

SHORT REPORT: ASSESSMENT OF THE WORLD HEALTH ORGANIZATION SCHEME FOR CLASSIFICATION OF DENGUE SEVERITY IN NICARAGUA

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Abstract. The World Health Organization (WHO) scheme for classification of dengue severity was evaluated in a three-year study of 1,671 confirmed dengue cases in three Nicaraguan hospitals. The WHO classification of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) was compared with the presence of hemorrhagic manifestations, signs of vascular permeability, marked thrombocytopenia, and shock in 114 infants, 1,211 children, and 346 adults. We found that strict application of the WHO criteria fails to detect a significant number of patients with severe manifestations of dengue, especially in adults.

The four serotypes of the mosquito-borne dengue virus (DEN1–4) cause a spectrum of illness ranging from the self-limiting dengue fever (DF) to more severe, life-threatening forms of the disease termed dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue continues to spread throughout tropical and subtropical regions worldwide, affecting an estimated 50–100 million people each year.¹

DHF/DSS was first defined in 1974² based on studies of children in Southeast Asia in the 1960s.³ The principal requirements for a DHF classification are hemorrhagic manifestations, vascular permeability (plasma leakage), and thrombocytopenia (platelet count $\leq 100,000/\text{mm}^3$); the additional presence of hypotension or narrow pulse pressure along with clinical signs of shock designates DSS. DHF/DSS has served as a useful classification of severe dengue to aid in disease identification for treatment, epidemiologic surveillance, and studies of dengue pathogenesis. However, as dengue spreads into new regions worldwide, geographic and age-related differences are being observed in the range of clinical manifestations, and variations are apparent in the capacity of sites to adhere to the strict case definition established by the World Health Organization (WHO).^{4–7} In this short report, we examine the application of the WHO scheme in hospitalized dengue patients in Nicaragua, compared with the documented presence of the four key clinical manifestations associated with severe dengue.

This study was conducted from January 1999 to December 2001 in three major hospitals in the two largest cities in Nicaragua: the national pediatric reference hospital, Hospital Infantil Manuel de Jesús Rivera, and the Hospital Roberto Calderon in Managua and the Hospital Escuela Oscar Danilo Rosales Arguello in León. For details of the study design, see the accompanying paper by Hammond and others.⁸ The study was reviewed and approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley, and the Ethical Review Committee of the Centro Nacional de Diagnóstico y Referencia of the Nicaraguan Ministry of Health.

The WHO and Pan American Health Organization criteria

were used to classify dengue severity.^{9,10} Dengue fever and DF with hemorrhagic manifestations (DFHem) were considered mild disease, and DHF and DSS were considered severe disease syndromes. Dengue hemorrhagic fever was defined as fever with hemorrhagic manifestations, thrombocytopenia (platelet count $\leq 100,000/\text{mm}^3$), and hemoconcentration or other signs of plasma leakage; DSS was defined as DHF plus either hypotension for age (systolic pressure < 80 mm of Hg for those < 5 years of age and < 90 mm of Hg for those ≥ 5 years of age) or narrow pulse pressure (≤ 20 mm of Hg)¹⁰ in the presence of clinical signs of shock (e.g., slow capillary filling, cold clammy skin). Alongside the DHF/DSS classification, severe clinical manifestations of dengue were defined as internal hemorrhage, plasma leakage, shock, and/or platelet count $\leq 50,000/\text{mm}^3$. Internal hemorrhage consisted of melena, hematemesis, hematuria, and/or menorrhagia. Signs of plasma leakage included the presence of pleural effusion, ascites, and/or hemoconcentration ($\geq 20\%$ increase in hematocrit over the value at discharge or hematocrit values $\geq 20\%$ of the normal value for age and sex).⁴ Shock was characterized by narrow pulse pressure or hypotension with or without documented clinical signs of shock. A confirmed dengue case was determined by the presence of DEN-specific IgM antibodies, a ≥ 4 -fold increase in the titer of total antibodies to dengue virus in paired acute and convalescent sera, and/or detection of dengue virus by reverse transcription–polymerase chain reaction or virus isolation. Laboratory methods are described in the accompanying paper by Hammond and others.⁸ Data were entered and analyzed using Epi-Info (Centers for Disease Control and Prevention, Atlanta, GA). Crude odds ratios (ORs) and their Cornfield 95% confidence intervals (CIs) were calculated using chi-square analysis for significance.

Of 3,173 suspected dengue cases that came to the study hospitals, 1,671 were confirmed as positive for dengue virus infection, including 114 infants, 1,211 children, and 346 adults. One thousand eighty-five (65%) patients were seen at the hospitals in Managua and 586 (35%) patients were attended at the hospital in León. Since the DEN-2 serotype predominated over the entire period studied, data from all three years were combined.

To evaluate how effectively the WHO classification scheme distinguished between mild and severe disease, four key severe clinical manifestations associated with dengue (shock,

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plasma leakage, marked thrombocytopenia, and internal hemorrhage) were investigated. First, marked thrombocytopenia was determined by analyzing different cut-off values for platelet counts with respect to their association with the other critical manifestations of DHF/DSS. The significant association of $\leq 150,000$ platelets/mm³ or $\leq 100,000$ platelets/mm³ with the presence of shock, plasma leakage and/or internal hemorrhage was found to be driven by patients with platelet counts $\leq 50,000$ /mm³ (OR = 4.14, 95% CI = 3.22–5.32) (Table 1). Discrete groupings of platelet counts $> 50,000$ /mm³ either showed no significant association or were significantly associated with the absence of the severe manifestations of dengue, while ranges of platelet counts $\leq 50,000$ /mm³ demonstrated a significant association (Table 1).

Infants (0–11 months of age), children (1–14 years old), and adults (≥ 15 years old) were evaluated separately. Of laboratory-confirmed dengue cases, 34 (30%) infants, 249 (21%) children, and 22 (6%) adults were classified as DHF/DSS cases (Table 2). A much larger proportion of patients presented with at least one severe clinical manifestation; namely, 73 (64%) infants, 668 (55%) children, and 124 (36%) adults, although still following the same age-related trend as DHF/DSS.

Close examination of the clinical signs associated with DHF/DSS showed that more than half of dengue patients of all ages with shock did not fulfill the criteria of DHF/DSS and that the DHF/DSS classification did not capture 82% of all adult cases with one or more of the severe manifestations (Figure 1). Of dengue cases classified as the milder DF/DFHem, 39 (49%) infants, 419 (44%) children, and 102 (32%) adults presented with at least one severe clinical manifestation. Furthermore, more than 50% of infants with shock, more than 50% of children with internal hemorrhage, shock,

TABLE 1
Association of grades of thrombocytopenia with the presence of shock, plasma leakage, or internal hemorrhage*

Platelet count	Manifestations absent N (%)	Manifestations present N (%)	Total N	OR	(95% CI)
$\leq 150,000$	522 (46)	603 (54)	1,125	2.72	(2.08–3.56)
$\leq 100,000$	356 (41)	513 (59)	869	3.05	(2.44–3.83)
$\leq 50,000$	126 (28)	317 (72)	443	4.14	(3.22–5.31)
$> 150,000$	245 (70)	104 (30)	349	0.37	(0.28–0.48)
100,001–150,000	166 (65)	90 (35)	256	0.53	(0.40–0.71)
50,001–100,000	230 (54)	196 (46)	426	0.90	(0.71–1.13)
30,001–50,000	68 (32)	144 (68)	212	2.63	(1.91–3.62)
20,001–30,000	26 (23)	89 (77)	115	4.10	(2.57–6.60)
$\leq 20,000$	32 (28)	84 (73)	116	3.10	(2.00–4.82)

* OR = odds ratio; CI = confidence interval.

or severe thrombocytopenia, and more than 60% of adults with any of the four severe manifestations—internal hemorrhage (80%), plasma leakage (60%), shock (77%), severe thrombocytopenia (73%)—were not classified as having DHF/DSS.

The WHO classification of DHF/DSS has been used effectively to recognize severe dengue, particularly in Asia and increasingly in other regions, to assess epidemiologic trends, to investigate dengue pathogenesis, and to guide clinical management. As dengue spreads worldwide, there is emerging recognition that the DHF/DSS criteria may not be universally useful for clinical management and case classification. This could be due to lack of technology or resources for the frequent monitoring needed to capture the data necessary to fulfill the case requirements,^{11–13} or the result of geographic and age-related variations in clinical manifestations^{4–7} from those initially observed in children in Southeast Asia,³ who formed the basis for the WHO schema.²

TABLE 2
Presentation of the four severe clinical manifestations of DHF/DSS and classification by World Health Organization criteria in infants, children, and adults*

	Without severe manifestation† N (%)	With severe manifestation† N (%)	DF/DFHem N (%)	DHF N (%)	DSS N (%)
Infants					
Total	41 (36)	73 (64)	80 (70)	24 (21)	10 (9)
Year					
1999	16 (38)	26 (62)	30 (71)	8 (19)	4 (10)
2000	6 (32)	13 (68)	14 (74)	3 (16)	2 (11)
2001	19 (36)	34 (64)	36 (68)	13 (25)	4 (8)
Age (months)					
Mean (SD)	6.4 (2.3)	6.1 (2.3)	6.3 (2.4)	6.5 (2.1)	5.1 (1.4)
Children					
Total	543 (45)	668 (55)	962 (79)	185 (15)	64 (5)
Year					
1999	239 (47)	265 (53)	407 (81)	77 (15)	20 (4)
2000	101 (47)	114 (53)	188 (87)	16 (7)	11 (5)
2001	203 (41)	289 (59)	367 (75)	92 (19)	33 (7)
Age (years)					
Mean (SD)	7.9 (3.5)	7.3 (3.1)	7.6 (3.3)	7.3 (3.3)	6.8 (2.9)
Adults					
Total	222 (64)	124 (36)	324 (94)	20 (6)	2 (1)
Year					
1999	85 (77)	26 (23)	107 (96)	4 (4)	0 (0)
2000	80 (68)	37 (32)	114 (97)	2 (2)	1 (1)
2001	57 (48)	61 (52)	103 (87)	14 (12)	1 (1)
Age (years)					
Mean (SD)	28.9 (12.7)	29.5 (12.8)	29 (12.8)	32 (12.3)	38.5 (21.9)

* DHF/DSS = dengue hemorrhagic fever/dengue shock syndrome; DF/DFHem = dengue fever/DF with hemorrhagic manifestations.

† Presence of any of the following severe clinical manifestations: internal hemorrhage, signs of plasma leakage, shock, platelet count $\leq 50,000$ /mm³.

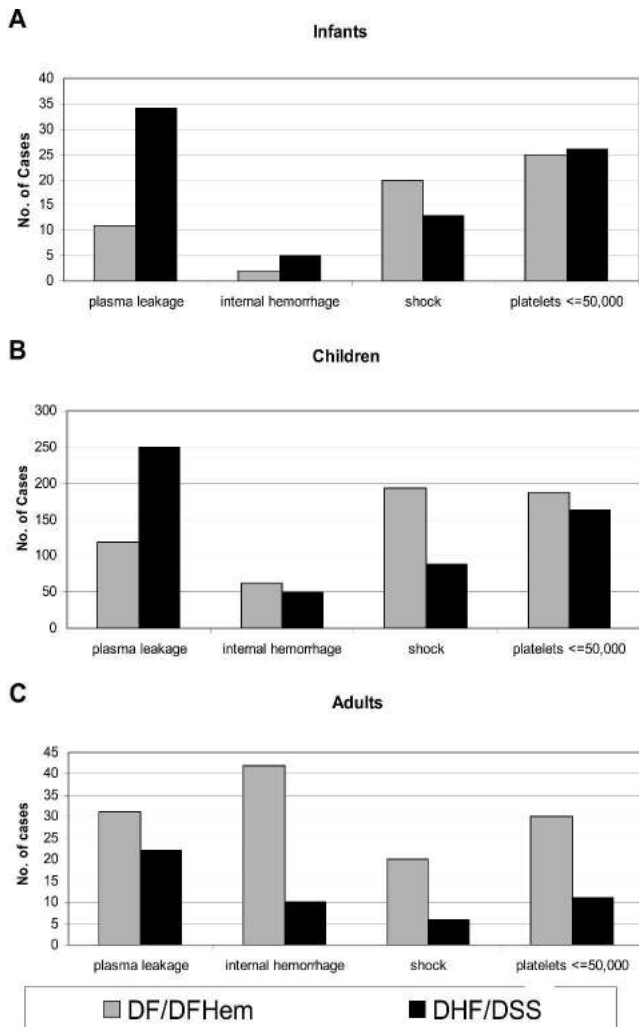


FIGURE 1. Presence of severe clinical manifestations of dengue in cases classified by World Health Organization (WHO) criteria as dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) or classic dengue fever. The number of cases with internal hemorrhage, shock, signs of plasma leakage (hemoconcentration, pleural effusion, and/or ascites) and/or marked thrombocytopenia (platelet count $\leq 50,000/\text{mm}^3$) is plotted in relation to the WHO/Pan American Health Organization classification as DHF/DSS or classic dengue fever (DF) or dengue fever with hemorrhagic manifestations (DFHem).⁴ **A**, Infants, < one year of age; **B**, Children, 1–14 years of age; **C**, Adults, > 14 years of age.

As a result, when the WHO criteria are strictly followed, many severe cases, including those that involve shock and fatality, may be missed.^{4–6,14–16} In addition, the tendency to refer to dengue cases with shock as DSS or to associate bleeding or plasma leakage with DHF has led numerous clinicians and investigators to either loosely apply the WHO definitions when not all criteria are present^{13,17–21} or to invent new categories.^{4,22,23} This makes it difficult to compare dengue severity across regions and even between studies. Finally, whether DHF/DSS is itself a syndrome that is distinct from other severe dengue syndromes is still unclear.^{4,5,22,24}

In this study, in addition to traditional DHF/DSS, we assessed the presence of four principal severe clinical manifestations that are associated with dengue; namely, internal hemorrhage, plasma leakage, shock, and marked thrombocytopenia.

We found that the DHF/DSS classification did not capture most cases exhibiting the principal manifestations under investigation. Of confirmed dengue cases classified as the milder DF/DFHem, 32–49% had at least one severe clinical manifestation. In infants, more than half of all cases with shock were not classified as DHF/DSS, and in children, more than half the cases with internal hemorrhage, shock, or severe thrombocytopenia were not classified as DHF/DSS. Similar results have been reported in other studies of pediatric dengue in Asia and the South Pacific.^{5,6} We also found that in adults, more than two-thirds of all cases with any of the four severe manifestations were not classified as DHF/DSS. The dearth of data regarding dengue in adults in general and our demonstration that the ability of DHF/DSS to classify severe illness in adults is particularly poor, together with potential shifts in the burden of disease to older ages resulting from vector control measures,^{7,25} expanding mosquito and virus introductions,^{26,27} or possibly in the future the use of a vaccine, all highlight the importance of the deficiency of the application of the WHO criteria to dengue in adults.

Overall, these results suggest that the burden of severe dengue is underestimated when strict DHF/DSS guidelines are enforced. The data presented here emphasize the importance of standardized multi-country clinical studies to develop terminology and treatment algorithms that consider geographic and age-related variations and that are useful in clinical management and epidemiology of the spectrum of dengue and its severe manifestations.

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