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Predominance of Severe Plasma Leakage in Pediatric Patients With Severe Dengue in Puerto Rico

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Abstract

Background.—We evaluated clinical and laboratory findings among patients with nonsevere or severe dengue in Puerto Rico to examine whether clinical manifestations vary by age.

Methods.—During 2012–2014, we enrolled patients who arrived at the emergency department with fever or history of fever within 7 days of presentation. Serum samples were tested for dengue virus (DENV) by reverse transcriptase-polymerase chain reaction (RT-PCR) and IgM enzyme-linked immunosorbent assay (ELISA). Severe dengue was defined as severe plasma leakage or shock, severe bleeding, or organ involvement at presentation, during hospitalization, or follow-up.

Results.—Of 1089 dengue patients identified, 281 (26%) were severe. Compared to those with nonsevere dengue, patients with severe dengue were more often aged 10–19 years (55% vs 40%, $P < .001$) and hospitalized (87% vs 30%, $P < .001$). Severe plasma leakage or shock was more common among children aged 0–9 (59%) or 10–19 years (86%) than adults (49%) ($P < .01$).

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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Severe bleeding was less common among 10–19 year olds (24%) compared to 0–9 year olds (45%) and adults (52%; $P < .01$).

Conclusions.—Severe plasma leakage was the most common presentation among children, highlighting important differences from adults. Vaccination against dengue could help prevent severe dengue among children in Puerto Rico.

Keywords

dengue; severe; plasma leakage; Puerto Rico; children

Dengue virus (DENV) and other arboviruses transmitted by *Aedes aegypti* mosquitoes, including Zika and chikungunya viruses, present an increasing public health challenge in tropical and subtropical regions. There are 4 genetically and antigenically distinct clades, thought of as serotypes (DENV-1–4) [1]. Following an infection with one DENV serotype, the resulting antibodies are initially broadly cross-reactive with other DENV serotypes and provide short-term cross-protection, but over time become serotype specific to provide long-lasting protection against the infecting serotype [2].

Dengue is endemic throughout the tropics and subtropics, with an estimated 3.83 billion people (roughly 53% of the global population) living in areas suitable for DENV transmission, including much of Asia, Africa, and the Americas [3]. Over the past 3 decades, dengue incidence and severity across Latin America has increased substantially [4]. In Puerto Rico, dengue has been endemic since at least the 1960s and epidemics occurred roughly every 3–5 years until chikungunya [5] and Zika virus outbreaks [6] occurred in 2014 and 2015–2016, respectively, after which dengue transmission has remained low. During the last major epidemic in 2012–2013, more than 30 000 suspected dengue cases were reported, approximately 16 000 of which had diagnostic evidence of DENV infection confirmed by reverse transcription polymerase chain reaction (RT-PCR) [7], including 69 fatal cases (Centers for Disease Control and Prevention [CDC], unpublished data, 2019). Reported dengue cases likely underestimate the true burden of dengue in Puerto Rico, as recent estimates suggest that for every reported hospitalized dengue patient there were an additional 5–9 unreported hospitalized cases, and for every reported ambulatory dengue case there were an additional 21–115 unreported ambulatory cases [8].

Typically, <5% of persons with dengue will progress to severe dengue, a more severe and potentially fatal form of the disease. Age, comorbidities, host genetics, and virus strain are risk factors for severe dengue, with heterotypic secondary infections being the most prominent factor associated with severe dengue [2]. The most common form of severe dengue differs from un-complicated dengue by the presence of increased vascular permeability, leading to plasma leakage into the peritoneum, pleural cavity, or pericardium. If not recognized and treated in a timely manner, the patient may progress to hypovolemic shock, metabolic acidosis, major hemorrhagic manifestations, or death. At present, no effective antiviral treatments are available for dengue. The mainstay for preventing morbidity and mortality is timely and appropriate supportive care, particularly among patients with severe dengue. The case-fatality ratio for severe dengue can be 10%

or higher when untreated but can be reduced to less than 1% with appropriate clinical management [9].

The first Food and Drug Administration-approved dengue vaccine, CYD-TDV (chimeric yellow fever-dengue-tetravalent dengue vaccine) manufactured by Sanofi Pasteur, was recently recommended by the Advisory Committee on Immunization Practices (ACIP) for children aged 9–16 years who live in an endemic area in the Unites States and have laboratory evidence of prior DENV infection [10]. Understanding the proportion of dengue and severe dengue in this age group, and whether the severe disease clinical manifestations and complications are different among children compared to adults, is important for clinical management and vaccine prioritization. We utilized data from the Sentinel Enhanced Dengue Surveillance System (SEDSS) to compare clinical and laboratory findings among patients with nonsevere dengue to those with severe dengue and explore differences in manifestations of severe dengue by age.

METHODS

Study Enrollment and Data Collection

SEDSS is a facility-based acute febrile illnesses surveillance system that operates at 2 clinical sites in southern Puerto Rico: Saint Luke's Episcopal Hospital located in Ponce (SLEH-Ponce), a 425 inpatient bed, tertiary care teaching hospital that has approximately 50 000 annual emergency department (ED) visits; and SLEH-Guayama, a 161 inpatient bed hospital that received approximately 35 000 annual ED visits [11]. We analyzed clinical and laboratory data from patients with diagnostic evidence of dengue enrolled in SEDSS during 2012–2014.

A detailed description of the SEDSS methods have been previously published [11]. In brief, patients who presented to the emergency room at either SEDSS site were eligible for enrollment if fever was present or they reported a history of fever in the last 7 days. The SEDSS protocol was approved by the Ponce Health Sciences University Institutional Review Board and all participants gave informed consent. A form was completed at enrollment to document clinical characteristics and laboratory findings. Hospitalized participants had their clinical course summarized via the hospital admission abstraction form. Blood, urine, nasopharyngeal, and oropharyngeal specimens were collected from all participants for diagnostic testing. Convalescent blood and urine and additional clinical information were collected at the follow-up visit 7–10 days after hospital discharge. Specimens were processed and transported to CDC Dengue Branch in San Juan, Puerto Rico for diagnostic testing.

Dengue Diagnostic Testing

Serum specimens collected ≤6 days postonset (DPO) were tested by DENV-serotype–specific real-time, reverse transcriptase-polymerase chain reaction assay (rRT-PCR) [12]. Specimens collected ≥ 4 DPO were tested by IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) anti-DENV IgM Capture [13]. Serostatus was

determined by testing RT-PCR–positive specimens collected <7 DPO by anti-DENV IgG ELISA [14].

Definitions

Participants were patients who were offered and accepted enrollment in SEDSS. Dengue cases were participants that tested positive for dengue by rRT-PCR or anti-DENV IgM ELISA. Primary DENV infection was a dengue case for which anti-DENV IgG antibody was not detected, and those with secondary DENV infection had anti-DENV IgG antibody in specimens collected ≤5 DPO. Dengue clinical case classifications followed the 2009 World Health Organization (WHO) guidelines [15]. Dengue warning signs were defined by abdominal pain or tenderness; persistent vomiting (ie, ≥ 3 episodes of emesis in <24 hours); pleural effusion or ascites; mucosal bleeding defined as bleeding from gums or nose, vaginal bleeding, or hematuria; lethargy or restlessness; hepatomegaly (ie, liver enlargement >2 cm); or hemoconcentration.

Dengue cases were classified as severe dengue if at enrollment or follow-up 7–10 days DPO they developed severe dengue manifestations, defined as (1) severe plasma leakage or shock; (2) severe bleeding; or (3) severe organ impairment (definitions provided in Box 1 and Supplementary Table 1).

Data Analysis

We compared the distribution of demographic variables, clinical signs and symptoms, and laboratory findings between dengue and severe dengue cases using R statistical package. We used the Mann-Whitney-Wilcoxon test to compare medians and χ^2 test to estimate the difference in proportions. Separate multivariate logistic regression models explored the association of laboratory findings and clinical symptoms with severe dengue, adjusted by age and DPO. Interaction terms between variables significantly associated with severe dengue in bivariate analyses and age were evaluated. Separate adjusted odds ratios (OR) by age category are presented. Because anti-DENV IgM antibody may remain detectable for several months and potentially result in false-positive cases due to prior rather than acute infection, we conducted a sensitivity analysis that only included dengue cases confirmed by RT-PCR. Findings and significant associations were unchanged when IgM ELISA cases were excluded.

RESULTS

During 2012–2014, a total of 1089 dengue cases were enrolled in SEDSS, of which 720 (66%) tested positive by RT-PCR and 369 (34%) by anti-DENV IgM ELISA only. A total of 281 (26%) cases had severe dengue and 808 (74%) did not (Table 1). Median age among severe dengue cases was 16 years compared to 15 years among nonsevere cases ($P = .04$); 55% of severe dengue cases and 40% of nonsevere cases were aged 10–19 years ($P < .001$). Nealy half (45%) of severe dengue cases occurred among 9–16 year olds, the age group for whom the CYD-TDV dengue vaccine is currently recommended. Severe dengue cases presented for care significantly later in the clinical course than nonsevere cases (mean DPO, 4 [range, 0–7] vs 3 [0–7], respectively, $P < .001$). A total of 483 (44%) dengue cases

were hospitalized, including 87% (245/281) of severe dengue cases and 30% (238/808) of nonsevere cases. Of the 36 severe dengue cases not hospitalized at the study sites, 2 were transferred to another facility, 30 had severe bleeding, and 4 had severe plasma leakage or shock. There was no difference in age or sex between hospitalized and nonhospitalized severe cases. Of the 238 nonsevere cases that were hospitalized, 32% had a comorbidity and 81% had at least 1 warning sign.

Of 719 dengue cases that could be classified as primary or secondary DENV infections, 87% (159/183) of severe dengue cases had secondary DENV infection compared to 76% (407/536) of nonsevere cases ($P = .003$). Among 720 dengue cases for which the infecting DENV was identified, most (94%) were infected with DENV-1, followed by DENV-4 (5%) and DENV-2 (<1%). Among cases infected with DENV-1, 24% (161/679) were severe, compared to 40% (23/38) of DENV-4 cases ($P = .04$). Almost all severe cases infected with DENV-4 (92%) or DENV-1 (84%) were secondary infections. Severe dengue cases compared to nonsevere dengue cases more frequently had leukopenia (77% and 57%, respectively, $P < .001$), thrombocytopenia (74% and 31%, respectively, $P < .001$), low albumin (86% and 44%, $P < .001$), and hemoconcentration (11% vs 4%, $P < .001$). Similar differences were observed when limiting analysis to laboratory tests conducted at presentation (Supplementary Table 2). After adjusting for age and DPO, leukopenia (aOR, 1.4; 95% confidence interval [CI], 1.0–2.1; $P < .001$), thrombocytopenia (aOR, 5.3; 95% CI, 3.8–7.4) and secondary DENV infection (aOR, 2.0; 95% CI, 1.2–3.3) were significantly more prevalent among patients with severe dengue. These associations varied by age, with few significant interactions (Supplementary Table 3). Low albumin and thrombocytopenia had a stronger association with severe dengue among cases aged 10–19 years. Secondary DENV infection was only associated with severe dengue among children and not among adults, as most adults had secondary infections.

Many signs and symptoms were more prevalent among severe dengue cases. Those that persisted after adjusting for age and DPO were: jaundice, rash, petechia/purpura, facial or neck erythema, pruritic skin, red or swollen joints, diarrhea, and irritability. Warning signs were significantly more common among severe dengue cases, and the association remained significant after adjusting by age and DPO for mucosal bleeding (18% vs 11%, $P = .01$), nervousness/anxiety (51% vs 34%, $P < .001$), abdominal pain (78% vs 58%, $P < .001$), persistent vomiting (41% vs 24%, $P < .001$), and signs of fluid accumulation (9% vs 0.6%, $P < .001$). Interactions between age and selected clinical findings showed difference in the association of abdominal pain and severe dengue by age (Supplementary Table 3), with a stronger association among cases aged 10–19 years.

Characteristics of Severe Dengue Cases

Among all severe dengue cases, the most common manifestation of severe dengue was severe plasma leakage/shock (71%) followed by severe bleeding (35%). Most severe bleeding was gastrointestinal and less frequently pulmonary (Table 2). Organ involvement (9%) was an uncommon manifestation of severe dengue. Few cases had multiple manifestations of severe dengue, including 8% with severe bleeding and severe plasma leakage/shock, and 5% with organ involvement and another manifestation (Figure 1).

Frequency of severe bleeding was significantly higher among adults compared to 10–19 year olds (52% vs 24%; OR, 0.3; 95% CI, .2–.5) (Table 3). Frequency of organ involvement was similar across age groups (9%–13%). Compared to adults (49%), severe plasma leakage/shock was significantly more common among cases aged 10–19 years (86%; OR, 6.4; 95% CI, 3.5–12.1) or 0–9 years (59%; OR, 1.7; 95% CI, .8–3.6) (Table 3). This association remained significant after adjusting for serostatus.

Most severe dengue cases had leukopenia (84%). Thrombocytopenia was common among those aged 10–19 years (87%), but less frequent among those aged <10 years (45%) or >19 years (66%) (Table 3). The association between thrombocytopenia and age remained significant after adjusting by serostatus. Severe bleeding was more common among those with platelet counts greater than 100 000/microL, as it occurred with a frequency of 35%, 24%, and 51% among those with a platelet count of <50 000/microL, 50 000–100 000/microL, and >100 000 platelets/microL, respectively. In contrast, severe plasma leakage was more common among those with the lowest platelet count, and was 78%, 82%, and 49% among those with a platelet count of <50 000/microL, 50 000–100 000/microL, and >100 000 platelets/microL, respectively ($P < .001$).

Most dengue and severe dengue cases had evidence of past DENV infection. Among 719 with IgG testing available, there were 24 severe dengue cases with primary DENV infections, 2 were among infants, 18 among ages 1–19 years, and 4 cases among adults. Of the 24 severe primary DENV cases, 12 had severe plasma leakage alone; 6 had severe bleeding alone; 2 had severe plasma leakage and severe bleeding; 1 had severe plasma leakage, severe bleeding, and shock; 1 had severe bleeding, plasma leakage, and organ involvement; 1 had organ involvement and plasma leakage; and 1 had shock alone.

DISCUSSION

We report the results of an emergency department- and hospital-based study conducted during the most recent dengue epidemic in Puerto Rico. In this study, more than two-thirds of cases of dengue and severe dengue were among patients aged 0–19 years. Most severe dengue cases and one-third of nonsevere cases were hospitalized, underscoring the burden to the health care system during dengue outbreaks. Most dengue patients in this study were experiencing secondary DENV, and as expected secondary DENV infection was more common among those with severe dengue as documented in other studies [16]. This study shows important differences in severe dengue manifestation among children versus adults: while severe plasma leakage was the most common manifestation for severe dengue among children, severe bleeding was more common among adults.

CYD-TDV is the only dengue vaccine approved and recommended for use in the United States, in children aged 9–16 years who live in endemic areas and have diagnostic evidence of prior DENV infection. Although CYD-TDV is not likely to reduce DENV transmission at the population level, it is highly efficacious in reducing the risk of disease, hospitalizations, and severe dengue among seropositive children [10]. As an estimated 250 000 children live in Puerto Rico and half are estimated to be seropositive [10], routine vaccination among this age group can be an important tool to combat dengue and reduce hospital burden during

outbreaks. Nonetheless, as CYD-TDV is only recommended for children aged 9–16 years, and important morbidity occurs among younger and older individuals [10], alternative or additional approaches to reduce the burden of dengue will be needed. Furthermore, this vaccine can increase the risk of severe dengue if administered to sero-negative children. Therefore, prevaccination screening with highly specific tests must be implemented as part of a vaccination program, which complicates logistics. Vaccines developed by Takeda (TAK-003) and NIH/Merck (TV003/TV005) have completed or are in phase 3 clinical trials [17, 18], may not require prevaccination screening, and could be used for a broader age range, thus having potentially a larger impact on herd immunity if they are recommended for use by ACIP.

In this study, secondary infection was associated with severe dengue among pediatric patients, and most nonsevere dengue cases were also experiencing secondary infection. Multiple epidemiologic studies have shown that the risk of severe disease is higher during a secondary DENV infection than during a primary infection [16]. Nearly 1 of every 10 severe dengue cases resulted from primary DENV infections, similar to previous reports [16]. The severe dengue cases among primary DENV infections mainly occurred among younger participants, two-thirds of whom presented with plasma leakage and one-third with severe bleeding. Although antibody-dependent enhancement can lead to higher viremia and subsequently severe dengue, it is not the only explanation for the manifestations of severe dengue. Occurrence of severe dengue in primary infections could result from a higher inoculum, viral strain, serotype, or host factors [19–21].

The rate of hospitalization in this study was high, similar to what has been reported in Asia but lower than in other parts of Latin America [22]. This may be influenced by recruitment for our study being based at major referral hospitals with a bias towards more severe cases and hospitalizations. This burden of dengue on the health care system has significant economic impact. The global average estimated cost per dengue case is US$70.10 (95% uncertainty interval, $66.66–$74.63) for cases admitted to hospital, and $51.16 ($49.80–$53.71) for an ambulatory case [23]. In contrast, the cost of hospitalizing dengue patients in Puerto Rico (US$2132; 95% CI, 1705–2558) is substantially higher than the global average (US$70.10) [24, 25]. Similarly, the disability-adjusted life year (DALY) losses due to dengue in Puerto Rico are on the same order of magnitude of those due to malaria, tuberculosis, or hepatitis elsewhere in Latin America and the Caribbean [26]. Hence, implementation of dengue vaccination in Puerto Rico, even if only among 9–16 year olds initially, could have economic impact.

The most common presentation of severe dengue was severe plasma leakage followed by severe bleeding. Our findings support the generally accepted view that severe vascular leakage is more common in children [27, 28]. Age is known to influence intrinsic vascular permeability, with children demonstrating a lower threshold for leakage than adults [27]. Shock was uncommon and present in less than one-tenth of severe dengue patients. Contrary to previous reports suggesting that hemorrhage in children is rare and associated with shock [20, 27], we observed hemorrhage in one-third of severe dengue cases among children aged <10 years. Co-occurrence of severe plasma leakage/shock and hemorrhage was uncommon. While thrombocytopenia was highly prevalent among severe dengue cases, it was not

associated with hemorrhage in this study but was associated with severe plasma leakage, as reported elsewhere [29].

Whereas strengths of this study include utilization of a relatively large sample size and identification of dengue patients among all age groups, there were several limitations. We did not have results on serostatus and serotype among all participants. DENV-1 predominated during the study and findings may not be generalizable to other serotypes. Most participants with plasma leakage were classified as severe because of low albumin, which can be caused by other chronic comorbidities such as liver injury; however, most patients with plasma leakage were children among whom comorbidities were uncommon. Dengue cases were defined as either IgM positive or PCR positive, which may have led to some misclassification. However, a sensitivity analyses including only PCR-positive cases found similar results. Also, clinical findings were not available for dengue cases transferred or admitted to other facilities, hence the frequency of some manifestations and patient outcomes may have been underestimated. Last, definition of severe dengue was based on WHO criteria and included signs of gastrointestinal bleeding. Gastrointestinal bleeding without shock, hemodynamic instability, or need for blood transfusion may not indicate clinically severe dengue [11], in particular if it was self-reported, as in this study. Hence, some cases of severe dengue may have been misclassified. This helps explain why 34 cases of severe dengue were not hospitalized; self-reported data on severe bleeding could have been ruled out by clinicians after exploring further, resulting in the patient being discharged.

This study is one of the larger studies describing severe dengue in the current literature and contributes to the understanding of the prevalence of the different manifestations of severe dengue. Because most severe dengue cases were among children aged 10–19 years, the currently approved dengue vaccine for children and adolescents aged 9–16 years could help reduce disease and hospitalizations among this group. Clinicians should be aware of the different manifestations of severe dengue in children versus adults and carefully evaluate pediatric patients for plasma leakage, which may be harder to identify than severe hemorrhage. This may help clinicians to initiate supportive management rapidly and judiciously.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.

Definition of Severe Dengue

Severe plasma leakage or shock	Severe dengue defined as (1) severe plasma leakage or shock; OR (2) severe bleeding; OR (3) severe organ impairment	
	Shock OR respiratory distress AND plasma leakage Shock, any of 3 criteria:	
	1. Shock listed in medical assessment at any time	Respiratory distress and plasma leakage, both criteria:
	2. Use of vasopressors, inotropics, or vasodilators; use of albumin	1. Respiratory compromise: any of the following
		Tachypnea
	3. Pulse pressure <20 mmHg OR hypotension OR drop in systolic blood pressure >40 mmHg AND any 2 of the following:	Respiratory distress
		Accessory muscles use
		Supplemental oxygen
		Intubation
		2. Plasma leakage: any of the following
		Pleural effusion
	Elevated heart rate	Pericardial effusion
	Capillary refill > 2 seg	Ascites
	Mottled skin	Free fluid in abdomen
	Thready, weak pulse	Hematocrit change >20% during illness
	Pale and/or cold skin	Hematocrit value >20% above baseline
	Blue skin or lips	for age and sex at any time Albumin low for age
	Cyanotic limbs	
	Cold limbs	
Severe bleeding	Any of the following:	
	Blood transfusion	
	Hematochezia	
	Melena	
	Hematemesis	
Severe organ involvement	Any of the following:	
	AST or ALT ≥ 1000 U	
	Intubation/mechanical ventilation	
	PT INR ≥ 1.5	
	Encephalopathy	
	Myocarditis	
	Acute hepatitis	
	Glasgow score <11	
	Aseptic meningitis	
	Acute paralysis	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; PT, prothrombin time.

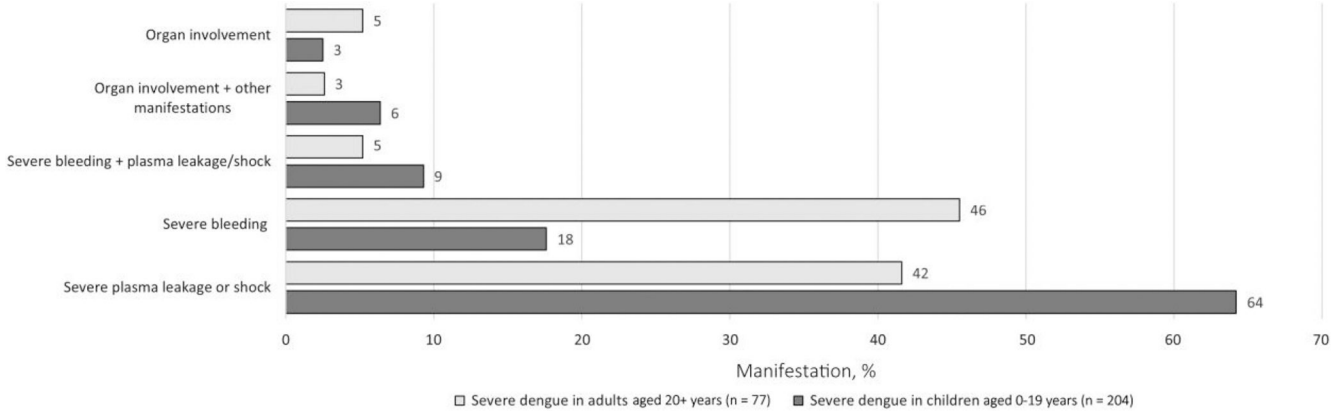

Figure 1.

Combination of manifestations of severe dengue, Sentinel Enhanced Dengue Surveillance System, Puerto Rico, 2012–2014.

Table 1.

Demographic Characteristics and Clinical Laboratory Findings Among Patients With Dengue and Severe Dengue, Sentinel Enhanced Dengue Surveillance System, Puerto Rico, 2012–2014

Characteristic	Total, No. (%) (n = 1089)	Severe, No. (%) (n = 281)	Nonsevere, No. (%) (n = 808)	*P* Value,[a] Severe vs Nonsevere
Sex				
Male	579 (53.2)	158 (56.2)	421 (52.1)	.26
Female	510 (46.8)	123 (43.8)	387 (47.9)	.26
Age, y, median (range)	15.3 (0–97.1)	16.1 (0.2–82.8)	14.9 (0–97.1)	.04
0–9	274 (25.2)	49 (17.4)	225 (27.8)	.001
10–19	478 (43.9)	155 (55.2)	323 (40.0)	.001
20–29	119 (10.9)	25 (8.9)	94 (11.6)	.25
30–39	59 (5.4)	15 (5.3)	44 (5.4)	1.0
40–49	47 (4.3)	9 (3.2)	38 (4.7)	.37
50+	112 (10.3)	28 (10.0)	84 (10.4)	.93
Year of recruitment				
2012	418 (42.8)	115 (48.5)	303 (40.9)	.05
2013	455 (46.6)	108 (45.6)	347 (46.9)	.78
2014	104 (10.6)	14 (5.9)	90 (12.2)	.01
Days after illness onset, median (range)	3 (0–7.0)	4 (0–7.0)	3 (0–7.0)	<.001
<3	417 (38.3)	63 (22.4)	354 (43.8)	<.001
3–5	592 (54.4)	191 (68.0)	401 (49.6)	<.001
6–7	80 (7.3)	27 (9.6)	53 (6.6)	.12
Disposition				
Admitted	483 (44.4)	245 (87.2)	238 (29.5)	<.001
Died	1 (0.1)	0 (0)	1 (0.1)	1.0
Sent home	602 (55.3)	34 (12.1)	568 (70.3)	<.001
Transferred	3 (0.3)	2 (0.7)	1 (0.1)	.34
Duration of hospitalization among those hospitalized	n = 483	n = 245	n = 238	
Duration of hospitalization in days, median (range)	3.0 (0–14.0)	3.5 (0–14.0)	3.0 (1.0–10.0)	<.001
Secondary DENV infection	n = 719	n = 183	n = 536	
No	153 (21.3)	24 (13.1)	129 (24.1)	

Characteristic	Total, No. (%) (n = 1089)	Severe, No. (%) (n = 281)	Nonsevere, No. (%) (n = 808)	*P* Value,[a] Severe vs Nonsevere
Yes	566 (78.7)	159 (86.9)	407 (75.9)	.003
Infecting DENV	n = 720	n = 176	n = 544	
DENV-1	679 (94.3)	161 (91.5)	518 (95.2)	.09
DENV-2	3 (0.4)	0 (0)	3 (0.6)	.75
DENV-4	38 (5.3)	15 (8.5)	23 (4.2)	.04
Laboratory findings				
Highest AST U/L, median (range)	104 (10–8111)	153 (13–8111)	86 (10–909)	<.001
AST <50 U/L	129 (22.8)	49 (19.4)	80 (25.4)	.11
AST 51–500 U/L	388 (68.4)	164 (65.1)	224 (71.1)	.15
AST 501–1000 U/L	38 (6.7)	27 (10.7)	11 (3.5)	.001
AST >1000 U/L	12 (2.1)	12 (4.8)	0 (0)	<.001
Lowest ALT U/L, median (range)	87 (160–7548)	136 (20–7548)	68 (16–968)	<.001
ALT <50 U/L	161 (28.3)	49 (19.4)	112 (35.4)	<.001
ALT 51–500 U/L	364 (64.0)	170 (67.2)	194 (61.4)	.18
ALT 501–1000 U/L	39 (6.9)	29 (11.5)	10 (3.2)	<.001
ALT >1000 U/L	5 (0.9)	5 (2.0)	0 (0)	.0396
Lowest WBC/microL, median (range)	3400 (800–24 000)	2900 (800–19 000)	3700 (900–24 000)	<.001
WBC ≤4000 cells/microL	661 (62.2)	212 (76.5)	449 (57.2)	<.001
WBC 4001–10000 cells/microL	358 (33.7)	60 (21.7)	298 (38)	<.001
WBC >10000 cells/microL	43 (4.0)	5 (1.8)	38 (4.8)	.04
Lowest PLT/microL, median (range)	11 4000 (2000–511 000)	62 000 (2000–457 000)	134 000 (3000–511 000)	<.001
PLT < 50000/microL	158 (14.9)	87 (31.3)	71 (9.1)	<.001
PLT 50 000–100 000/microL	294 (27.7)	119 (42.8)	175 (22.3)	<.001
PLT >100 000/microL	609 (57.4)	72 (25.9)	537 (68.6)	<.001
Thrombocytopenia <100 000 platelets/microL	452 (42.6)	206 (74.1)	246 (31.4)	<.001
Highest hematocrit %, median (range)	41.2 (28.5–57.4)	41.3 (28.9–55.5)	41.0 (28.5–57.4)	.95
Hemoconcentration	60 (5.6)	30 (10.8)	30 (3.8)	<.001
Low albumin g/dL	309 (65.5)	208 (85.6)	101 (44.1)	<.001
Lowest albumin g/dL, median (range)	3.2 (1.9–5.0)	3.1 (1.9–4.1)	3.4 (2.0–5.0)	<.001

Data are No. (%) except where indicated.Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DENV, dengue virus; PLT, platelets; WBC, white blood cell; U/L, units per litre; microL, microlitre; dL, decilitre; g, grams.

[a] Calculated with the Mann-Whitney-Wilcoxon test to compare medians and χ^2 test to estimate the difference in proportions.

Table 2.

Signs and Symptoms Associated With Severe Dengue Among Laboratory-Positive Dengue Patients, Sentinel Enhanced Dengue Surveillance System, Puerto Rico, 2012–2014

Characteristic	Total, No. (%) (n = 1089)	Severe, No. (%) (n = 281)	Nonsevere, No. (%)(n = 808)	P^a Value
Comorbidities				
Any chronic medical condition	339 (31.1)	81 (28.8)	258 (31.9)	.37
Asthma	203 (18.6)	50 (17.8)	153 (18.9)	.7380
Coronary heart disease	37 (3.4)	12 (4.3)	25 (3.1)	.4554
Diabetes	70 (6.4)	14 (5.0)	56 (6.9)	.3144
High blood pressure	87 (8.0)	19 (6.8)	68 (8.4)	.4513
High cholesterol	44 (4.0)	11 (3.9)	33 (4.1)	1.0000
Cancer	16 (1.5)	3 (1.1)	13 (1.6)	.7175
Thyroid	43 (3.9)	8 (2.8)	35 (4.3)	.3560
Sickle cell disease	7 (0.6)	2 (0.7)	5 (0.6)	1.0000
Other	23 (2.1)	7 (2.5)	16 (2.0)	.7854
Signs and symptoms				
Eye pain	614 (57.2)	165 (58.7)	449 (56.6)	.59
Headache	915 (84.0)	245 (87.2)	670 (82.9)	.11
Jaundice/icteric sclera	57 (5.3)	35 (12.5)	22 (2.8)	<.001
Red conjunctiva	614 (57.2)	165 (58.7)	449 (56.6)	.59
Skin rash	613 (56.9)	191 (68.0)	422 (53.0)	<.001
Petechia/purpura	383 (35.4)	137 (48.8)	246 (30.7)	<.001
Facial and/or neck erythema	637 (59.3)	190 (68.3)	447 (56.2)	<.001
Pruritic skin	412 (38.3)	132 (47.1)	280 (35.2)	<.001
Chills	867 (80.2)	245 (87.5)	622 (77.7)	<.001
Muscle/bone/back pain	833 (77.5)	237 (84.6)	596 (75.0)	.001
Joint pain	667 (62.5)	194 (69.3)	473 (60.0)	.007
Red/swollen joints	177 (16.7)	61 (22.0)	116 (14.8)	.008
Cough	475 (44.1)	136 (48.7)	339 (42.5)	.08
Rhinorrhea	356 (33.1)	105 (37.6)	251 (31.5)	.07
Sore throat	410 (38.3)	118 (42.1)	292 (37.0)	.14
Anorexia	869 (80.8)	250 (89.6)	619 (77.7)	<.001
Nausea	744 (69.5)	222 (79.9)	522 (65.9)	<.001
Diarrhea	449 (41.9)	148 (53.2)	301 (37.9)	<.001
Dizziness	674 (62.5)	205 (73.2)	469 (58.8)	<.001
Tiredness, lethargy	953 (88.1)	266 (95.3)	687 (85.6)	<.001
Irritability	357 (33.2)	127 (45.4)	230 (28.9)	<.001
Seizure	19 (1.8)	9 (3.2)	10 (1.2)	.06
Warning signs				
Mucosal bleeding	140 (12.9)	51 (18.1)	89 (11.1)	.01
Nose/gums	100 (9.2)	36 (12.8)	64 (8.0)	.02
Unusual vaginal	26 (8.8)	10 (11.0)	16 (7.9)	.52

Characteristic	Total, No. (%) (n = 1089)	Severe, No. (%) (n = 281)	Nonsevere, No. (%)(n = 808)	P^a Value
Macroscopic blood in urine	26 (2.4)	13 (4.7)	13 (1.6)	.009
Abdominal pain	679 (63.1)	218 (77.9)	461 (57.9)	<.001
Vomiting (3 or more episodes in day)	304 (28.1)	115 (40.9)	189 (23.6)	<.001
Nervousness, anxiety	410 (38.3)	142 (51.1)	268 (33.8)	<.001
Hemoconcentration	60 (5.6)	30 (10.8)	30 (3.8)	<.001
Fluid accumulation				
Ascites	2 (0.8)	2 (1.3)	0 (0)	.68
Pleural effusion	23 (4.0)	21 (8.4)	2 (0.6)	<.001
Any fluid accumulation	24 (4.2)	22 (8.8)	2 (0.6)	<.001
Signs of respiratory distress				
Tachypnea	491 (46.3)	209 (75.5)	282 (36.0)	<.001
Signs of shock				
Any sign of poor circulation	716 (65.7)	219 (77.9)	497 (61.5)	<.001
At least 2 signs of poor circulation	210 (19.3)	69 (24.6)	141 (17.5)	.0120
Narrow pulse pressure	21 (2.0)	9 (3.2)	12 (1.5)	.14
Hypotension	71 (15.0)	47 (19.4)	24 (10.4)	.009
Drop systolic blood pressure	15 (3.4)	10 (5.3)	5 (2.0)	.11
Use of vasopressors	4 (0.8)	4 (1.7)	0 (0)	.14
Diagnoses of shock	1 (0.1)	1 (0.4)	0 (0)	.58
Severe dengue classification				
Severe bleeding	99 (9.1)	99 (35.2)	0 (0)	
Vomit with blood	28 (2.6)	28 (10.0)	0 (0)	
Feces with blood	17 (1.6)	17 (6.0)	0 (0)	
Black tarry stools	49 (4.5)	49 (17.4)	0 (0)	
Pulmonary hemorrhage	2 (0.4)	2 (0.9)	0 (0)	
Any blood product received	17 (3.6)	17 (7.0)	0 (0)	
Severe plasma leakage + shock	200 (18.4)	200 (71.2)	0 (0)	
Severe plasma leakage	187 (17.2)	187 (66.5)	0 (0)	
Fluid accumulation plus respiratory distress	16 (2.7)	16 (6.3)	0 (0)	
Shock	22 (2.0)	22 (7.8)	0 (0)	
Severe organ involvement	24 (4.0)	24 (9.3)	0 (0)	

[a]Calculated with the Mann-Whitney-Wilcoxon test to compare medians and χ^2 test to estimate the difference in proportions.

Table 3.

Difference in Severe Dengue Manifestations and Selected Laboratory Parameters by Age, Sentinel Enhanced Dengue Surveillance System, Puerto Rico, 2012–2014

Criteria for severe dengue	Total No. Severe Dengue Cases in Each Category (n = 281)	No. (%, Row)	*P* Value[a]	Odds Ratio[a] (95% CI)
Severe bleeding	281	99 (35.2)		
0–9 y	49	22 (44.9)	.44	0.8 (.4–1.5)
10–19 y	155	37 (23.9)	.0000	0.3 (.2–.5)
20+ y	77	40 (51.9)	Reference	
Severe plasma leakage or shock	281	200 (71.2)		
0–9 y	49	29 (59.2)	.1380	1.7 (.8–3.6)
10–19 y	155	133 (85.8)	<.001	6.4 (3.5–12.1)
20+ y	77	38 (49.4)	Reference	
Severe organ involvement	257	24 (9.3)		
0–9 y	39	5 (12.8)	.54	1.5 (.4–5.3)
10–19 y	152	13 (8.6)	.95	1.0 (.4–2.9)
20+ y	66	6 (9.1)	Reference	
Select laboratory values				
Secondary DENV infection	183	159 (86.9)		
0–9 y	30	24 (80.0)	.27	0.5 (.1–1.8)
10–19 y	114	100 (87.7)	.68	0.8 (.2–2.4)
20+ y	39	35 (89.7)	Reference	
Leukopenia (WBC ≤4000 cells/microL)	277	212 (76.5)		
0–9 y	47	29 (61.7)	.80	0.9 (.4–1.9)
10–19 y	155	135 (87.1)	<.001	3.8 (1.9–7.4)
20+ y	75	48 (64.0)	Reference	
Thrombocytopenia (<100 000 platelets/microL)	278	206 (74.1)		
0–9 y	47	21 (44.7)	.02	0.4 (.2–.9)
10–19 y	155	135 (87.1)	.001	3.1 (1.6–6.2)
20+ y	76	50 (65.8)	Reference	
Low albumin (g/dL)	243	208 (85.6)		
0–9 y	37	28 (75.7)	.53	1.4 (.5–3.6)
10–19 y	147	139 (94.6)	<.001	7.5 (3.1–19.5)
20+ y	59	41 (69.5)	Reference	
High AST or ALT (>500 U/L)	252	41 (16.3)		
0–9 y	38	4 (10.5)	.73	0.8 (.2–2.8)
10–19 y	152	29 (19.1)	.36	1.5 (.7–3.7)
20+ y	62	8 (12.9)	Reference	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; DENV, dengue virus; WBC, white blood cell; U/L, units per litre; microL, microlitre; dL, decilitre; g, grams.

[a]Odds ratios adjusted by days postonset.