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Factors Associated with Correct Dengue Patient Admission Practices in Puerto Rico with Respect to 2009 World Health Organization Guidelines

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ABSTRACT

Factors Associated with Correct Dengue Patient Admission Practices in Puerto Rico with Respect to 2009 World Health Organization Guidelines

By Nicole M. Roth

Background: Dengue is a major public health concern with an estimated 96 million clinically apparent infections in 2010. This paper describes an observational study of the association of the clinical and demographic characteristics of dengue patients with criteria for hospital admission according to the 2009 World Health Organization (WHO) guidelines.

Methods: The Sentinel-Enhanced Dengue Surveillance System (SEDSS) is a population-based acute febrile illness (AFI) surveillance and clinical research platform. Patients with AFI presenting to SEDSS sites are identified by triage nurses and offered enrollment. During May 6, 2012–May 7, 2013, a total of 595 patients accepted enrollment in SEDSS and had laboratory evidence of dengue virus infection. The outcome of interest in the study was an admission decision by the physician that followed the 2009 WHO dengue guidelines. The exposure of interest was criteria for admission as outlined by the 2009 WHO guidelines, which categorizes patients into three groups. Group A patients do not have any warning signs or coexisting conditions and may recover at home. Group B patients have dengue warning signs or coexisting conditions (e. g. diabetes, pregnancy) and Group C patients any manifestations of severe dengue, such patients require hospitalization.

Results: Of the 595 study participants, sixty-seven (11%) were classified as Group A, of which 75% were correctly admitted. Four hundred sixty-nine were classified as Group B and 59 were classified as Group C, of which 49% and 66% were correctly admitted, respectively. Diagnosis of dengue at presentation was significantly associated with correct admission decision (OR: 4.4, CI: 3.0–6.39). Group B patients with abdominal pain, persistent vomiting, or increase in hematocrit concurrent with decrease in platelet count had increased odds of correctly being admitted. Group A patients with rash, bone pain, or back pain had increased odds of correctly being discharged.

Conclusions: This study identified underutilization of the 2009 WHO dengue admission guidelines Strict utilization of the guidelines would result in a significant increase in the hospitalization burden by dengue patients, and therefore further investigation into the specific criteria that can be used to safely monitor patients as outpatients is needed.

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BACKGROUND

Dengue continues to grow as a substantial public health burden in incidence and geographical range with an estimated 390 million dengue virus (DENV) infections in 2010 and evidence of local DENV transmission in nearly 130 countries throughout the tropics during 1990–2012 (1, 2). Dengue is an acute febrile illness (AFI) caused by any of four dengue virus types (DENV- 1–4) that are transmitted via the bite of infected *Aedes agypti* and *Ae. albopictus* mosquitoes (3). Primary DENV infection results in long-lived homotypic immunity and short-lived heterotypic immunity that lasts on average 1–3 years (4-6). Approximately 75% of DENV infections are subclinical, and infection with any DENV can result in the full range of clinical outcomes ranging from a self-limiting, febrile illness to potentially fatal severe dengue (7). Currently there are no approved antiviral drugs for dengue, and treatment focuses on the use of isotonic fluids to maintain hemodynamic status (8). Early and appropriate clinical management can reduce the case fatality rate of hospitalized dengue patient from as high as 10% to less than 0.5% (8, 9).

Spectrum of Illness

Following an incubation period typically lasting 4–7 days, dengue presents in three phases: febrile, critical, and recovery (8, 10). The febrile phase begins abruptly, lasts 2–7 days, and is often accompanied by skin erythema, generalized body pain, myalgia, arthralgia, and headache. On days 3–7 of illness, defervescence typically occurs and marks the beginning of the critical phase, which typically lasts 24–48 hours, after which most patients recover. Patents who deteriorate during the critical phase often present with or develop warning signs that indicate potential for progression to severe dengue. These patients are likely to recover with early and judicious intravenous rehydration. In some patients, however, severe plasma leakage occurs, which may lead to shock (8). Patients with manifestations of severe dengue have one or more of: plasma leakage leading to shock and/or fluid accumulation; severe bleeding; or severe organ

impairment. For patients who survive the 24–48 hour critical phase, general well-being improves and hemodynamic status stabilizes during the following 48–72 hours of the final phase of the illness, the recovery phase (8).

Dengue Case Classification

In 2009, the World Health Organization (WHO) revised the clinical case classification scheme of dengue from the previous 1997 classification of undifferentiated fever, dengue fever, and dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) to dengue, dengue with warning signs, and severe dengue (8). The 2009 dengue case classification scheme divides patients into three mutually inclusive categories: dengue without warning signs, dengue with warning signs, and severe dengue (Figure 1). Dengue cases are defined as individuals who live in or have recently traveled to a dengue endemic area, have fever, and also have at least two of: nausea, vomiting, rash, aches and pains, positive tourniquet test, or leukopenia. Warning signs that are associated with development of severe dengue are: abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement, and increase in hematocrit with a rapid decrease in platelet count. Severe dengue is defined by severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe hemorrhage, or organ impairment (8).

The 2009 WHO *Dengue: Guidelines for diagnosis, treatment, prevention and control* outlines recommended practices for hospital admission of dengue patients using the dengue case classification scheme and other demographic characteristics. The admission criteria outlined by the 2009 WHO dengue guidelines separate dengue patients into three categories (Figure1). Group A patients are able to tolerate fluids, pass urine every six hours, and do not have any warning signs; such patients are recommended to be sent home to recover. Patients in Group B present with any dengue warning sign, have coexisting conditions (e.g., pregnancy, diabetes), or live far from a health facility or alone and thus require admission for in-hospital observation. Group C

comprises patients that have manifestations of severe dengue, and thus require admission for emergency and aggressive management (8).

Advantages and Disadvantages of the 2009 WHO Dengue Case Classification

The shift in the dengue classification scheme and hospital admission guidelines has received both praise and critique. The 1997 dengue case classification was largely based on pediatric cases from Thailand, and changes in the epidemiology of dengue resulted in criticism in the lack of utility for clinical case management (11-13). A multi-center study in dengue endemic regions found classification of dengue cases based on level of severity to have the greatest potential for utility in clinical case management (14). The shift to an illness viewed as presenting in a spectrum rather than two distinct entities (dengue fever and dengue hemorrhagic fever) has proved useful in identifying cases with potential for severe disease progression and describing all forms of severe dengue (13). While no single warning sign has been found to predict severe disease outcome, the presence of five or more warning signs has been observed to be associated with five times greater odds of developing severe dengue ($P = 0.02$) (15, 16). However, there has been concern that admitting all patients with warning signs will increase the total number of hospital admissions. During a retrospective study of laboratory confirmed dengue patients using the 2009 WHO dengue guidelines as criteria for hospital admission, there was a 31% and 33% increase in recommended hospital admission for severe dengue and non-severe dengue patients, respectively, when compared with actual admission practices (17). Conversely, the study found the absence of warning signs as an indicator that a patient can be successfully managed with ambulatory care.

Dengue in Puerto Rico

In the United States, dengue is endemic in the Caribbean and US-Affiliated Pacific Islands. Puerto Rico first reported an outbreak of dengue-like illness in 1899, and dengue has been endemic on the island since the 1960s (18, 19). Dengue is a reportable condition in Puerto

Rico, and the Puerto Rico Department of Health (PRDH) has maintained the healthcare provider-initiated passive dengue surveillance system (PDSS) for several decades (19). PDSS has enabled detection of multiple dengue epidemics, the most recent having occurred during 2012–2013, the longest epidemic in Puerto Rico history (19, 20). The largest outbreak on the island occurred in 2010 when nearly 27,000 suspected dengue cases were reported to PDSS. In non-epidemic years, 3,000–9,000 dengue cases are reported (21). However, due to the nature of passive surveillance, PDSS under-represents the burden of dengue on the island due to underreporting, misdiagnosis, and clinically inapparent cases.

During 2005–2006 a pilot enhanced dengue surveillance system was implemented at a health center in southern Puerto Rico, and identified nearly three times higher rates of dengue cases compared with that of PDSS (22). In 2012, the Centers for Disease Control and Prevention (CDC) Dengue Branch established the Sentinel Enhanced Dengue Surveillance System to serve as a platform to better describe the epidemiology and clinical course of dengue and other acute febrile illnesses in Puerto Rico. This hospital-based surveillance system actively recruits acute febrile illness patients presenting to or being transferred to emergency departments at SEDSS sites in Ponce and Guayama (19). SEDSS began recruitment on May 7, 2012, and during the first year of recruitment enrolled 2,231 patients with AFI (23).

In the past decade dengue clinical management and treatment in Puerto Rico has been evaluated, identifying gaps between knowledge and practices of clinicians, and consequently efforts have been made to lessen these gaps. A retrospective case study of fatal suspected dengue patients from the 2007 dengue epidemic in Puerto Rico found that none of 11 fatal laboratory-confirmed dengue patients were managed according to the WHO guidelines, highlighting the need to evaluate clinicians' diagnosis and clinical management of dengue (9). A survey of 708 physicians on the island identified limited knowledge of dengue management, suboptimal utilization of WHO guidelines, and prominent underreporting (24). Findings from the survey aided in the development of a post graduate dengue clinical management course CDC Dengue

Branch (CDC DB). In August 2010, during the largest recorded dengue epidemic, the Secretary of Health of Puerto Rico mandated all physicians in Puerto Rico take the course conducted by the end of October, and in that year more than 8,000 physicians participated in the course (24, 25). Following implementation of the course an evaluation of physician practices on management and treatment of dengue comparing 2008–2009 practices with practices from 2011. The evaluation found an improvement in clinical practices and a reduction in case fatality rate from 0.5% to 0.3% (26).

SEDSS not only provides a platform to study the clinical course of dengue in Puerto Rico, but also the management and treatment practices of clinicians associated with the signs and symptoms of dengue. Previous studies in Puerto Rico have evaluated treatment practices associated with dengue in admitted patients. There is a need to investigate the clinical practices associated with dengue cases of lesser severity, as only ~5% of clinically apparent dengue cases progress to severe dengue (7). A greater understanding of the full range of clinical practices associated with the full clinical spectrum of dengue will help to improve clinical practices.

In a dengue endemic region, dengue patients have the potential to place a significant burden on the health care system, especially during epidemics when patients may overwhelm available services at hospitals and doctors' offices. During these times, accurate and timely diagnosis and management of patients is essential. An understanding of inconsistencies between admission decisions and recommended practices will highlight areas that may need to be targeted for improving practices to reduce unnecessary hospitalization and unnecessary morbidity by improving hospitalization of outpatients at risk for developing severe disease. The purpose of this study is to determine the proportion of patients presenting to the emergency room that were managed in accordance with the 2009 WHO dengue guidelines, and examine the association between demographic and clinical characteristics of dengue patients following the 2009 WHO guidelines for hospital admission.

METHODS

The Sentinel-Enhanced Dengue Surveillance System (SEDSS) is a population-based study designed to improve the descriptions of the epidemiology and clinical outcomes of dengue patients in Puerto Rico. This paper describes an analysis of SEDSS data examining the association of demographic and clinical characteristics of laboratory-confirmed dengue patients with an accurate decision by physicians according to the 2009 WHO *Dengue: guidelines for diagnosis, treatment, prevention and control*. Data was collected at hospital-based SEDSS sites in Ponce and Guayama, Puerto Rico during May 7, 2012–May 6, 2013. The Emory University Institutional Review Board determined that this study did not require IRB review because it does not meet the definitions of research involving human subjects.

Study Population

Puerto Rico is an unincorporated territory of the United States located in the northeastern Caribbean Sea and, in 2013, had a population of 3,615,086 residents (27). The study population included patients transferred to or seeking care in the Emergency Department (ED) at Saint Luke's Episcopal Hospital in Ponce, a tertiary care hospital, and Saint Luke's Episcopal Hospital in Guayama, a secondary acute-care hospital. Both SEDSS sites are located in southern Puerto Rico with a combined coverage area of 853,389 people in 20 municipalities. All patients seeking care in the ED or transferred for direct admission with documented fever or history of fever lasting ≤7 days were identified by triage nurses and recruited for enrollment in SEDSS. If the patient agreed to participate and provided consent, they were enrolled in SEDSS. Study participants and clinicians completed a case investigation form (CIF) regarding demographics, signs and symptoms, and medical history. Blood, urine, and nasopharangeal specimens were collected and tested for evidence of infection with >20 pathogens including the four DENVs, influenza and other respiratory viruses, *Leptospira spp*. bacteria, *Burkholderia pseudomallei*, and enterovirus. Convalescent specimens were collected from in-patients upon discharge. Out-

patients were asked to return for collection of a convalescent specimen ≥7 days after illness onset and provided a small monetary incentive upon return. Inclusion criteria for the study described in this paper required patients to have laboratory-confirmed DENV infection.

Outcome

The outcome of interest in the study was correct patient admission decision according to the 2009 WHO *Dengue: guidelines for treatment, prevention, and control*. The WHO provides guidelines for admission of dengue patients by classifying patients into three treatment categories based on patients' demographic, signs and symptoms, and medical history: Groups A, B, and C. Group A patients are considered able to recover from illness at home with monitoring of symptoms for potential warnings of severe disease progression, and therefore the recommended admission decision is ambulatory care. Patients in Group B require monitoring of potential for progression to severe dengue, and therefore hospital admission is recommended. Group C patients require emergency treatment, and thus require hospital admission. Group A patients who received ambulatory care and Group B and Group C patients who were admitted to the hospital were classified as receiving the correct admission decision. Group A patients who were admitted to the hospital and Group B and Group C patients who received ambulatory care were classified as receiving the incorrect admission decision.

Exposure

The exposure of interest in the study was the criteria for hospital admission that have been outlined by the 2009 WHO dengue admission guidelines. Criteria for hospital admission was determined by patients' demographic characteristics and signs and symptoms present at time of presentation to the hospital. Dengue patients without warning signs are categorized Group A. Dengue patients with warning signs or coexisting conditions such as pregnancy, infancy, old age, or history of chronic disease (e.g. diabetes mellitus and renal failure), were categorized as Group B. Patients with severe plasma leakage with shock and/or fluid accumulation with respiratory

distress, severe hemorrhage, and/or severe organ impairment are categorized as Group C. Due to the design of the study, signs and symptoms that are included in the dengue case classification but were not able to be analyzed due to missing laboratory results or information not being collected are: positive tourniquet test, clinical fluid accumulation (pleural effusions), liver enlargement, albumin level as an indicator for plasma leakage, and AST and ALT levels as indicators for liver impairment. Demographic criteria included in the guidelines that were not a part of the analysis were: obesity and living far from a medical facility or alone due to missing responses or data not being collected.

Covariates

Covariates analyzed for possible interaction and/or confounding included: age, sex, days from illness onset to when the patient sought care, suspicion of dengue by the physician, and the SEDSS visit site. Suspicion of dengue in patients was defined by a diagnosis of dengue by the physician during the initial evaluation prior to the availability of the patient's laboratory results.

Statistical Analysis

All statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC). The signs and symptoms used from the dengue case classification included: nausea, rash, body pain, leukopenia, abdominal pain, persistent vomiting, mucosal bleeding, restlessness, increase in hematocrit concurrent with a decrease in platelet count, severe plasma leakage, signs of shock, hemorrhage, and organ impairment. Additional variables included in the criteria for hospital admission include: chronic diseases, pregnancy, and age. Simple imputation was used for missingness in variables missing ≤5% of observations.

Descriptive statistics for the study population by correct admission decision were calculated. Bivariate associations were calculated with Chi-square, Mood's Median and Fisher's Exact test statistics to identify unadjusted associations between demographic and clinical characteristics and correct admission decision for all patients. Bivariate associations of signs and

symptoms and demographic characteristics were calculated individually for Group B and Group C patients.

Multivariate logistic regression was used to calculate adjusted odds ratios and 95% confidence intervals of the association of admission group with the correct admission decision by physicians. Variables considered as covariates included: age, sex, suspicion of dengue by the physician, days from illness onset to hospital visit, and visit site. Collinearity between all considered terms and Goodness of Fit, using the Hosmer Lemeshow statistic, of potential models were assessed. Interaction of covariates with exposure was tested using the chunk test and backwards elimination. Confounding was tested by observing the change in estimate and precision of possible models. Inclusion of variables in the model was decided at the 0.10 level of significance. The final model contained Group, an interaction term of Group and suspicion of dengue, and suspicion of dengue and time from illness onset to hospital visit as confounders.

Multivariate logistic regression analysis was calculated individually for each Group. The exposure variables considered for Group A included nausea, rash, headache, eye pain, joint pain, bone pain, back pain, calf muscle pain, and leukopenia. The exposure variables considered for Group B included: abdominal pain; persistent vomiting; mucosal bleeding; restlessness; decrease in hematocrit concurrent with increase in platelet count; chronic diseases: asthma, cancer, chronic heart disease, chronic liver disease, coronary obstructive pulmonary disease, diabetes, high blood pressure, high cholesterol, immunodeficiency, sickle cell disease, and thyroid disease; pregnancy; and infancy or old age. The exposure variables considered for Group C included: blood in vomit, blood in urine, blood in stool, black tarry stool, unexpected vaginal bleeding, and seizures. Variables considered as covariates included: age, sex, suspicion of dengue by the physician, days from illness onset to hospital visit, and visit site. Inclusion of variables in the model was decided at the 0.10 level of significance. The final model for Group A patients included: nausea, rash, bone pain, and back pain as exposure variables and sex, suspicion of dengue, time from illness onset to hospital visit as confounders. The final model for Group B patients included abdominal

pain, persistent vomiting, increase in hematocrit concurrent with decrease in platelet count, cancer, infancy, and old age as exposure variables and suspicion of dengue, time from illness onset to hospital visit as confounders.

RESULTS

During May 7, 2012–May 6, 2013, a total of 9,407 patients presented to SEDSS sites with fever (Figure 2). Of these, 6,706 (71%) were offered enrollment in SEDSS, and 2,213 (33%) agreed to participate. Of patients enrolled in SEDSS, 1,366 (62%) had an etiologic agent of AFI identified, of which 636 (47%) had evidence of DENV infection. Twenty-two (3%) dengue patients were excluded from the analysis due to co-infection. Nineteen (3%) patients were excluded from the analysis because they presented with subclinical infections and did not have any signs or symptoms outlined by the dengue case classification scheme. The final study population contained 595 participants.

Categorization of admission group of all study patients by correct admission decision according to the 2009 WHO dengue guidelines is presented in Table 1. Admission group categorization was based on the signs and symptoms the patient had at the time of presentation to the hospital. Signs and symptoms that are included in the dengue case classification but were not able to be analyzed due to missing laboratory results or information not being collected are: positive tourniquet test, clinical fluid accumulation (pleural effusions), liver enlargement, albumin level as an indicator for plasma leakage, and AST and ALT levels as indicators for liver impairment. Demographic criteria included in the guidelines that were not a part of the analysis were: obesity and living alone or far from a medical facility.

Of the 595 study participants, 318 (53.4%) received the correct admission decision (Table 1). Eleven percent of the study population was classified as Group A, 79% of patients were classified as Group B, and 10% of patients were classified as Group C. Of the 67 patients classified as Group A, 50 (75%) were correctly sent home for recovery. Forty-nine percent of the 469 patients classified as Group B and 66% of the 59 patients classified as Group C were correctly admitted to the hospital for care. The unadjusted odds of receiving the correct admission decision was three times greater in Group A compared with that of Group B ($P < 0.0001$).

Patients in Group C had 34% decreased odds of correct admission decision compared with that of Group A patients ($P = 0.29$).

Demographic and hospital admission characteristics and bivariate associations with correct admission decision of the study population are presented in Table 2. Nearly half of the study population was female and with a median age of 15 years. Sex and age were not statistically significantly associated with correct admission decision. Three days was the median time from illness onset to hospital visit. Forty-four percent of patients were diagnosed as a suspected dengue during the initial physician evaluation. Suspected dengue patients had five times the odds of receiving the correct admission ($P < 0.0001$). Forty-eight percent of the study population was admitted to the hospital, of which 17 (6%) were admitted to the hospital when the WHO guidelines recommend the patient be sent home for recovery. Eighty-nine percent of the study population met the criteria for hospital admission.

The dengue case classification and dengue signs and symptoms are presented in Table 3. The dengue case classification presented in Table 3 categorizes patients into mutually exclusive categories. Sixteen percent of the study population had dengue without warning signs, 74% of the population had dengue with warning signs, and 10% of the population was classified as severe dengue. Patients with dengue warning signs had 40% decreased odds of receiving the correct admission decision of in-hospital care compared with that of dengue patients without warning signs ($P = 0.03$).

Nausea (76%), body pain (98%), and leukopenia (78%) were observed in the majority of the population, whereas roughly half had rash (47%) (Table 3). Presentations of either leukopenia ($P = 0.0001$) or rash ($P < 0.0001$) resulted in greater than two times the odds of correct admission decision. Abdominal pain was present in approximately 60% of the population and was the most common warning sign observed. Persistent vomiting was the only warning sign with a statistically significant difference between those with the correct admission decision and those with the incorrect decision. Patients with persistent vomiting had 1.5 times the odds of having the

correct admission decision as those without persistent vomiting ($P = 0.03$). Patients with hemorrhagic manifestation had two times the odds of receiving the correct admission decision ($P = 0.03$). Two percent of patients had severe organ impairment, all due to seizures, the proportions of which did not differ by adherence to the guidelines.

A total of 469 (79%) patients presented with the demographic and clinical criteria for Group B (Table 4). Group B patients with abdominal pain ($P = 0.02$) or mucosal bleeding ($P = 0.01$) had 1.6 times the odds of receiving the correct admission decision compared with that of patients without abdominal pain or mucosal bleeding. The presence of three ($P < 0.0001$) warning signs resulted in a statistically significant increased odds of correct admission decision. Very few (1.5%) of the study participants had four of the observed warning signs and no patients had five warning signs. Thirty-four percent of Group B patients reported having chronic disease history; however, no chronic disease was statistically significantly associated with correct admission decision. All pregnant patients received the correct admission decision of hospital admission. Neither infancy nor old age was statistically significantly associated with an increased odds of correct admission decision.

Of the 469 Group B patients, 139 (30%) patients had only one warning sign with no other indications for hospital admission. Seventy-nine patients had abdominal pain alone, 39 patients had restlessness alone, 16 patients had persistent vomiting alone, and five patients had mucosal bleeding alone. Twenty-seven patients had a chronic disease and three patients had extreme age as the only indicators for hospital admission.

The warning signs of Group C patients are presented in Table 5. Of the 59 patients classified as severe dengue, 51 (86%) reported dengue warning signs. Such patients had four times the odds of receiving the correct admission decision compared with that of severe dengue patients that did not have warning signs ($P = 0.11$). The most common warning signs of severe dengue patients were abdominal pain (70%) or restlessness (66%). Less than half of severe dengue patients with warning signs had persistent vomiting (41%), and few patients had mucosal

bleeding (5%) or a decrease in hematocrit concurrent with increase in platelet count (2%). Of the 51 severe dengue patients with warning signs, two patients had four warning signs, 17 patients had three warning signs, 17 patients had two warning signs, and 15 patients had one warning signs. Of the patients with one warning sign, 10 patients had restlessness alone and five patients had restlessness alone.

Multivariate associations of admission group with correct admission decision from logistic regression are presented in Table 6. Analysis revealed an interaction between admission group and suspicion of dengue by physician. For patients suspected of having dengue, the odds of correct admission decision was 2.3 times greater for patients in Group B and 5.3 times greater for patients in Group C when compared with that of Group A patients ($P = 0.02$). For patients not suspected of having a dengue the odds of correct admission decision was decreased by 76% for Group B patients and decreased by 94% for Group C patients compared with that of Group A patients ($P < 0.0001$). When controlling for admission group and days from illness onset to hospital visit, patients diagnosed as suspected dengue had 4.4 times the odds of receiving the correct admission compared with patients who were not suspected as having dengue ($P < 0.0001$). After controlling for admission group and suspicion of dengue, patients who sought care one day later in progression of illness had 30% greater odds of receiving the correct admission decision ($P < 0.0001$).

Multivariate logisitic regression of Group A patients identified nausea, rash, bone pain, and back pain as significant symptoms for the correct admission decision (Table 7). The presence of nausea resulted in 79% decreased odds of correct admission decision of at home recovery compared with Group A patients without nausea after controlling for all other statistically significant variables ($P = 0.10$). Rash ($P = 0.07$) or back pain ($P = 0.09$) separately resulted in nearly five times the odds of correct admission in Group A patients compared with patients without either symptom. The odds of correct admission decision for Group A patients with bone pain was four times that of patients without bone pain ($P = 0.08$). When controlling for the signs

and symptoms of Group A, diagnosis of suspected dengue, and time from illness onset to when care was sought, females had 5.6 times the odds of correct admission decision, of being sent home for recovery, compared with that of males ($P = 0.05$). Suspicion of dengue was associated with decreased odds of correct admission decision by 76% compared with Group A patients who were not suspected of dengue virus infection ($P = 0.09$). Group A patients who sought care one day later in illness progression had roughly half the odds of receiving the correct admission decision compared with that of Group A patients who sought care one day earlier ($P = 0.01$).

Multivariate logistic regression analysis of Group B patient demographics and warning signs are presented in Table 8. Abdominal pain, persistent vomiting, and an increased hematocrit concurrent with decrease in platelet count were the warning signs statistically significantly associated with the correct admission decision of hospital admission. Abdominal pain increased the odds of correct admission decision by 70% in Group B patients when controlling for other demographic characteristics and warning signs ($P =0.04$). The odds of correct admission decision for Group B patients with persistent vomiting was nearly two times that of Group B patients without persistent vomiting ($P = 0.01$). Group B patients with a decrease in hematocrit concurrent with an increase in platelet count had 7.5 times the odds of correct admission decision compared with Group B patients without such warning sign ($P = 0.10$). Cancer was the only chronic disease significantly associated with correct admission decision; however, Group B patients with history of cancer had 85% decreased odds of correct admission decision ($P = 0.08$). The odds of correct admission decision for infants and elderly patients was 5.1 and 10.8 times that of patients of non-extreme ages ($P = 0.02$ and 0.0007, respectively). Group B patients diagnosed as suspected dengue had 7.6 times the odds of correct admission decision compared with that of Group B patients not diagnosed as suspected dengue ($P < 0.0001$). Patients who sought care one day later in illness progression had 50% greater odds of receiving the correct admission decision when controlling for the other demographic characteristics and warning signs ($P < 0.0001$). Regression

analysis for Group C patients determined that no exposure variables were significant in determining the correct admission decision.

DISCUSSION

In this retrospective study of admission decision practices of physicians for dengue patients at SEDSS sites in Puerto Rico an underutilization of the 2009 WHO dengue guidelines for admission was observed, with only 53% of patients receiving the recommended admission practice. Using the 2009 WHO dengue admission guidelines, 89% of the study population met the criteria for hospital admission, however only 48% of patients were hospitalized. The largest proportion (79%) of patients were categorized as Group B, which is composed of patients with dengue warning signs, patients with coexisting conditions (e.g., pregnancy, diabetes), and infants and elderly dengue patients. Such patients are recommended to be admitted to the hospital for observation. Group B patients with abdominal pain, persistent vomiting, or an increase in hematocrit concurrent with a decrease in platelet count had increased odds of correctly being admitted to the hospital. Patients without dengue warning signs or coexisting conditions are categorized as Group A; such patients are able to safely recover at home with monitoring of symptoms. The presence of rash, bone pain, or back pain or the absence of nausea in Group A patients was statistically significantly associated with correct admission decision by physicians. Severe dengue patients, who are categorized as Group C and require hospital admission and emergency treatment, did not have any statistically significant symptoms associated with the correct hospital admission practice. Sixty-six percent of Group C patients were correctly admitted to the hospital for care.

Diagnosis of a suspected DENV infection in the entire study population was associated with greater than four times the odds of receiving the correct admission decision compared with patients who were not suspected of having dengue. However, only 44% of the study population was diagnosed as suspected dengue. This may suggest that inconsistencies between the 2009 WHO recommended admission practices and actual practices are due to a lack of recognition as to which patients are potentially infected with DENV rather than incorrect admission practices of

physicians. Suspicion of dengue increased the odds of correct admission decision in Group B, whereas in Group A suspicion of dengue decreased the odds of correct admission decision. Due to patients in Group A and Group B having opposing correct outcomes, this suggests an association of suspicion of dengue with hospitalization.

Time from illness onset to hospital visit was also associated with physicians making the correct admission decision. Overall patients who sought care later in illness progression had greater odds of correct admission decision. Time from illness onset demonstrated the same pattern in Group A and Group B as suspicion of dengue with increased odds of correct admission decision of Group B patients and decreased odds of correct admission decision of Group A patients for who sought care later in illness progression. This may be due to patients further in illness progression showing a greater number of signs and symptoms of dengue, and therefore physicians may be more likely to recognize dengue.

Group B patients made up the greatest proportion of the study population since most (93%) had one or more warning signs. While dengue warning signs are outlined by the WHO as indicators for potential for progression to severe dengue, they may be more specific than sensitive in predicting progression to severe dengue. Thirty percent of the study population dictated as Group B had only one dengue warning sign with no other indications for hospital admission. This was largely (57%) due to patients only presenting with abdominal pain, and as a result 7% of the study population was categorized as having the incorrect admission decision with abdominal pain as the only indication for hospitalization. Although clinicians did not strictly abide by 2009 WHO guidelines in hospitalization of Group B patients, the need for hospitalization of such patients was likely low as compared to dengue patients with more than one warning sign or Group C patients. Such clinical decision-making may be necessary during times of high rate of dengue patient presentation, such as during the epidemic of 2012-2013 during which this study population was enrolled. Future studies should determine if similar practices occurred or if adherence to Group B patient admission recommendations occurred during non-epidemics.

Numerous studies have discussed the utility in the 2009 WHO dengue classification scheme; however, they also note the potential for an increased case load which accompanies the new guidelines (11, 28, 29). Few studies have observed the association of the 2009 WHO dengue admission guidelines with actual admission practices by physicians. One such study in Singapore analyzed the use of dengue warning signs for admitting patients compared with physicians' decisions to admit dengue patients finding the use of warning signs for admission would result in two–three times the number of cases being admitted (17). Additionally, the authors found patients with elevated transaminases or a single brief hypotensive episode were able to be safely managed as outpatients.

Multiple studies have observed the association between warning signs and progression to severe dengue. A study in Singapore found no single warning sign to be sensitive in predicting severe dengue (16). However, the authors found persistent vomiting, enlarged liver, increased hematocrit concurrent with decreased platelet count, clinical fluid accumulation, and the presence of any three or four warning signs to be highly specific for severe dengue. Numerous studies have found abdominal pain to be associated with progression to severe dengue (30-32), and therefore discharging patients with abdominal pain as the only indication for hospital admission would not be recommended.

Strengths and Limitations

To our knowledge this is the first study in Puerto Rico examining the association of the 2009 WHO dengue guidelines for admission with actual physician admission practices. One key strength of the study is that the population examined consisted of both all patients presenting with clinically apparent illness, including both inpatients and outpatients. In considering the results of this study it should be kept in mind that physicians are required to make on-the-spot decisions that take into consideration a greater number of factors than can be captured through analyzing a set list of demographics and symptoms alone. A major limitation in the study was the fact that a

positive tourniquet test, liver enlargement, clinical fluid accumulation, and laboratory values were not able to be analyzed as criteria for admission; inclusion of such criteria would have likely identified a greater proportion of the study population requiring hospital admission. Additionally, due to the fact that both clinical practice and the epidemiology of dengue varies by region, this study may not be externally valid in other regions outside of Puerto Rico or Latin America. In particular, 73% of the study population was under the age of 20, and therefore the findings of the study may be more applicable to decisions made about children and adolescents.

Future Studies

Future investigations should examine the specific demographic and clinical characteristics associated with the decision to admit patients so as to get a better understanding of reasons for admission. Other treatment practices should also be investigated to ensure practices within the hospital setting are utilizing the recommend guidelines. Finally, investigation into the severity outcomes of patients who were admitted and patients who were treated as outpatients to see which symptoms are associated with severe dengue in the target population.

Conclusions

Our study observed patients with clinical suspicion of dengue having greater odds of adherence to patient admission practices as recommended by WHO. Abdominal pain, persistent vomiting, and increase in hematocrit concurrent with decrease in platelet count were the warning signs observed to be associated with correct admission of dengue patients with warning signs. Strict use of the 2009 WHO dengue guidelines for admission would result in a substantial increase in the number of dengue cases admitted to the hospital, and therefore further investigation is need to determine which of the WHO criteria can be used to safely monitor patients at home. Dengue will continue to have a significant burden on residents of the tropics unless a vaccine or other sustainable and effective intervention is identified. Properly managing

and admitting dengue patients is necessary to reduce mortality while minimizing the burden of patients that can be effectively treated through ambulatory care.

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TABLES

Table 1: Unadjusted association of admission group classification with correct admission decision by physician for laboratory-confirmed dengue patients at SEDSS sites in Puerto Rico during May 7, 2012–May 6, 2013 (N = 595).

Characteristics	All Dengue Patients N = 595	Correct Admission Decision n = 318	Incorrect Admission Decision n = 277	Unadjusted OR	95% CI	*P* value*
Admission Group						
Group A	67 (11.3%)	50 (15.7%)	17 (6.1%)	Reference		
Group B	469 (78.8%)	229 (72.0%)	240 (86.6%)	0.32	(0.18, 0.58)	<0.0001
Group C	59 (9.9%)	39 (12.3%)	20 (7.2%)	0.66	(0.31, 1.43)	0.29

Test Statistic: *Chi-square

Table 2: Unadjusted associations of demographic and hospital admission characteristics with correct admission decision by physician for laboratory-confirmed dengue patients at SEDSS sites in Puerto Rico during May 7, 2012–May 6, 2013 (N = 595).

Characteristics	All Dengue Patients N = 595		Correct Admission Decision n = 318		Incorrect Admission Decision n = 277		Unadjusted OR	95% CI		*P* value*
Female	287	(48.2%)	152	(47.8%)	135	(48.7%)	0.96	(0.70,	1.33)	0.82
Age (years), median (range)	15	(<1 – 88)	15	(<1 – 82)	14	(<1 – 88)				0.33◊
Days from illness onset to hospital visit, median (range)	3	(0 – 23)	4	(0 – 23)	3	(0 – 10)				0.07◊
Suspected dengue	260	(43.7%)	194	(61.0%)	66	(23.8%)	5.00	(3.50,	7.15)	<0.0001
Hospital admission	285	(47.9%)	268	(84.3%)	17	(6.1%)	81.98	(46.08,	145.85)	<0.0001
Criteria for hospital admission	528	(88.7%)	268	(84.3%)	260	(93.9%)	0.35	(0.20,	0.62)	0.0002

Test Statistic: *Chi -square, ◊Mood's Median

Table 3: Unadjusted associations of dengue case classification and dengue signs and symptoms with correct admission decision by physician for laboratory-confirmed dengue patients at SEDSS sites in Puerto Rico during May 7, 2012 – May 6, 2013 (N = 595).

	All Dengue Patients N = 595		Correct Admission Decision n = 318		Incorrect Admission Decision n = 277		Unadjusted OR	95% CI		*P* value*
Dengue Case Classification†										
Dengue without Warning Signs	98	(16.5%)	61	(19.2%)	37	(13.4%)	Reference			
Dengue with Warning Signs	438	(73.6%)	218	(68.6%)	220	(79.4%)	0.60	(0.38,	0.94)	0.03
Severe Dengue	59	(9.9%)	39	(12.3%)	20	(7.2%)	1.18	(0.60,	2.33)	0.63
Dengue Signs and Symptoms										
Probable Dengue										
Nausea	450	(75.6%)	238	(74.8%)	212	(76.5%)	0.91	(0.63,	1.33)	0.63
Rash	277	(46.6%)	175	(55.0%)	102	(36.8%)	2.10	(1.51,	2.92)	<0.0001
Body pain‡	581	(97.7%)	312	(98.1%)	269	(97.1%)	1.55	(0.53,	4.51)	0.42
Leukopenia	465	(78.2%)	268	(84.3%)	197	(71.1%)	2.18	(1.46,	3.24)	0.0001
Warning Signs										
Abdominal pain	369	(62.0%)	202	(63.5%)	167	(60.3%)	1.15	(0.82,	1.60)	0.42
Persistent vomiting	163	(27.4%)	99	(31.1%)	64	(23.1%)	1.50	(1.04,	2.17)	0.03
Mucosal bleeding	37	(6.2%)	24	(7.6%)	13	(4.7%)	1.66	(0.83,	3.32)	0.15
Restlessness	282	(47.4%)	151	(47.5%)	131	(47.3%)	1.01	(0.73,	1.39)	0.96
Increase in hematocrit concurrent with decrease in platelet count	7	(1.2%)	6	(1.9%)	1	(0.4%)	5.31	(0.64,	44.36)	0.13^
Severe Dengue										
Severe hemorrhage	48	(8.1%)	33	(10.4%)	15	(5.4%)	2.02	(1.07,	3.81)	0.03
Severe organ impairment˜	12	(2.0%)	7	(2.2%)	5	(1.8%)	1.22	(0.38,	3.90)	0.73

Test Statistic: *Chi-square, ^Fisher's Exact

†Mutually exclusive

‡Body pain includes: headache, eye pain, joint pain, bone pain, back pain, and calf muscle pain

˜All due to seizure

Table 4: Unadjusted associations of dengue warning signs, chronic disease history, pregnancy, and age amongst laboratory-confirmed dengue patients by correct admission decision by physician of Group B patients at SEDSS sites in Puerto Rico during May 7, 2012 – May 6, 2013 (N = 469).

	All Group B Dengue Patients N = 469		Correct Admission Decision n = 229		Incorrect Admission Decision n = 240		Unadjusted OR	95% CI	*P* value*
Dengue warning signs	438	(93.4%)	218	(95.2%)	220	(91.7%)	1.80	(0.84, 3.85)	0.12
Abdominal pain	328	(69.9%)	172	(75.1%)	156	(65.0%)	1.62	(1.09, 2.42)	0.02
Persistent vomiting	139	(29.6%)	80	(34.9%)	59	(24.6%)	1.65	(1.10, 2.46)	0.01
Mucosal bleeding	34	(7.3%)	21	(9.2%)	13	(5.4%)	1.76	(0.86, 3.61)	0.12
Restlessness	243	(51.8%)	123	(53.7%)	120	(50.0%)	1.16	(0.81, 1.67)	0.42
Increase in HCT concurrent with decrease in platelet count	6	(1.3%)	5	(2.2%)	1	(0.4%)	5.33	(0.62, 46.02)	0.11^
Number of Warning Signs									
One warning sign	201	(42.9%)	89	(38.9%)	112	(46.7%)	0.73	(0.50, 1.05)	0.09
Two warning signs	169	(36.0%)	80	(34.9%)	89	(37.1%)	0.91	(0.62, 1.33)	0.63
Three warning signs	61	(13.0%)	44	(19.2%)	17	(7.1%)	3.12	(1.72, 5.64)	<0.0001
Four warning signs	7	(1.5%)	5	(2.2%)	2	(0.8%)	2.66	(0.51, 13.83)	0.28^
Chronic disease history	159	(33.9%)	75	(32.8%)	84	(35.0%)	0.90	(0.62, 1.33)	0.61
Asthma	92	(19.6%)	44	(19.2%)	48	(20.0%)	0.95	(0.60, 1.50)	0.83
Coronary heart disease	14	(3.0%)	4	(1.8%)	10	(4.2%)	0.41	(0.13, 1.32)	0.12
Diabetes	34	(7.3%)	14	(6.1%)	20	(8.3%)	0.72	(0.35, 1.45)	0.35
High blood pressure	36	(7.7%)	19	(8.3%)	17	(7.1%)	1.19	(0.60, 2.34)	0.62
High cholesterol	20	(4.3%)	12	(5.2%)	8	(3.3%)	1.60	(0.64, 4.00)	0.31
Thyroid disease	18	(3.8%)	7	(3.1%)	11	(4.6%)	0.66	(0.25, 1.72)	0.39
Other†	13	(2.8%)	3	(1.3%)	10	(4.2%)	3.28	(0.89, 12.06)	0.06
Pregnancy	5	(1.1%)	5	(2.2%)	0	(0.0%)			0.03^
Age									
Infancy (≤1 years)	14	(3.0%)	9	(3.9%)	5	(2.1%)	1.92	(0.63, 5.83)	0.24
Old age (≥65 years)	19	(4.1%)	13	(5.7%)	6	(2.5%)	2.35	(0.88, 6.28)	0.08

Test Statistic: *Chi-square, ^Fisher's Exact test

†Other diseases include: cancer, chronic liver disease, chronic obstructive pulmonary disease, immunodeficiency, sickle cell disease

Table 5: Unadjusted associations of warning signs with correct admission decision by physician of Group C dengue patients at SEDSS sites in Puerto Rico during May 7, 2012 – May 6, 2013 (N = 59).

	All Group C Dengue Patients N = 59	Correct Admission Decision n = 39	Incorrect Admission Decision n = 20	Unadjusted OR	95% CI	*P* value*
Severe Dengue with warning signs	51 (86.4%)	36 (92.3%)	15 (75.0%)	4.00	(0.85, 18.90)	0.11^
Abdominal pain	41 (69.5%)	30 (76.9%)	11 (55.0%)	2.72	(0.86, 8.64)	0.08
Persistent vomiting	24 (40.7%)	19 (48.7%)	5 (25.0%)	2.85	(0.86, 9.38)	0.08
Mucosal bleeding	3 (5.1%)	3 (7.7%)	0 (0.0%)			0.54^
Restlessness	39 (66.1%)	28 (71.8%)	11 (55.0%)	2.08	(0.68, 6.41)	0.20
Increase in HCT concurrent with decrease in platelet count	1 (1.7%)	1 (2.6%)	0 (0.0%)	5.33	(0.62, 46.02)	1.00^
Number of Warning Signs						
One warning sign	15 (25.4%)	8 (20.5%)	7 (35.0%)	0.48	(0.14, 1.60)	0.23
Two warning signs	17 (28.8%)	13 (33.3%)	4 (20.0%)	2.00	(0.55, 7.21)	0.28
Three warning signs	17 (28.8%)	13 (33.3%)	4 (20.0%)	2.00	(0.55, 7.21)	0.28
Four warning signs	2 (3.4%)	2 (5.1%)	0 (0.0%)			0.54^

Test Statistic: *Chi-square, ^Fisher's Exact test

Table 6: Adjusted odds ratios (ORs) and confidence intervals (CIs) of admission group by suspicion of dengue, and days from illness onset to hospital visit with correct admission decision by physicians at SEDSS sites in Puerto Rico during May 7, 2012 – May 6, 2013 (N = 595).

	Adjusted OR	95% CI	*P* value
Admission Group			
Patients diagnosed as suspected dengue			
Group A	Reference		0.02
Group B	2.29	(1.13, 4.65)	
Group C	5.25	(1.27, 21.66)	
Patients not diagnosed as suspected dengue			
Group A	Reference		<0.0001
Group B	0.24	(0.14, 0.43)	
Group C	0.06	(0.02, 0.18)	
Suspected dengue	4.38	(3.01, 6.39)	<0.0001
Days from illness onset to hospital visit	1.31	(1.18, 1.45)	<0.0001

Table 7: Adjusted odds ratios (ORs) and confidence intervals (CIs) of Group A symptoms, sex, suspicion of dengue, and days from illness onset to hospital visit with correct admission decision by physicians in Group A patients at SEDSS sites in Puerto Rico during May 7, 2012 – May 6, 2013 (N = 67).

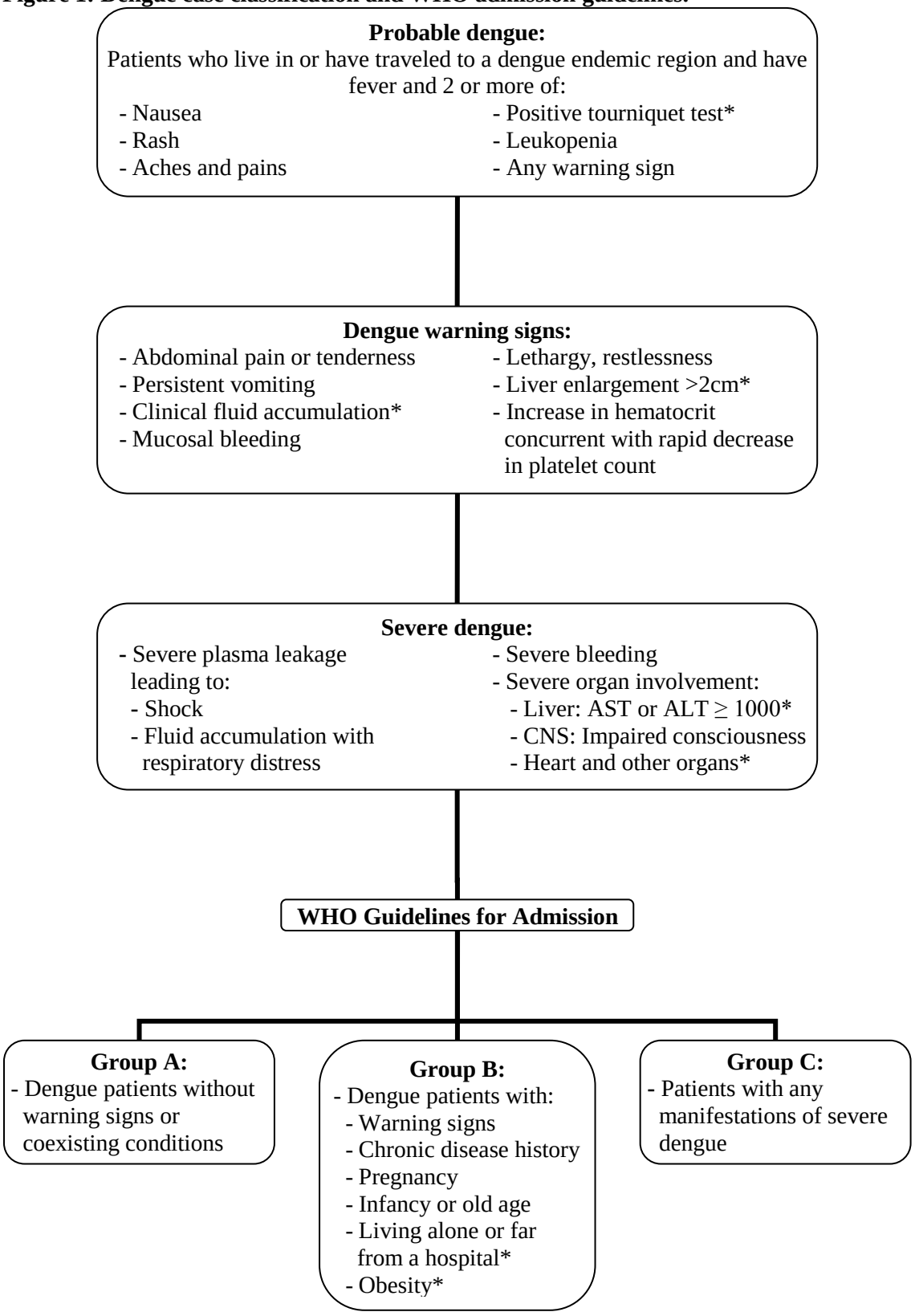
	Adjusted OR	95% CI	*P* value
Nausea	0.21	(0.03, 1.34)	0.10
Rash	4.84	(0.89, 26.29)	0.07
Bone pain	3.95	(0.84, 18.67)	0.08
Back pain	4.91	(0.80, 30.22)	0.09
Female	5.57	(1.00, 31.13)	0.05
Suspected dengue	0.24	(0.05, 1.24)	0.09
Days from illness onset to hospital visit	0.45	(0.25, 0.81)	0.01

Table 8: Adjusted odds ratios (ORs) and confidence intervals (CIs) of warning signs, chronic diseases, infancy or old age, suspicion of dengue, and days from illness onset to hospital visit with correct admission decision by physicians in Group B patients at SEDSS sites in Puerto Rico during May 7, 2012 – May 6, 2013 (N = 469).

	Adjusted OR	95% CI	*P* value
Abdominal pain	1.71	(1.02, 2.86)	0.04
Persistent vomiting	1.94	(1.17, 3.20)	0.01
Increase in hematocrit concurrent with decrease in platelet count	7.49	(0.69, 81.59)	0.10
History of cancer	0.15	(0.02, 1.30)	0.08
Infancy	5.06	(1.28, 19.97)	0.02
Old age	10.77	(2.75, 42.22)	0.0007
Suspected dengue	7.58	(4.79, 12.00)	<0.0001
Days from illness onset to hospital visit	1.51	(1.33, 1.73)	<0.0001

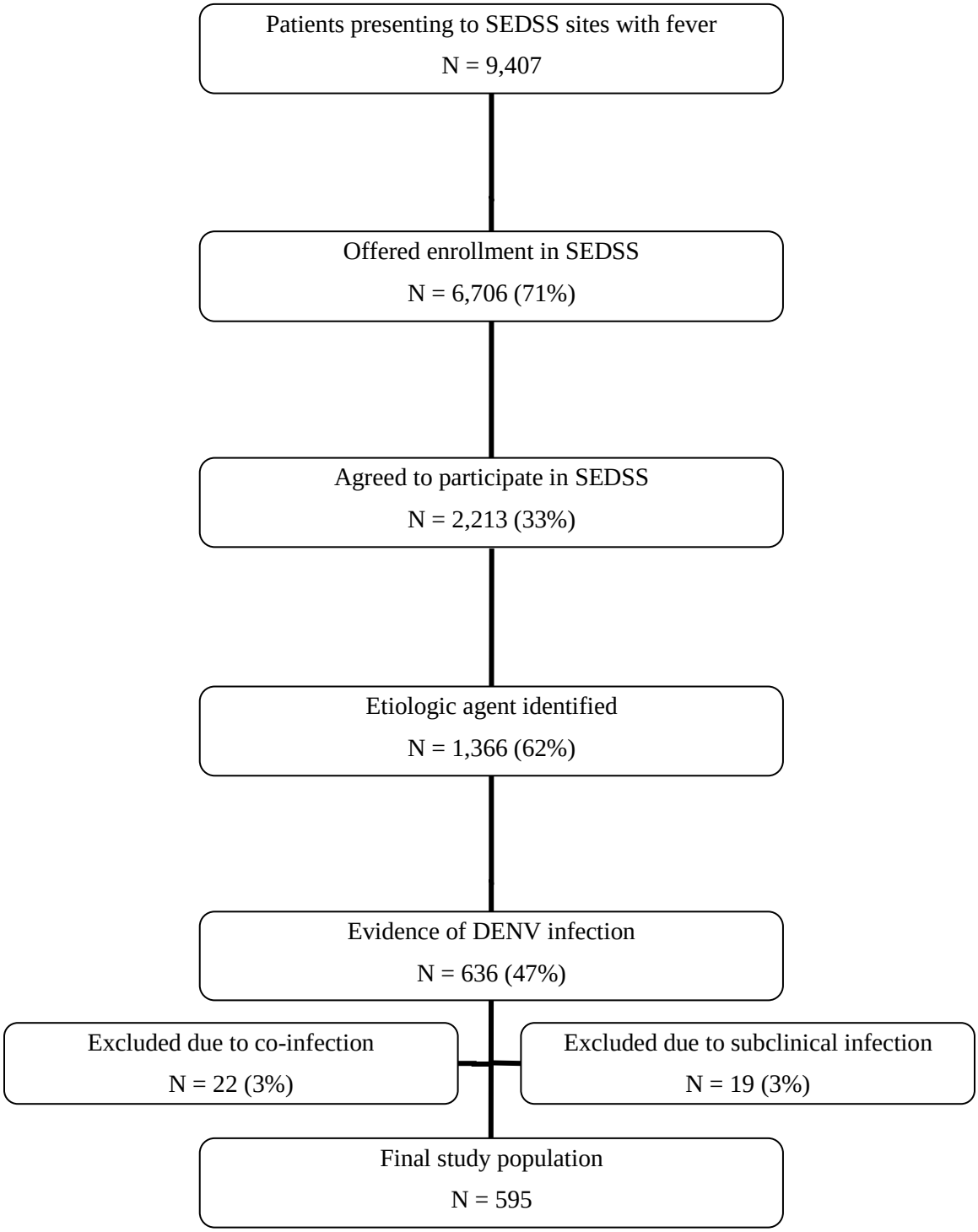
FIGURES

Figure 1: Dengue case classification and WHO admission guidelines.



*****Demographic criteria and signs and symptoms unable to be analyzed due to study design

Figure 2: Schematic of SEDSS patient enrollment and study population during May 7, 2012 – May 6, 2013.



APPENDIX

IRB Determination

October 28, 2014

Nicole M. Roth
Emory University
Rollins School of Public Health

RE: Determination: No IRB Review Required
Title: *Use of the 2009 WHO dengue treatment guidelines to improve hospital admission practices of suspected dengue patients*

Dear Ms. Roth:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" involving "human subjects" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will conduct a secondary analysis of hospital admission following an AFI in suspected dengue patients in Puerto Rico. There are no plans to link data to identifiers.

Please note that this determination does not mean that you cannot publish the results. If you have questions about this issue, please contact me.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Will Smith, BA
Research Protocol Analyst

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