

Evaluation of the WHO classification of dengue disease severity during an epidemic in 2011 in the state of Ceará, Brazil

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In 2009, the World Health Organization (WHO) issued a new guideline that stratifies dengue-affected patients into severe (SD) and non-severe dengue (NSD) (with or without warning signs). To evaluate the new recommendations, we completed a retrospective cross-sectional study of the dengue haemorrhagic fever (DHF) cases reported during an outbreak in 2011 in northeastern Brazil. We investigated 84 suspected DHF patients, including 45 (53.6%) males and 39 (46.4%) females. The ages of the patients ranged from five-83 years and the median age was 29. According to the DHF/dengue shock syndrome classification, 53 (63.1%) patients were classified as having dengue fever and 31 (36.9%) as having DHF. According to the 2009 WHO classification, 32 (38.1%) patients were grouped as having NSD [4 (4.8%) without warning signs and 28 (33.3%) with warning signs] and 52 (61.9%) as having SD. A better performance of the revised classification in the detection of severe clinical manifestations allows for an improved detection of patients with SD and may reduce deaths. The revised classification will not only facilitate effective screening and patient management, but will also enable the collection of standardised surveillance data for future epidemiological and clinical studies.

Key words: dengue fever - classification criteria - warning signs - Brazil

Dengue is an acute viral disease transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes and is considered the most important viral disease transmitted by arthropods worldwide (Guzmán & Kouri 2001, Guha-Sapir & Schimmer 2005, Simmons et al. 2012). The expansion of the geographic distribution and the overall incidence of dengue have increased steadily over the past six decades (Descoux et al. 2012). The disease is currently disseminated in over 100 countries from all continents, including Europe, which recently experienced an epidemic on Madeira Island (Portugal) (Sousa et al. 2012). Dengue outbreaks also impose high costs to health services and to the economic systems of these countries (Suaya et al. 2009, Baly et al. 2012). In the XXI century, Brazil has recorded most of the reported cases of dengue in the world, accounting for approximately 61% of all cases reported to the World Health Organization (WHO) (Teixeira 2009). Southeast Asia was the region most affected by dengue in the mid-1990s. Since then, Central and South American coun-

tries have been experiencing an increasing number of reported dengue cases (Teixeira 2009). The disease has been more prevalent in adults; however, in recent years, a progressive reduction in the ages of the patients affected by dengue haemorrhagic fever (DHF) has been observed in Brazil (Teixeira 2009, Cavalcanti et al. 2011). A major weakness in the surveillance of severe dengue (SD) cases is the difficulty of categorising these cases according to the classification adopted by the WHO in 1997 [DHF/dengue shock syndrome (DSS) classification] (WHO 1975, 1997). This classification is useful for the clinical management of patients, but SD cases do not frequently meet all of the criteria for classification according to this system (Bandyopadhyay et al. 2006, Narvaez et al. 2011). The emergence of dengue with an atypical involvement of specific organs, such as the central nervous system, liver, lungs and heart, highlighted this difficulty (Araújo et al. 2011, 2012a, b, Verna et al. 2011, Dussart et al. 2012). This disease presentation leads to an acute dengue infection with a severe multisystem manifestation (Borawake et al. 2011, Morriolo et al. 2011), which does not fit the criteria previously defined for severity surveillance.

Due to these limitations, Brazil chose to adopt the new category dengue with complications (DWC) in 2001. For the Brazilian Ministry of Health (MS), every suspected case of dengue fever (DF) progressing to a SD form that does not completely fit the DHF/DSS criteria should be considered DWC, especially in the presence of one the following: neurological manifestation, cardiac dysfunction, liver failure, gastrointestinal bleed-

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ing, pleural effusion, pericardial effusion and/or ascites, thrombocytopenia $< 20,000/\text{mm}^3$, leukopenia $< 1,000/\text{mm}^3$ or fatal suspected cases of dengue (SVS/MS 2011a). This new category is exclusively used in Brazil and makes evaluation very difficult when comparing cases with other dengue transmission areas worldwide.

Based on these difficulties and after a multicentre dengue study DENGue COntrol was conducted, a new classification of dengue cases was proposed in 2009 by the WHO. This proposal defines two main categories - SD and non-severe dengue (NSD) - and the NSD form can present with or without warning signs (WHO 2009, Alexander et al. 2011).

The aim of this study was to retrospectively evaluate a cohort of suspected DHF cases reported in a referral hospital in northeastern Brazil according to the 2009 WHO classification.

SUBJECTS, MATERIALS AND METHODS

This is a retrospective cross-sectional study of suspected DHF cases reported to a referral hospital for infectious diseases in the city of Fortaleza in the state of Ceará (CE), northeastern Brazil, during its largest dengue epidemic of 2011.

Patients and definitions - All study patients were investigated for being reported as suspected cases of DHF. However, some of the cases did not have laboratory confirmation and did not undergo additional tests such as ultrasound and chest X-ray, which would be needed to confirm cavitory effusions. Notification data were acquired from the Notifiable Diseases Information System. This investigation included all of the cases reported as suspected DHF at the referral unit. Following the report of a suspected case, the epidemiological surveillance team performed the proper investigation for the confirmation or exclusion of each case (Cavalcanti et al. 2010, Araújo et al. 2011, SVS/MS 2011a). All reported cases were required to be accompanied by a serum sample, but this was not always permitted by the patient.

DF was defined as an acute febrile illness (history of fever less than 7 days) accompanied by at least two of the following clinical findings: nausea, vomiting, headache, arthralgia, retro-orbital pain, rash, myalgia, haemorrhagic manifestations and leukopenia. Because of the lack of specificity of these clinical signs and symptoms, laboratory evidence of dengue virus (DENV) infection was required for a confirmed diagnosis.

The definition of DHF consists of the presence of all of the five following criteria: fever (history of fever less than 7 days), haemorrhagic evidence (spontaneous bleeding or a positive tourniquet test), thrombocytopenia (platelet count $< 100,000 \text{ cells}/\text{mm}^3$), plasma leakage evidence (pleural effusion, ascites, hypoalbuminaemia or haemoconcentration greater than 20% related to baseline) and at least one positive test for dengue [the non-structural protein 1 (NS1), M antibody capture ELISA (MAC-ELISA), viral isolation or reverse transcription-polymerase chain reaction (RT-PCR)] (SVS/MS 2011b).

The definition of DWC was considered for patients that did not fulfil the DHF criteria, but presented with

at least one of the following: neurological manifestation, cardiac dysfunction, liver failure, gastrointestinal bleeding, pleural effusion, pericardial effusion and/or ascites, thrombocytopenia $< 20,000/\text{mm}^3$, leukopenia $< 1,000/\text{mm}^3$ or fatal suspected case of dengue (SVS/MS 2011a).

The definition of NSD is somewhat similar to that of DF: a combination of two symptoms and signs in the acute febrile individual and coming from an area of known dengue endemicity. In addition, abdominal pain and tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness and liver enlargement are considered warning signs for potentially SD.

The definition of SD was considered for cases including any of the following: plasma leakage leading to shock or respiratory distress, severe bleeding or organ failure (e.g., elevated liver enzyme levels, impaired consciousness or heart failure) (WHO 2009, Alexander et al. 2011, Srikiatkachorn et al. 2011). A confirmed case of dengue was considered for those who had a positive laboratory result for at least one of the techniques used (MAC-ELISA, NS1, viral isolation or RT-PCR).

Data collection - Medical records, notification forms used by the MS and the results of laboratory tests were systematically retrieved for all reported cases during the study period. Data were collected from May 2011-March 2012 through a structured questionnaire including age, gender, signs and symptoms, warning signs, evidence of shock (signs of poor perfusion and hypotension), effusions (ascites, pleural effusion, pleural effusion and respiratory distress) and laboratory results. Leukopenia was considered as $< 1,000/\text{mm}^3$, hypoalbuminaemia as serum albumin $< 3 \text{ g/dL}$, liver injury as aspartate aminotransferase or alanine aminotransferase $> 1,000/\text{L}$ and severe thrombocytopenia as platelet count $< 20,000/\text{mm}^3$.

To address the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of the DHF/DSS classification and WHO classification of 2009 for the detection of SD, each classification was compared to the other. Patients classified as DHF or DSS were considered SD and those classified as DF were considered NSD. For the WHO classification of 2009, patients classified as having SD were considered severe and those with dengue, with or without warning signs, were considered NSD (Narvaez et al. 2011).

All data were stored in Microsoft Office Access v. 2003 and analysed using Epi Info v. 3.5.1 and terminated in accordance with both the classification used currently in Brazil [adapted from WHO (1997)] and the new classification (WHO 2009).

Ethics - This study followed the ethical principles of research involving human subjects and Resolution 196/96 from the National Health Council of Brazil and has been approved by the Ethical Review Board from Christus University Centre and São José Hospital (protocol # 011/2011). All patients' chart identification information was codified to retain the subjects' confidentiality.

RESULTS

In 2011, a large dengue epidemic occurred in CE. Disease transmission was recorded in 161 municipalities (87.5%), with an incidence of 670.98/100,000 inhabitants. Three different DENV serotypes were simultaneously isolated: DENV-1 (98.7%), DENV-3 (0.4%) and DENV-4 (0.9%). Despite the recent introduction of DENV-4 in CE in 2011, that epidemic was mainly caused by DENV-1, which had only rarely been recorded in the region since 2002.

Among the 102 cases reported as DHF in this period, 84 (82.4%) were seen at the São José Hospital. Of the 84 patients investigated for suspected DHF, 45 (53.6%) were male and the median age was 29 years old (5-83) (Table I).

TABLE I

Demographic characteristics, signs and symptoms during a dengue epidemic in northeastern Brazil, 2011

Age (years)	n/total (%)
≤ 15	16/84 (19)
> 15	68/84 (81)
Sex	
Female	39 (46.4)
Male	45 (53.6)
Signs and symptoms	
Headache	74/77 (96.1)
Nausea	44/47 (93.6)
Myalgia	70/75 (93.3)
Rash	60/68 (88.2)
Exanthema	60/68 (88.2)
Retro-orbital pain	37/42 (88.1)
Arthralgia	31/37 (83.8)
Dizziness	47/57 (82.5)
Abdominal pain	61/76 (80.3)
Vomit	57/73 (78.1)
Cough	30/50 (60)
Dyspnoea	20/64 (31.3)
Haemorrhagic manifestations	70/80 (87.5)
Petechiae	51/63 (81)
Mucosal bleeding	28/69 (40.6)
Gastrointestinal bleeding	21/66 (31.8)
Haematemesi	14/63 (22.2)
Positive tourniquet test	8/37 (21.6)
Melena	9/59 (15.3)
Epistaxis	8/58 (13.8)
Haematuria	4/34 (11.8)
Extravasation of plasma	
Pleural effusion	12/21 (57.1)
Cavitary effusion	16/31 (51.6)
Ascites	10/20 (50)
Plasma leakage	31/75 (41.3)
Laboratory values	Median (min-max)
Platelet count	18,000 (12,000-85,000)
Leukocyte count	3,380 (900-9,800)
Haematocrit	39.2 (15.5-57.5)

According to the adapted DHF/DSS classification (1997), one (1.2%) patient was classified as having DF, 31 (36.9%) as having DHF and 52 (61.9%) as having DWC (Tables II, III). The WHO classification of 2009 categorised the investigated patients as follows: 32 NSD [4 (4.8%) without warning signs and 28 (33.3%) with warning signs] and 52 (61.9%) SD (Table II).

The most frequently reported signs and symptoms were headache 74/77 (96.1%), nausea 44/47 (93.6%), myalgia 70/75 (93.3%), rash 60/68 (88.2%), retro-orbital pain 37/42 (88.1%), arthralgia 31/37 (83.8%), dizziness 47/57 (82.5%), abdominal pain 61/76 (80.3%), vomiting 57/73 (78.1%) and dyspnoea 20/64 (31.3%). Bleeding evidence was found in 70/80 patients (87.5%). Mucosal bleeding was detected in 28/69 (40.6%) and petechiae in 51/63 (81%) and the tourniquet test was performed in 44% of patients, with 21.6% positivity (Table I).

TABLE II

Comparison between dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS) classification for reporting severe cases during a dengue epidemic in northeastern Brazil, 2011

	NSD n (%)	NSD with warning signs n (%)	SD n (%)	Total n (%)
DF	3 (75)	18 (64.3)	32 (61.5)	53 (63.1)
DHF	1 (25)	10 (35.7)	20 (38.5)	31 (36.9)
DSS	-	-	-	-
Total	4 (100) (4.8 of total)	28 (100) (33.3 of total)	52 (100) (61.9 of total)	84 (100) -

DF: dengue fever; NSD: non-severe dengue; SD: severe dengue.

TABLE III

Comparison between dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS) classification adapted by Brazilian Ministry of Health (2011) and the DHF/DSS classification for reporting severe dengue (SD) cases during a dengue epidemic in northeastern Brazil, 2011

	NSD n (%)	NSD with warning signs n (%)	SD n (%)	Total n (%)
DF	-	1 (3.6)	-	1 (1.2)
DWC	3 (75)	17 (60.7)	32 (61.5)	52 (61.9)
DSS	-	-	-	-
DHF	1 (25)	10 (35.7)	20 (38.5)	31 (36.9)
Total	4 (100) (4.8 of total)	28 (100) (33.3 of total)	52 (100) (61.9 of total)	84 (100) -

DF: dengue fever; DWC: dengue with complications; NSD: non-severe dengue.

Among patients evaluated with at least two haematocrit counts, the lowest result showed a median value of 35.5% (15.4-45.6%) and the highest of 43.5% (30.3-57.5%). Leukocyte count varied between 900-9,800/mm³ and platelet count showed a median of 18,000/mm³ (1,200-85,000) (Table I).

Plasma leakage was identified in 31/75 (41.3%) patients, with cavity effusion in 16/31 (51.6%). A severe impairment of organs was reported in 24/83 (28.9%) cases, with an emphasis on cardiorespiratory changes present in 8/26 (30.8%) patients (Table IV). A positive IgM (MAC-ELISA) was detected in 75/84 (89.3%) cases.

Considering the DHF/DSS classification, which is still the current classification adopted in Brazil, only 31 (36.9%) out of 84 cases reported as suspected DHF fulfilled all DHF criteria. The other 52 cases were classified as DWC, an exclusive category adopted in Brazil for SD cases not enrolled as DHF/DSS. All of the patients had fever, thrombocytopenia and laboratory confirmation of dengue infection, but 22/44 (54.5%) showed no plasma leakage and 19/52 (36.5%) showed no evidence of bleeding. The main severity criterion for 27/52 (51.9%) patients was platelet count < 20,000/mm³.

Regarding the WHO classification of 2009, 52/84 cases were considered SD; 31 (100%) had been previously classified as DHF and another 21 (40.4%) had been classified as DWC.

The WHO classification of 2009 showed 60.4% sensitivity [confidence interval (CI) 95% 46.0-73.5] and

35.5% specificity (CI 95% 19.2-54.6) to capturing SD cases. It also showed a PPV of 61.5% (CI 95% 47.0-74.7) and a low NPV of 34.4% (CI 95% 18.6-53.2) (Table V).

DISCUSSION

In this study, we compared two classifications of dengue - the DHF/DSS classification (and adapted by the MS) and the WHO classification of 2009 - through a retrospective analysis of cases diagnosed during the largest epidemic of dengue registered in CE. In the 1980s, a broad consensus emerged from dengue experts worldwide that the traditional DF/DHF/DSS classification was essentially retrospective and overly complex, limiting its usefulness for patient management and global surveillance (Akbar et al. 2012). Previous studies have addressed the difficulties in classifying dengue cases according to the DHF/DSS classification (Bandyopadhyay et al. 2006, Basuki et al. 2010, Barniol et al. 2011), but this is the first case series study evaluating the Brazilian scenario for potentially SD cases. Moreover, Srikiatkachorn et al. (2011) discuss the limitations of the WHO classification of 2009 because of its inclusion of a greater number of unspecific signs and symptoms and the difficulties associated with confirming the damage to organs in the absence of plasma leakage.

Considering the SD cases, the DHF/DSS classification and the WHO classification of 2009 would have identified 31 (36.9%) and 52 (61.9%) cases, respectively. The WHO classification of 2009 showed a higher speci-

TABLE IV
Severe clinical manifestations presents during a dengue epidemic in northeastern Brazil, 2011

Severe clinical manifestations	Values	DHF/DSS n/total (%)	Dengue with warning signs n/total (%)	SD n/total (%)	DWC n/total (%)
Bleeding	Mild	10/28 (35.7)	11/28 (39.3)	17/28 (60.7)	18/28 (64.3)
Bleeding	Severe	7/21 (33.3)	3/21 (14.3)	18/21 (85.7)	14/21 (66.7)
Leukocytes	< 1,000	1/2 (50)	-	2/2 (100)	1/2 (50)
Leukocytes	1,000-5,000	23/68 (33.8)	26/68 (38.2)	38/68 (55.9)	44/68 (64.7)
Platelets	> 5,000	7/14 (50)	2/14 (14.3)	12/14 (85.7)	7/14 (50)
Platelets	≤ 20,000	18/47 (38.3)	18/47 (38.3)	26/47 (55.3)	29/47 (61.7)
Platelets	> 20,000	13/37 (35.1)	10/37 (27)	26/37 (70.3)	23/37 (62.2)
Abdominal pain	-	25/61 (41)	20/61 (32.8)	41/61 (67.2)	35/61 (57.4)
Persistent vomiting	-	21/57 (36.8)	18/57 (31.6)	39/57 (68.4)	36/57 (63.2)
Dizziness	-	15/47 (31.9)	15/47 (31.9)	31/47 (66)	32/47 (68.1)
Gravity					
Organ involvement	-	10/24 (41.7)	-	24/24 (100)	14/24 (58.3)
Cardiac abnormality	-	5/8 (62.5)	-	8/8 (100)	3/8 (68.1)
Shock	-	7/22 (31.8)	-	22/22 (100)	15/22 (68.2)
Dyspnoea	-	9/20 (45)	-	20/20 (100)	11/20 (55)
Cavitary effusions	-	8/16 (50)	-	16/16 (100)	8/16 (50)
Admitted to treatment	-	20/61 (32.8)	3/61 (4.9)	58/61 (95.1)	41/61 (67.2)
Ambulatory	-	8/23 (34.8)	20/23 (87)	3/23 (13)	15/23 (65.2)

DHF: dengue haemorrhagic fever; DSS: dengue shock syndrome; DWC: dengue with complications; SD: severe dengue.

ficity in capturing the most SD cases, as found in Taiwan (Tsai et al. 2013). This specificity may help to improve the risk classification and the health care provided to patients upon first admission to health facilities. However, this classification system could lead to an overload in the health services network if the network is not well-prepared, as suggested by Srikiatkachorn et al. (2011). From this perspective, the WHO classification of 2009 could also serve as a stimulus for a reorganisation of health services, making them ready to intervene strategically and promptly for patients with warning signs and those already considered severe, as suggested by Horstick et al. (2012).

Another relevant point of comparison is that the less rigid demand for laboratory criteria in the WHO classification of 2009 brings with it the possibility of concluding case reports in a timely manner by clinical and surveillance teams, bringing together experts and preventing discrepancies in clinical and epidemiological reports. An example of such a discrepancy was the creation, by the MS, of a new clinical category - DWC - to meet the request of clinicians who did not accept the fact that patients were dying of SD in Brazil, without meeting any of the DHF criteria and had to be finally reported as having DF. This unique inclusion of DWC is already widespread in the service routine and epidemiological surveillance in Brazil, which is currently responsible for 60% of DF cases worldwide (Teixeira 2009). This situation impairs the ability to compare dengue cases with any other country that uses the DHF/DSS classification. In 2011, CE reported the largest dengue outbreak in its history, with 457 DWC cases and a fatality rate exceeding 10%, higher than the estimated rate for DHF cases (7.5%). This fatality rate suggests that more SD were escaping DHF/DSS classification and these deaths would most likely not be accounted for in the official statistics, as they did not fit as DHF or DSS. Considering this aspect, less than 40%

of these cases would have been classified as severe. The revised case classification, with its simplified structure, will facilitate effective screening, risk classification and patient management and improve comparative analyses of surveillance data from different countries (Basuki et al. 2010). The most severe manifestations of dengue, such as severe haemorrhage, severe leukopenia, thrombocytopenia, severe shock, effusions and severe organ involvement, were more frequently found in cases of SD compared to cases of DHF, indicating a greater sensitivity in the identification of cases that are more severe.

In the DHF/DSS classification (1997), among the 84 suspected cases, only 36.9% were confirmed as DHF. Moreover, the tourniquet test, which is considered a good predictor of risk (Kalayanarooj et al. 1999), was only used in 44% of patients, with very low positivity (21.6%). The severe impairment of organs was reported in 28.9% patients. Research carried out in Nicaragua (Balmaseda et al. 2005) noted difficulties in detecting patients with these severe manifestations, especially in adults; this challenge was confirmed by our findings, most likely due to an underreporting of medical evaluation in hospital files/charts.

Defining the plasma leakage is another great difficulty in dengue patients. In most cases, there is a need for repeated blood tests to identify the haemoconcentration. This same difficulty was observed in another dengue epidemic in Brazil in 2008, where 53.8% of patients with SD did not meet the haemoconcentration criteria and were not classified as DHF (Gupta et al. 2010). The identification of effusions through X-ray or ultrasonography assessment is rarely available in current practice and could be costly in public health settings (Cavalcanti et al. 2010). Gupta et al. (2010) also highlighted the difficulty in diagnosing signs of plasma extravasation using research methods that can be costly.

The revised WHO classification of 2009 for SD appears to have higher sensitivity (60.4%), although it is no longer more specific (35.5%) than the DHF/DSS classification. These data are similar to recent reports from Nicaragua (Narvaez et al. 2011, Gutiérrez et al. 2013) and are the first evidence from Brazil. However, the diversity of criteria used to define severity among the studies may explain the differences in sensitivity and specificity. The absence of a gold standard with which to compare these classifications requires caution when evaluating this information.

In our experience thus far, the 2009 WHO classification has been more sensitive in detecting and more helpful for reporting SD cases in this epidemic. This classification made it feasible to classify a greater number of SD cases, which could contribute to a better and timelier management of patients and thus avoid or decrease fatalities. Improvements in early diagnosis and risk prediction for severe disease are undoubtedly needed and research efforts in this area are on-going. However, the use of secondary data, even with research records and medical records, poses limitations to the quality and external validity of our data. Prospective studies are needed to better define the warning signs and to evaluate the benefits of the new classification in different settings.

TABLE V

Concordance between dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS) classification and WHO (2009) classification for reporting severe cases (SD) during a dengue epidemic in northeastern Brazil, 2011

1997 classification	2009 WHO classification		
	Dengue with/without warning signs	SD	Total
Dengue fever	21	32	53
DHF/DSS	11	20	31
Total	32	52	84

negative predictive values: 34.4% [confidence interval (CI) 95% 18.6-53.2]; positive predictive values: 61.5% (CI 95%, 47.0-74.7); sensitivity: 60.4% (CI 95%, 46.0-73.5); specificity: 35.5% (CI 95%, 19.2-54.6).

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