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Clinical Characteristics and Outcomes Among Travelers With Severe Dengue:

A GeoSentinel Analysis

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Abstract

Background: Dengue virus is a flavivirus transmitted by *Aedes* mosquitoes and is an important cause of illness worldwide. Data on the severity of travel-associated dengue illness are limited.

Objective: To describe the epidemiology, clinical characteristics, and outcomes among international travelers with severe dengue or dengue with warning signs as defined by the 2009 World Health Organization classification (that is, complicated dengue).

Design: Retrospective chart review and analysis of travelers with complicated dengue reported to GeoSentinel from January 2007 through July 2022.

Setting: 20 of 71 international GeoSentinel sites.

Patients: Returning travelers with complicated dengue.

Measurements: Routinely collected surveillance data plus chart review with abstraction of clinical information using predefined grading criteria to characterize the manifestations of complicated dengue.

Results: Of 5958 patients with dengue, 95 (2%) had complicated dengue. Eighty-six (91%) patients had a supplemental questionnaire completed. Eighty-five of 86 (99%) patients had warning signs, and 27 (31%) were classified as severe. Median age was 34years (range, 8 to 91 years); 48 (56%) were female. Patients acquired dengue most frequently in the Caribbean (n = 27 [31%]) and Southeast Asia (n = 21 [24%]). Frequent reasons for travel were tourism (46%) and visiting friends and relatives (32%). Twenty-one of 84 (25%) patients had comorbidities. Seventy-eight (91%) patients were hospitalized. One patient died of nondengue-related illnesses. Common laboratory findings and signs were thrombocytopenia (78%), elevated aminotransferase (62%),

bleeding (52%), and plasma leakage (20%). Among severe cases, ophthalmologic pathology (n = 3), severe liver disease (n = 3), myocarditis (n = 2), and neurologic symptoms (n = 2) were reported. Of 44 patients with serologic data, 32 confirmed cases were classified as primary dengue (IgM+/IgG−) and 12 as secondary (IgM−/IgG+) dengue.

Limitations: Data for some variables could not be retrieved by chart review for some patients. The generalizability of our observations may be limited.

Conclusion: Complicated dengue is relatively rare in travelers. Clinicians should monitor patients with dengue closely for warning signs that may indicate progression to severe disease. Risk factors for developing complications of dengue in travelers need further prospective study.

Primary Funding Source: Centers for Disease Control and Prevention, International Society of Travel Medicine, Public Health Agency of Canada, and GeoSentinel Foundation.

Dengue is the most widely occurring arboviral infection globally and is endemic in approximately 130 countries. Approximately 50 to 100 million cases of symptomatic dengue virus (DENV) infection are reported annually (1). The global age-standardized incidence rate of dengue was estimated to have tripled to 1371 per 100 000 population in 2017 compared with 1990 (2). In the same time span, the reported number of dengue-related deaths increased from 16957 to 40467 (2).

Classifying dengue severity and predicting outcomes for patients with dengue can be challenging. The 2009 World Health Organization (WHO) dengue classification, which is the most recent, distinguishes dengue with warning signs and severe dengue. Warning signs in a patient with dengue include abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, and increasing hematocrit with decreasing platelets (3). The recognition of warning signs may facilitate timely triage of patients at risk for severe dengue (4). Severe dengue is defined as dengue with any of the following: severe plasma leakage leading to shock or respiratory distress, severe hemorrhage as determined by the clinician, or organ failure (3). The inclusion of organ failure in the definition increases the sensitivity to identify severe dengue (4). The 2009 WHO dengue classification system was also met with scrutiny because of its incomplete inclusion of disease severity manifestations and use of arbitrary laboratory cutoffs (5).

International travel is a known risk for acquiring dengue. Dengue was recently identified as the leading cause of acute undifferentiated febrile illness among travelers returning to Europe from all continents except Africa (6). Attack rate estimates among travelers to endemic regions range from 10 to 30 per 1000 person-months but depend on travel destination, duration, and seasonality (7–9). The clinical course of dengue among travelers is most frequently uncomplicated (10–13). Transmission intensity of DENV in the destination country; secondary dengue; time interval since the preceding dengue episode or other flavivirus exposure; seasonality; exposure during epidemic years; and host factors, such as older age and comorbidities, have been identified as risk factors for severe dengue in travelers (9).

The objective of this analysis was to describe the epidemiology, clinical manifestations, and outcomes of a large cohort of international travelers with severe dengue and dengue with warning signs using the GeoSentinel network surveillance platform.

Methods

GeoSentinel (https://geosentinel.org), a collaboration between the Centers for Disease Control and Prevention and the International Society of Travel Medicine, is a global clinical care-based surveillance system that monitors infectious diseases and other adverse health events that may affect international travelers and migrants. GeoSentinel comprises 71 clinical sites in 29 countries on 6 continents, where expert travel and tropical medicine clinicians diagnose and treat patients.

Project Design

Patients were eligible for inclusion when seen with complicated dengue at GeoSentinel sites from January 2007 through July 2022. A supplemental data collection form (Supplement, available at Annals.org) was deployed to all GeoSentinel sites that submitted complicated dengue cases and collected information on patient demographic characteristics (for example, age and sex), travel history (for example, country of DENV exposure and duration of travel), medical history (for example, history of flavivirus vaccination and comorbidities), symptoms, dengue-related clinical findings (for example, thrombocytopenia and bleeding), clinical testing (for example, imaging, ophthalmologic examination, and dengue diagnostic test results), and clinical course (for example, vital signs, hospitalization, admission to an intensive care unit [ICU], coinfections, need for sick leave, and death). Data were abstracted via retrospective chart review by qualified health personnel. All data were reviewed in detail; in the event of missing or unclear data, the respective site was queried to complete or clarify data questions to maintain consistency and quality. Physical examination and testing were done at the discretion of the individual patient's treating clinicians.

GeoSentinel's surveillance data collection protocol and the supplemental complicated dengue questionnaire have been reviewed by a human subjects advisor at Centers for Disease Control and Prevention's National Center for Emerging and Zoonotic Infectious Diseases and has been determined to be public health surveillance and not human subjects research.

Definitions

The GeoSentinel database diagnostic coding includes 2 dengue network-specific codes: dengue fever and complicated dengue. Dengue fever is defined by GeoSentinel as a compatible clinical illness with fever, rash, and arthralgia with appropriate exposure history (that is, a clinical diagnosis) and no evidence of complications, with laboratory testing as defined below. Complicated dengue is defined by GeoSentinel as confirmed or probable dengue with evidence of severe dengue (that is, adapted from the 2009 WHO guidelines) or confirmed or probable dengue with warning signs only (per WHO guidelines) (3). Confirmed cases of dengue were defined as a compatible clinical illness and appropriate exposure history with either DENV isolation, a positive DENV-specific result on reverse

transcriptase polymerase chain reaction, positive nonstructural protein 1 (NS1) antigen detection, and/or seroconversion (defined as a 4-fold increase in IgG anti-DENV antibody titers). A probable case of dengue was defined as a compatible clinical illness and appropriate exposure history with either a single positive DENV IgM result or high positive DENV IgG result.

If anti-DENV IgM was present and anti-DENV IgG was not present in acute phase sera of confirmed cases, the dengue episode was classified as a primary dengue. If only anti-DENV IgG antibody was present in acute phase sera of confirmed cases, the episode was classified as a secondary (or subsequent) dengue (14).

Given challenges with the 2009 WHO classification, we retrospectively graded dengue severity for the purpose of the current analysis by applying standardized clinical end point definitions (adapted from Tomashek and colleagues [15]). These consensus end points were developed by internationally recognized experts using a Delphi method to harmonize data collection and improve comparability of clinical outcomes between dengue clinical trials. The consensus end points include grades of severity for plasma leakage, bleeding, thrombocytopenia, liver disease, neurologic disease, and myocarditis. In line with the consensus end points (Table 1), we captured only alanine aminotransferase elevations greater than 10 times the upper limit of normal.

Statistical Analysis

Data were abstracted from medical charts at each site and manually entered by site personnel into a Research Electronic Data Capture (REDCap) database, version 12.0.8 (Vanderbilt University), at the Institute of Tropical Medicine in Antwerp, Belgium. Data were analyzed using SAS, version 9.4 (SAS Institute). All analyses were descriptive. The denominator for each frequency calculation was the number of patients with available data for each given variable.

Role of the Funding Source

Centers for Disease Control and Prevention staff contributed technical expertise to epidemiology, data analytics and interpretation, and manuscript writing.

Results

Study Population

Before the COVID-19 pandemic, the GeoSentinel network observed steadily increasing numbers of returning travelers with dengue over time, capturing a maximum of 835 records in 2019.

Ninety-five of 5958 (2%) dengue records entered in the GeoSentinel database from January 2007 through July 2022 met the criteria for complicated dengue. Of these 95 records, accessible medical records were available for 86 (91%) patients. At these sites ($n = 20$), data were retrieved, and supplemental questionnaires were completed (Table 2). Forty-eight of 86 (56%) patients were female. Median age was 34 years (range, 8 to 91 years), and 6 patients were younger than 18 years. Patients most frequently acquired dengue in the

Caribbean (*n* = 27 [31%]), Southeast Asia (*n* = 21 [24%]), and Oceania (*n* = 11 [13%]) (for individual country breakdown, see Appendix Table 1, available at Annals.org). The most frequent reasons for travel were tourism (*n* = 39 [46%]) and visiting friends and relatives (*n* = 27 [32%]). Fifty-eight of 86 (67%) patients with complicated dengue traveled less than 4 weeks, and 21 of 84 (25%) travelers with complicated dengue had medical comorbidities.

Diagnosis

Sixty-eight of 86 (79%) patients had confirmed dengue. Laboratory diagnosis methods were NS1 antigen detection (*n* = 40), reverse transcriptase polymerase chain reaction (*n* = 6), both NS1 antigen detection and reverse transcriptase polymerase chain reaction (*n* = 21), or seroconversion alone (*n* = 1). Dengue was diagnosed clinically in 7 (8%) patients (test results were not available in chart review but met the definition for complicated dengue per the GeoSentinel record) and by a single DENV IgM in 10 (12%) patients. For 1 patient, diagnostic information was missing. Serotyping of DENV was available for 15 patients and serotypes included DENV-1 (*n* = 6 [40%]), DENV-2 (*n* = 5 [33%]), and DENV-3 (*n* = 4 [27%]); no patients had DENV-4.

Prior dengue was reported by 6 of 86 (7%) patients. On the basis of serologic data available for 44 (51%) patients with complicated dengue, 32 of 44 (73%) had primary dengue and 6 (19%) of them were classified as severe dengue. Twelve of 44 (27%) had secondary (or subsequent) dengue, and 6 (50%) of them were classified as severe disease (Appendix Table 2, available at Annals.org). For the persons with secondary dengue, the following reasons for travel were recorded: visiting friends and relatives (*n* = 5), business (*n* = 3), student travel (*n* = 1), tourism (*n* = 1), expatriate travel (*n* = 1), and humanitarian aid (*n* = 1).

Classification of Cases Based on 2009 WHO Criteria

Eighty-five (99%) patients had warning signs, and 27 (31%) were classified as severe dengue on the basis of the 2009 WHO criteria (Table 3). One patient had severe dengue in the absence of warning signs; they had shock and altered mental status when presenting to the GeoSentinel site.

Clinical Presentation

Signs and laboratory findings of patients with complicated dengue are listed in Table 4; forty-four of 85 (52%) patients had evidence of bleeding, and 15 of 75 (20%) patients had signs of plasma leakage. Signs of neurologic disease were present in 5 of 80 (6%) patients, and 2 of 77 (3%) patients had myocarditis. Twenty-seven patients had an ophthalmologic examination done, and 6 (22%) had an abnormal examination, demonstrating maculopathy with acute vision loss (*n* = 2; one case was previously reported [16]), conjunctival hemorrhage (*n* = 2), retinal hemorrhage, and conjunctival injection. Sixty-three of 81 (78%) patients had thrombocytopenia. Nineteen of 81 (23%) patients had liver disease. Six of 75 (8%) patients had a coinfection, most frequently bacterial.

Outcomes

Seventy-eight of 86 (91%) patients were hospitalized, including 31 (36%) who were hospitalized during travel. Median duration of hospitalization was 5days (range, 1 to 99

days; interquartile range, 3 to 8 days). Thirteen of 77 (17%) patients were admitted to an ICU, for a median duration of 3.5days (range, 1 to 47 days; interquartile range, 3 to 8 days). Patients in the ICU more frequently had comorbidities (8 of 13 [62%] vs. 11 of 62 [18%]), coinfections (3 of 12 [25%] vs. 3 of 63 [5%]), severe thrombocytopenia (4 of 12 [33%] vs. 13 of 61 [21%]), severe bleeding (7 of 8 [88%] vs. 4 of 32 [13%]), evidence of moderate or severe plasma leakage (5 of 9 [56%] vs. 10 of 58 [17%]), severe liver disease (2 of 12 [17%] vs. 1 of 61 [2%]), and severe neurologic disease (1 of 4 [25%] vs. 0 of 61 [0%]) than those not in the ICU. One patient (1%) died. The patient had primary dengue per serology and positive NS1 antigen, multiple comorbidities, and was hospitalized in Martinique during travel before medical evacuation to France; death was attributed to complications from bacteremia, candidemia, and systemic lupus erythematosus. Among 31 of 42 (74%) patients with information available, complicated dengue was a cause of absenteeism after discharge.

Discussion

This is the largest series to date that describes the epidemiology and clinical characteristics of travelers with complicated dengue, including 25 patients with severe dengue. Complicated dengue was acquired by travelers to 6 regions (29 countries) and occurred among both children and adults. Overall, few patients with complicated (2%) dengue were reported to GeoSentinel in the 16-year time frame of this analysis. This observation is similar to previous reports that 0.5% to 11% of hospitalized travelers with dengue met WHO criteria for severe dengue and suggests that severe infection is rare among travelers (10–13). Most patients in our series had warning signs only; retrospective case series have reported frequencies of warning signs in up to one third of travelers with dengue (17).

After a diagnosis of dengue and identification of warning signs, supportive treatment greatly reduces the risk for poor outcomes among patients with dengue (3). Therefore, clinicians should consider admitting travelers with dengue and warning signs and monitor them closely for laboratory findings and signs that may indicate progression to severe disease. More than 90% of patients in this analysis were hospitalized and almost one fifth received ICU care. Seventy-five percent of travelers with complicated dengue did not have comorbidities, but patients with comorbidities were more frequently admitted to an ICU. Recent studies and meta-analyses showed that comorbidities, such as diabetes, hypertension, rheumatologic conditions, and renal disease, were risk factors for progression to severe dengue (18–23). Studies have also shown that comorbidities may contribute to in-hospital mortality (24). The 1 death in this analysis, although attributed to nondengue-related illnesses, was in a patient who had multiple comorbidities and a prolonged ICU stay. It is likely that comorbidities themselves contribute to the development of severe disease, but analogous to other viral infections, dengue may also exacerbate comorbidities and lead to ICU admissions. Patients with dengue and warning signs who have comorbidities may need to be monitored more closely for progression to severe disease.

We used consensus criteria for dengue intended as clinical trial end points to classify our data (15). Grading of dengue severity according to these criteria also seems relevant for use in surveillance and clinical practice. Categorizing clinical manifestations as moderate or severe may help clinicians to better determine progression to severe disease. The operational

similarity to other bedside disease classification and clinical scoring systems such as the Common Terminology Criteria for Adverse Events (25) could facilitate uptake of these grading criteria by clinicians caring for patients with complicated dengue. Most data needed for this grading system were available in the patient charts, indicating that the criteria used are already being collected by practicing clinicians. This grading system may also benefit physicians who are less familiar with the clinical spectrum of dengue by providing direction for clinical and laboratory monitoring. Research is needed to determine the value of applying this grading system in clinical management and prediction of clinical outcomes in patients with complicated dengue.

This analysis describes uncommon dengue manifestations, such as abnormal ophthalmologic examinations, neurologic disease, and myocarditis, that may have clinical management implications. Published reports vary widely on the incidence of these complications. As we observed in our case series, these manifestations are not systematically screened for in returning travelers with severe dengue and they are likely underdiagnosed (26–29). Our findings warrant further study to determine the frequency, management, and outcomes of uncommon complications to improve timely recognition and decrease morbidity.

The best strategy to reduce poor outcomes among patients with complicated dengue is prevention of infection. Travelers should be encouraged to adhere to mosquito bite precautions during travel and be advised to seek care at the onset of any clinical symptoms of dengue. In endemic areas, use of the first licensed tetravalent dengue vaccine CYD-TDV (Dengvaxia, Sanofi Pasteur) was recommended for vaccination of seropositive persons only because of excess risk for severe dengue and hospitalization after vaccination of seronegatives (30). Serostatus-independent efficacy and long-term protection against hospitalization of children and adolescents with virologically confirmed dengue was shown for Qdenga (TAK-003, Takeda), a tetravalent, live attenuated, recombinant dengue vaccine based on a DENV-2 backbone (31, 32). Although this vaccine was recently approved by the European Medicines Agency for use in persons aged 4 years or older, efficacy and effectiveness at preventing complicated dengue in travelers remains to be evaluated.

This study has some limitations. These retrospective convenience sample data limit the use of inferential statistics and cannot be used to estimate risk. We caution against the interpretation of reported frequencies as risk estimates. Because these data were collected primarily through chart review, data were not available for all variables on all patients. It is possible that not all cases of complicated dengue seen by GeoSentinel sites were captured. Many different assays are used for diagnosing dengue at the GeoSentinel network sites. We were only able to classify 44 patients with dengue as primary or secondary as outlined in the methods (14). Our method may overestimate the number of secondary dengue because of cross-reacting anti-DENV IgG antibodies resulting from prior flavivirus infections or vaccination (33). Methods with higher sensitivity to distinguish between primary and secondary infections, such as convalescent DENV inhibition enzyme-linked immunosorbent assay titers that use cutoffs developed for the gold-standard hemagglutination inhibition assay, would be preferred (34).

In conclusion, complicated dengue is relatively rare in travelers with dengue. Travel medicine clinicians should monitor travelers with dengue closely for laboratory findings and signs that may indicate progression to severe disease, even if the predictive value of warning signs in travelers has not been fully validated. The application of systematic grading of dengue disease using clinical trial metrics may aid in the management of dengue patients in nonendemic areas. Future prospective studies should investigate the utility of systematic grading of laboratory findings and signs in clinical settings to manage complicated dengue; the incidence and outcomes associated with uncommon manifestations that exacerbate dengue morbidity; and the safety, efficacy, and cost-effectiveness of vaccination in reducing the morbidity associated with complicated dengue in travelers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Appendix

Appendix Table 1.

Countries of Dengue Virus Exposure Among Patients Reported to GeoSentinel, 2007–2022 (n = 86)

Country	Patients, *n* (%)
Dominican Republic	11 (13)
Thailand	11 (13)
Cuba	7 (8)
Philippines	6 (7)
Indonesia	5 (6)
Kenya	5 (6)
India	4 (5)
Cambodia	4 (5)
French Guiana	3 (4)
Guadeloupe	3 (4)
Paraguay	3 (4)
Vietnam	3 (4)

Country	Patients, *n* (%)
Bolivia	2 (2)
Côte d'Ivoire	2 (2)
Martinique	2 (2)
Nepal	2 (2)
Barbados	1 (1)
Comoros	1 (1)
Haiti	1 (1)
Jamaica	1 (1)
Laos	1 (1)
Malaysia	1 (1)
Maldives	1 (1)
Myanmar	1 (1)
São Tomé	1 (1)
Sri Lanka	1 (1)
Suriname	1 (1)
Tanzania	1 (1)
Trinidad and Tobago	1 (1)

Appendix Table 2.

Baseline Characteristics and Frequencies of Warning Signs and Criteria of Severity in Primary and Secondary Dengue Virus Infections Reported to GeoSentinel, 2007–2022 ($n = 44$) *

Characteristic	Primary Infection	Secondary Infection
Female, *n/N* (%)	18/32 (56)	6/12 (50)
Median age (range), *y*	35 (23–43)	36 (32–41)
Reason for travel, *n/N* (%)		
Tourism	22/32 (69)	1/11 (9)
Business	4/32 (13)	3/11 (27)
Visiting friends and relatives	4/32 (13)	5/11 (46)
Humanitarian aid/missionary/volunteer	1/32 (3)	1/11 (9)
Student	1/32 (3)	1/11 (9)
Expatriate	0/32 (0)	1/11 (9)
Flavivirus vaccination, *n/N* (%)	8/19 (42)	4/5 (80)
Comorbidities, *n/N* (%)	6/32 (19)	0/10 (0)
Hospitalization, *n/N* (%)	31/32 (97)	12/12 (100)
Intensive care unit stay, *n/N* (%)	2/30 (7)	1/12 (8)
Thrombocytopenia, *n/N* (%)	28/32 (88)	11/12 (92)
Moderate	22/32 (69)	6/12 (50)
Severe	6/32 (19)	5/12 (42)
Bleeding manifestations, *n/N* (%)	18/32 (56)	9/12 (75)
Plasma leakage (total), *n/N* (%)	4/28 (14)	3/10 (30)
Moderate	2/28 (7)	2/10 (20)
Severe	1/28 (4)	1/10 (10)
Myocarditis, *n/N* (%)	0/29 (0)	1/10 (10)
Neurologic disease, *n/N* (%)	1/30 (3)	0/12 (0)
Liver disease (total), *n/N* (%)	23/29 (79)	5/11 (46)
Moderate	7/29 (24)	0/11 (0)
Severe	1/30 (3)	1/11 (9)
Abnormal ophthalmologic examination, *n/N* (%)	3/13 (23)	0/13 (0)
Severe disease, *n/N* (%)	6/32 (19)	6/12 (50)

n/N denotes the proportion of the count (n) and the number (N) of records available for analysis.

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Table 1.

Consensus Clinical End Point Definitions for Grading Dengue Severity*

Clinical End Point	Definitions
Plasma leakage	
Moderate plasma leakage	Person with no evidence of hemodynamic instability or respiratory compromise and evidence of plasma leakage, defined by >15% hematocrit change during the illness and/or evidence of a new pleural effusion, ascites, or cardiac effusion on ultrasonography or radiography
Severe plasma leakage	Person has evidence of hemodynamic instability or respiratory compromise and evidence of plasma leakage, defined by >20% hematocrit change during the illness and/or evidence of a new pleural effusion, ascites, or cardiac effusion on ultrasonography or radiography
Bleeding	
Moderate bleed	Person has bleeding with no evidence of shock or hemodynamic instability, but a local intervention is needed. This includes the following bleeds: large skin/injection site bleed needing pressure compress; nose/gum bleed needing local intervention (e.g., nasal or gum packing, use of adrena-line); gastrointestinal bleeding without shock or hemodynamic instability, or need for blood product but the bleed warrants that a type and crossmatch be done and closer monitoring; vaginal bleed with need for hormonal therapy and type and crossmatch to be done; or any bleed that persists after local measures are taken to stop bleeding (e.g., application of pressure) and bleed requires more intensive monitoring in an ICU or high dependency unit. [Note: There was no need for blood transfusion.]
Severe bleed	Person has any one of the following 4 types of bleeding: bleeding that involves a critical organ (e.g., central nervous system bleed), bleed leading to hemodynamic instability, bleed resulting in death or permanent disability (e.g., central nervous system bleed, intraocular bleed), or bleed that results in need for blood transfusion and requires monitoring in an ICU or high dependency unit
Thrombocytopenia	
Moderate	Platelet count 20–50 × 10^9 cells/L
Severe	Platelet count <20 × 10^9 cells/L
Liver disease	
Moderate (acute hepatitis) (person meets all 3 criteria)	1. Acute illness with discrete onset of signs and symptoms consistent with acute viral hepatitis (e.g., fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting, dark urine, clay-colored or light stools) 2. Alanine aminotransferase greater than 10 times the upper limit of normal and/or ≥400 U/L 3. Does not meet criteria for acute liver failure (i.e., no mental status changes and international normalized ratio <1.5)
Severe (acute liver failure) (person meets all 3 criteria)	1. Acute viral hepatitis 2. Change in mental status 3. New onset coagulopathy defined by an international normalized ratio ≥1.5
Neurologic disease	
Moderate (person meets all 3 criteria)	1. Abnormal neurologic examination with a Glasgow Coma Scale score ≥12 but <15 for <2 d duration 2. Neurologic involvement did not result in need for intubation, shunting, or intensive care 3. Neurologic involvement did not result in death or ongoing sequelae that impairs daily function for more than 48 h
Severe	Person has an abnormal neurologic examination with a Glasgow Coma Scale score <11 (adults) or pediatric Glasgow Coma Scale score <11 or a Blantyre coma score <3 (children), and person has: 1. Neurologic involvement resulting in death or ongoing sequelae that impairs daily function, and/or 2. Received or was thought to require intubation, shunting, or intensive care or high dependency unit level of care if an ICU is not available
Myocarditis	
Moderate (person meets either criterion)	1. Acute illness with discrete onset of signs and symptoms consistent with acute viral myocarditis (e.g., elevated troponin, creatine phosphokinase-MB, or ST2 above the laboratory upper limit of normal), or

Clinical End Point	Definitions
	2. Evidence of new onset cardiac arrhythmia and/or ST2 elevation >1 mm, QRS complex changes (Q waves >0.04 s and >0.25 of the amplitude of R wave), or symmetrical negative T waves
Severe (person meets either criteria 1 or 2, and criterion 3)	1. Acute illness with discrete onset of signs and symptoms consistent with acute viral myocarditis (e.g., elevated troponin, creatine phosphokinase-MB, or ST2 above the laboratory upper limit of normal), or 2. Evidence of new onset cardiac arrhythmia and/or ST-segment elevation >1 mm, QRS complex changes (Q waves >0.04 s and >0.25 of the amplitude of R wave), or symmetrical negative T waves; and 3. Need for inotropic support and/or has evidence of myocardial dysfunction from echocardiogram, (i.e., reduced left ventricular function despite adequate filling of left ventricle [normal left ventricle end diastolic diameter] and adequate volume status).

ICU = intensive care unit.

*Adapted from Tomashek KM, Wills B, See Lum LC, et al. Development of standard clinical endpoints for use in dengue interventional trials. PLoS Negl Trop Dis. 2018;12:e0006497. The work is made available under the Creative Commons CC0 public domain dedication (15).

Table 2.

Demographic Characteristics, Travel Details, and Medical History of Patients With Complicated Dengue Reported to GeoSentinel, 2007–2022 (n = 86)

Characteristic	Available Data	Missing Data
Demographic characteristic		
Median age (range), *y*	34 (8–91)	-
Female, *n* (%)	48 (56)	-
Travel history, *n* (%)		
Region of exposure	86 (100)	-
Caribbean	27 (31)	
Southeast Asia	21 (24)	
Oceania	11 (13)	
Sub-Saharan Africa	10 (12)	
South America	9 (11)	
South Central Asia	8 (9)	
Reason for travel	85 (99)	1 (1)
Tourism	39 (46)	
Visiting friends and relatives	27 (32)	
Business	10 (12)	
Humanitarian aid/missionary/ volunteer	6 (7)	
Student study abroad	2 (2)	
Expatriate	1 (1)	
Duration of travel	86 (100)	-
<2 wk	25 (29)	
≥2 to <4 wk	33 (38)	
≥4 to <12 wk	17 (20)	
≥12 wk	11 (13)	
Medical history, *n* (%)		
Comorbidities *	84 (98)	2 (2)
Any comorbidity	21 (25)	
Hypertension	7 (33)	
Diabetes	5 (23)	
Rheumatologic disease	4 (19)	
Chronic respiratory disease	3 (14)	
Obesity	3 (14)	
Cancer	2 (10)	
Congestive heart failure	2 (10)	
Neurologic disease	2 (10)	
Chronic kidney disease	1 (5)	
Vaccination history	48 (56)	38 (44)
Any flavivirus vaccine	23 (48)	
Yellow fever vaccine data	22 (96)	1 (4)

Characteristic	Available Data	Missing Data
Vaccine received	19 (86)	
Tickborne encephalitis vaccine data	20 (87)	3 (13)
Vaccine received	3 (15)	
Japanese encephalitis vaccine data	21 (91)	2 (9)
Vaccine received	5 (24)	
Prior dengue virus infection Based on history		
Yes	6 (7)	
No	57 (66)	
Unknown	23 (27)	
Based on serology[†]	44 (51)	42 (49)
Primary dengue virus infection	32 (73)	
Secondary dengue virus infection	12 (27)	

[*] Rheumatologic diseases included psoriasis vulgaris, rheumatoid arthritis, sarcoidosis, and systemic lupus erythematosus; chronic respiratory diseases included asthma without the use of steroids ($n = 3$); cancer included prostate cancer (not receiving chemotherapy) and unknown cancer type (receiving chemotherapy); and neurologic diseases included Alzheimer disease and migraines.

[†] If anti-DENV IgM was present and anti-DENV IgG was not present in acute phase sera of confirmed cases, the dengue episode was classified as a primary dengue. If only anti-DENV IgG antibody was present in acute phase sera of confirmed cases, the episode was classified as a secondary (or subsequent) dengue.

Table 3.

Classification of Patients With Complicated Dengue Reported to GeoSentinel Based on 2009 World Health Organization Classification Criteria, 2007–2022

Classification	Value, *n*/*N** (%)
Warning signs	85/86 (99)
Abdominal pain	40/85 (47)
Persistent vomiting	39/85 (46)
Fluid accumulation	13/85 (15)
Mucosal bleed	39/85 (46)
Lethargy/restlessness	65/85 (77)
Liver enlargement	8/85 (9)
Increasing hematocrit with rapid decrease in platelets	61/85 (72)
Severe	27/86 (31)
Severe plasma leakage leading to shock or fluid accumulation with respiratory distress	16/27 (59)
Severe bleeding	8/27 (30)
Severe organ involvement (severe neurologic, eye, liver, or heart disease)	10/27 (37)

* Values indicate the proportion of the count (*n*) and the number (N) of records available for analysis. The sums of numerators in this table exceed the denominators because manifestations overlapped.

Table 4.

Clinical Characteristics of 86 Patients With Complicated Dengue* Reported to GeoSentinel, 2007–2022

Characteristic	Available Data†	Missing Data, *n* (%)	Patients With Severe Disease‡
Symptoms			
Abdominal pain§	40/78 (51)	8 (9)	12 (30)
Vomiting§	39/83 (47)	3 (3)	13 (33)
Clinical findings			
Evidence of plasma leakage	15/75 (20)	11 (13)	15 (100)
Mild/moderate (pleural, pericardial, or peritoneal effusion but no hemodynamic instability or respiratory compromise)§‖	9/75 (12)	–	8 (89)
Severe (hemodynamic instability or respiratory compromise)‖¶	6/75 (8)	–	6 (100)
Bleeding manifestations	44/85 (52)	1 (1)	17 (39)
Mild (submucosal or subcutaneous bleeding)§	18/85 (21)	–	7 (39)
Moderate (required intervention but no hemodynamic instability)§	18/85 (21)	–	6 (33)
Severe (hemodynamic instability, blood transfusion, ICU, bleeding involving a critical organ, or leading to death/ disability)¶	8/85 (9)	–	8 (100)
Signs of neurologic disease	5/80 (6)	6 (7)	5 (100)
Mild (lethargy, restlessness)§	3/80 (4)	–	2 (67)
Moderate (Glasgow Coma Scale score <15 but ≥12 for <48 h)¶	1/80 (1)	–	1 (100)
Severe (Glasgow Coma Scale score <11, ICU, death, or sequelae >48 h)¶	1/80 (1)	–	1 (100)
Myocarditis¶	2/77 (3)	9 (10)	2 (100)
Hepatomegaly (>2 cm)§	8/73 (11)	13 (15)	5 (63)
Laboratory findings			
Liver disease	19/81 (23)	5 (6)	NA
Moderate (alanine aminotransferase >10× upper limit of normal)	16/81 (20)	–	5 (31)
Severe (alanine aminotransferase >10× upper limit of normal and change in mental status or new onset coagulopathy)¶**	3/81 (4)	–	3 (100)
Other end organ damage/dengue eye disease¶††	3/27 (11)	–	3 (100)
Other			
Splenomegaly	6/72 (8)	14 (16)	5 (83)

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Characteristic	Available Data†	Missing Data, *n* (%)	Patients With Severe Disease‡
Thrombocytopenia	63/81 (78)	5 (6)	24 (38)
Mild (platelet count 50–150 × 10^9 cells/L)	2/81 (3)	–	0 (0)
Moderate (platelet count 20–50 × 10^9 cells/L)	44/81 (54)	–	15 (34)
Severe (platelet count <20 × 10^9 cells/L)	17/81 (21)	–	9 (53)
Elevated alanine aminotransferase but <10 × upper limit of normal	31/81 (38)	–	0 (0)
Hospitalization			
At any point in clinical course	78/86 (91)	–	26 (33)
During travel	31/86 (36)	–	14 (45)
Duration of hospitalization	Median, 5 d (IQR, 3–8 d)	3 (4)	Median, 7 d (IQR, 5–10 d)
Intensive care admission	13/77 (17)	9 (10)	10 (77)
Duration of ICU stay	Median, 3.5 d (IQR, 3–8 d)	1 (8)	Median, 4.5 d (IQR, 2–8 d)
Presence of coinfections‡‡	6/75 (8)	3 (4)	3 (50)
Deaths	1/86 (1)	–	1 (100)

ICU = intensive care unit; IQR = interquartile range; NA = not applicable.

*Complicated dengue is defined as dengue with warning signs or severe dengue.

†Values indicate the proportion of the count (n) and the number (N) of records available for analysis, with percentages in parentheses, except where indicated.

‡Values are numbers (percentages) except where indicated.

§Warning sign (based on World Health Organization 2009 guidelines).

‖Respiratory compromise = increased respiratory rate for age, or signs of increased work of breathing, or need for additional support (including oxygen supplementation or intubation).

¶Severe disease.

**Coagulopathy was defined as international normalized ratio ≥1.5.

††Findings included maculopathy with acute vision loss ($n = 2$) and retinal hemorrhage ($n = 1$). Ophthalmologic examination was done at the discretion of the treating clinician.

‡‡Among 78 patients hospitalized at any time in their clinical course. Coinfections included *Clostridium difficile colitis, COVID-19, Enterococcus faecalis* urinary tract infection, *E. faecalis* and *Staphylococcus epidermidis* bacteremia with invasive candidiasis; pneumonia (unspecified) and urinary tract infection (unspecified), and strongyloidiasis.