rico provee un contexto para el personal clínico en periodos epidémicos y no epidémicos. Este repaso intenta equipar a los profesionales de la salud para mejorar la detección de dengue además de subrayar la relevancia de avances recientes en la prevención y el manejo del dengue en Puerto Rico.

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