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Evaluation of the 2009 WHO Dengue Case Classification in an Indonesian Pediatric Cohort

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Abstract. The classification of dengue virus-infected patients continues to be a challenge to researchers and clinicians in the field. The accuracy of the 1997 World Health Organization (WHO) dengue case definition has been debated for a decade, because the definition was very stringent, for instance, several researchers showed that apparently severe cases were misclassified as not severe. Therefore the WHO issued revised guidelines in 2009. Here, we retrospectively compared the performance of the WHO case definition of 2009 with the WHO case definition of 1997 in a detailed documented pediatric cohort from Indonesia. Intensive treatment intervention was used as an indicator of severity of disease. In line with our expectations, the 2009 WHO case classification proved to be significantly more specific, albeit less sensitive than the WHO case classification of 1997. We conclude that the revised classification is promising both from research and clinical perspectives, but validation of the classification criteria still needs to be addressed.

INTRODUCTION

To achieve universal consensus about the clinical case classification of dengue virus (DENV)-infected patients, the World Health Organization (WHO) released guidelines in 1974. Although these guidelines were updated several times, the utility and accuracy of classifying patients according to disease severity criteria have continued to be a matter of debate. Therefore, reassessment of the classification criteria has been proposed by several study groups,[1–5] prompting the WHO to issue a revised classification in 2009.[6]

In the original guidelines from 1997, patients are classified in three separate categories: dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).[7] DF was defined as an acute febrile illness with general complaints and a positive laboratory confirmation of DENV infection. The diagnosis of DHF was restricted for patients with the collective presence of fever, hemorrhagic tendency, thrombocytopenia, and signs of plasma leakage. DHF with signs of shock was classified as DSS.

The 2009 WHO guidelines distinguish between severe and non-severe dengue.[6] Severe dengue is defined by the occurrence of plasma leakage and/or fluid accumulation leading to shock or respiratory distress; and/or severe bleeding; and/or severe organ impairment. The non-severe dengue group is divided into patients with and without warning signs. Abdominal pain or tenderness, persistent vomiting, clinically manifest fluid accumulation, mucosal bleeding, lethargy and restlessness, hepatomegaly, and increase in hematocrit with a drop in platelet count are all listed as warning signs.

Moreover, the clinical course of a DENV infection is divided in three phases (i.e., the febrile, critical, and recovery phase). Patients in the febrile phase can already present with warning signs, which may precede the development of severe disease.[8] The critical phase usually starts around the time of defervescence and is characterized by progressive leukopenia together with a drop in the platelet count followed by plasma leakage and/or hemorrhage.

To evaluate the performance of the 2009 WHO case definition compared with the performance of the 1997 WHO case definition, we reassessed the clinical diagnosis of a cohort of DENV-infected children in Indonesia according to these criteria. Moreover, the utility and accuracy of both classification systems were assessed using the treatment received during admission.

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METHODS

From February 2001 until April 2003, this study was conducted at the Dr. Kariadi Hospital in Semarang, Indonesia.[2] In this area of central Java, dengue is endemic, and all four serotypes are circulating. Children aged 2–14 years admitted to the pediatric ward or the pediatric intensive care unit with a clinical suspicion of DENV infection were included. Written informed consent was obtained from a parent or legal guardian before inclusion. The ethical committee of the Dr. Kariadi Hospital had approved this study. Signs and symptoms, findings on physical examination, and routine laboratory test data were obtained at admission and during the stay in the hospital with a standardized case report form. The platelet count was determined daily. Moreover, at admission, the hematocrit was measured every 2 hours for the first 6 hours and then, every 6 hours until stable. For diagnostic purposes, a blood sample was obtained at the first and seventh day of admission. DENV infection was diagnosed by serotype-specific reverse transcription polymerase chain reaction (RT-PCR)[9] carried out on samples obtained at the day of admission, and/or detection of DENV-specific immunoglobulin M (IgM) serum antibodies (Focus Technologies, Cypress, CA) in the acute phase sample, and/or detection of a fourfold increase in the titer of IgG antibodies (Focus Technologies, Cypress, CA) in paired acute and convalescent sera. Patients with a positive laboratory diagnosis of DENV infection and a complete clinical dataset were selected for additional evaluation.

In terms of disease severity, patients were retrospectively classified according to both the 1997 and 2009 WHO case classification. According to the 1997 WHO case definition, the patients were classified in three groups.[7]

(1) DF: Presence of two or more of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, and leukopenia.
(2) DHF: all of the following symptoms should be present: fever; a hemorrhagic tendency (at least a positive tourniquet test); thrombocytopenia (≤ 100,000 cells/mm^3); evidence of

plasma leakage (at least a rise in hematocrit of ≥ 20% compared with the baseline value of the patient) or other signs of plasma leakage (such as pleural effusion and/or ascites).
(3) DSS: All four criteria of DHF should be met plus signs of shock such as hypotension for age (age < 5 years = < 80 mmHg, age ≥ 5 years = < 90 mmHg) and/or narrow pulse pressure (systolic minus diastolic blood pressure < 20 mmHg).

The following criteria were used to classify patients as having severe DENV infection according to the 2009 WHO case definition.[6]

(1) Severe plasma leakage and/or fluid accumulation leading to shock and/or respiratory distress. Presence of one of the following signs of shock: hypotension for age, narrow pulse pressure or signs of respiratory distress (dyspnoe [reported by physician] and tachypnoe [respiratory rate of > 40/minute], PaO_2:FiO_2 < 200 mmHg, and/or signs of respiratory acidosis in the astrup (PaO_2:FiO_2 and astrup data were only available if the patient was admitted to the pediatric intensive care unit).
(2) Significant bleeding: signs of internal hemorrhage like hemoptoe, hematemesis, melaena, or hematuria.
(3) Severe organ impairment: pulmonary edema, disseminated intravascular coagulation, encephalopathy, liver failure, and/or renal failure.

Patients who did not meet any of the criteria of a severe DENV infection according to the 2009 WHO case definition were classified as non-severe dengue. We did not distinguish between non-severe dengue with and without warning signs, because the clinical data related to warning signs were not complete; we feared that using a incomplete dataset would result in a biased picture of disease severity in the non-severe dengue patients.

In addition, we determined the phase of infection in which patients were admitted according to the 2009 WHO criteria The characteristics of the critical phase are defervescence (temperature below 38°C), progressive leucopenia, drop in platelet count, and plasma leakage. Patients were classified as being in the critical phase if their temperature was below 38°C or they had very severe thrombocytopenia (≤ 50,000/mm^3).[10] If these two conditions were not fulfilled, patients were still classified as being admitted in the critical phase if at least two of three of the following conditions were present: rise in hematocrit (≥ 20% increase compared with the baseline value of the patient), leukopenia (2–6 years = < 5,000/μL, > 6 years = < 4,500/μL), and/or thrombocytopenia (≤ 100,000 cells/mm^3).

To determine the utility and accuracy of the 1997 and 2009 classification systems in this setting, the treatment received during admission was assessed. A distinction was made between minor and intensive treatment intervention. The definition of intensive treatment intervention consisted of fluid replacement therapy distributed in a higher dose than the maintenance values as described in the 2009 WHO criteria (0–10 kg = > 4 mL/kg per hour, next 10 kg = > 40 + 2 × [weight patient - 10] mL per hour, > 20 kg = > 60 + 1 × [weight patient - 20] mL per hour; coagulation support [platelet infusion, fresh-frozen plasma, and/or fresh plasma]; and/or circulatory support [dopamine]).[6]

Whether patients received an intensive treatment intervention during admission was set as the condition (gold standard) to calculate sensitivity and specificity for both case classifications. The sensitivity was determined by dividing the number of patients with intensive treatment intervention and severe dengue or DHF/DSS by the total number of patients with an intensive treatment intervention. In addition, the specificity was calculated by dividing the true negatives (non-severe dengue or DF without treatment intervention) by the total number of patients without treatment intervention.

RESULTS

Patients (173) were selected from the cohort with a laboratory-confirmed diagnosis of DENV infection.

According to the 2009 classification, 69 patients (39.9%) suffered from non-severe and 104 patients (60.1%) suffered from severe DENV infection, whereas the 1997 WHO guidelines classified 24 patients (13.9%) as DF and 149 patients (86.1%) as DHF/DSS (Table 1). In the group diagnosed with severe DENV infection, 64 patients showed severe plasma leakage, 6 patients suffered from severe bleeding, 18 patients showed plasma leakage and bleeding, and 16 patients had signs of severe organ impairment. Table 1 describes the baseline characteristics of the patients at the day of admission in both classification systems. Many of the signs and symptoms listed are considered warning signs in the revised classification. Interestingly, the distribution of the signs and symptoms of the DF and non-severe group and the DSS and severe group are quite similar, whereas the DHF group seems to have a mixture of severe and non-severe patients.

Signs of shock, respiratory distress, internal hemorrhage, and organ impairment were used to classify patients as severe dengue according to the 2009 WHO case definition. Table 2 shows how often these severe symptoms appear in the three different patient groups of the 1997 WHO guidelines. Eight patients in the DF group present themselves with signs of shock. These patients failed to meet all four criteria of the 1997 WHO guidelines, like thrombocytopenia or hemorrhagic tendency, and were therefore not classified as DHF/DSS.

The majority of the patients in this cohort were admitted during the critical phase of their DENV infection (Tables 3 and 4). Patients with non-severe dengue or DF were more likely to get admitted during the febrile phase. Patients admitted in the critical phase had a lower temperature and platelet count and an increased hematocrit and leukocyte count compared with patients admitted in the febrile phase. Because the number of people admitted in the febrile phase of their disease was low ($N = 22$), we could not investigate the predictive value of warning signs with which patients may present in the febrile phase.

As a measure of disease severity, we also scored whether intensive treatment intervention was initiated during admission (Table 5). Of the patients in the non-severe dengue group according to the 2009 guidelines, 38 patients (55.1%) had received intensive treatment intervention compared with 13 patients (54.2%) classified as DF. Of the severe dengue group, 91 patients (87.5%) had received intensive treatment intervention, a slightly higher number than the 116 patients (77.9%) in the DHF/DSS group. It should be noted that, in the revised classification of 2009, all patients with plasma leakage combined with bleeding or organ impairment received an intensive treatment intervention. These results indicate that the 2009 classification system is more specific than the 1997

TABLE 1

Characteristics of the patients classified according to the 1997 and 2009 WHO dengue case definitions on the day of admission

	1997 WHO classification			2009 WHO classification	
	DF (*N* = 24)	DHF (*N* = 83)	DSS (*N* = 66)	Non-severe (*N* = 69)	Severe (*N* = 104)
General manifestations					
Day of fever*	3 (2.3–4.0)	4 (3.0–4.0)	4 (3.0–5.0)	3 (3.0–4.0)	4 (3.0–5.0)
Male:female ratio	10 (41.7% male)	39 (47.0% male)	34 (51.5% male)	29 (42.0% male)	54 (51.9% male)
Age (years)*	7 (4.0–10.5)	7 (5.0–10.0)	6 (5.0–7.8)	7 (6.0–10.5)	6 (4.0–8.0)
Temperature (°C)*	37.8 (37.3 –38.2)	37.7 (37.3–38.3)	37.8 (37.1–38.3)	37.9 (37.3–38.4)	37.5 (37.2–38.0)
Skin manifestations					
Ecchymosis	0	3 (3.6%)	6 (9.1%)	1 (1.4%)	8 (7.7%)
Exanthem	1 (4.2%)	0	3 (4.5%)	0	4 (3.8%)
Purpura	1 (4.2%)	0	4 (6.1%)	1 (1.4%)	4 (3.8%)
Petechiae	7 (29.2%)	40 (48.2%)	39 (59.1%)	33 (47.8%)	53 (51.0%)
Hemorrhagic manifestations					
Positive tourniquet test	14 (583%)	74 (89.2%)	30 (45.5%)	66 (95.7%)	52 (50.0%)
Gum bleeding†	0	1 (1.2%)	3 (4.5%)	0	4 (3.8%)
Epistaxis†	2 (8.3%)	13 (15.7%)	9 (13.6%)	12 (17.4%)	12 (11.5%)
Bleeding from venipuncture sites	1 (4.2%)	8 (9.6%)	18 (27.3%)	2 (2.9%)	25 (24.0%)
Hematemesis	0	6 (7.2%)	14 (21.2%)	0	20 (19.2%)
Melaena	0	5 (6.0%)	11 (16.7%)	0	16 (15.4%)
Hemoptoe	0	0	2 (3.0%)	0	2 (1.9%)
Hematuria	0	1 (1.2%)	1 (1.5%)	0	2 (1.9%)
Gastrointestinal manifestations					
Abdominal pain†	18 (75.0%)	65 (78.3%)	62 (93.9%)	48 (69.6%)	97 (93.3%)
Nausea	18 (75.0%)	63 (75.9%)	55 (83.3%)	51 (73.9%)	85 (81.7%)
Diarrhea	0	2 (2.4%)	2 (3.0%)	1 (1.4%)	3 (2.9%)
Vomiting†	14 (58.3%)	46 (55.4%)	40 (60.6%)	38 (55.1%)	62 (59.6%)
Hepatomegaly†	15 (62.5%)	53 (63.9%)	62 (93.9%)	39 (56.5%)	91 (87.5%)
Neurological manifestations					
Delirium†	0	2 (2.4%)	4 (6.1%)	0	6 (5.8%)
Irritability†	1 (4.2%)	1 (1.2%)	5 (7.6%)	0	7 (6.7%)
Decreased level of consciousness†	0	2 (2.4%)	7 (10.6%)	0	9 (8.7%)
Signs of plasma leakage					
Pleural effusion†	8 (33.3%)	35 (42.2%)	54 (81.8%)	16 (23.2%)	81 (77.9%)
Ascites†	0	3 (3.6%)	6 (9.1%)	0	9 (8.7%)
Pulse rate	112 (101–129)	116 (100–120)	120 (117–137)	110 (100–120)	120 (115–132)
Systolic blood pressure (mmHg)*	98 (80–100)	100 (90–105)	80 (70–89)	100 (98–100)	80 (70–90)
Respiratory manifestations					
Dyspnoe	1 (4.2%)	3 (3.6%)	12 (18.2%)	1 (1.4%)	15 (14.4%)
Respiratory rate*	28 (24–28)	28 (24–28)	30 (28–34)	28 (24–28)	30 (28–32)
Laboratory values					
Hematocrit (%)*†	37.5 (33.2–40.1)	41.2 (37.1–44.7)	42.7 (39.7–47.4)	40.1 (35.1–43.0)	42.6 (37.4–46.7)
Platelet count (/mm^3)*†	115,500 (55,500–142,750)	67,000 (42,000–90,000)	42,500 (29,000–65,750)	85,000 (57,500–120,000)	49,000 (31,000–69,000)
Leukocyte count (×10^9/L)*	4.3 (3.0–5.8)	4.6 (3.2–6.6)	5.2 (3.9–7.1)	4.2 (3.2–5.9)	5.2 (3.8–7.9)

DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome.
* Values in median and interquartile range.
† Listed as a warning sign in the 2009 classification.

TABLE 2
The occurrence of signs and symptoms of severe dengue in the 1997 WHO dengue case definition

	DF (N = 24)	DHF (N = 83)	DSS (N = 66)
Signs of shock (total)	8	22	58
Hypotension for age	7	0	48
Narrow pulse pressure	3	0	10
Compensated shock	1	22	0
Respiratory distress (total)	0	3	22
Dyspnoe	1	3	19
Tachypnoe	0	2	14
PaO_2:FiO_2 < 200 mmHg	1	2	9
Hemorrhage (total)	0	10	28
Melaena	0	7	22
Hematemesis	0	6	21
Hematuria	0	1	4
Hemoptoe	0	0	6
Organ impairment (total)	1	3	12
Disseminated intravascular coagulation	1	1	9
Liver failure	0	0	0
Renal failure	0	0	0
Encephalopathy	0	2	4

DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome.

classification system, with specificities of 70.5% and 25.0%, respectively. Not unexpectedly, the 2009 guidelines proved to be less sensitive than the 1997 guidelines, with sensitivities of 70.5% and 89.9%, respectively.

DISCUSSION

In the present study, we compared the utility and accuracy of the 1997 and 2009 WHO clinical case classifications for dengue in a cohort of Indonesian children. Taking intensive treatment intervention as an indicator of severe disease, we conclude that the latter classification is more specific, albeit at the cost of a lower sensitivity.

A major concern about the 1997 WHO case definition was that the criteria were too stringent, and therefore, patients with severe disease manifestations were misclassified as DF cases.[4,5,10,11] This problem also becomes evident in our study in which eight patients diagnosed as DF according to the 1997 classification do present themselves with signs of shock. With the revised classification, these patients are apparently accurately diagnosed as having severe dengue. However, a concern about the 2009 classification is that loosening the case definition may result in more hospital admissions, because more patients will be classified as severe dengue cases. Nevertheless, because misclassification of patients with a life-threatening condition is less acceptable, revision of the 1997 WHO case definition was indeed warranted.

Another problem of the 1997 WHO case classification is that the platelet count and hematocrit levels play a pivotal role in establishing the diagnosis. In this study, all patients included were monitored carefully, and therefore, no data were lacking. However, in daily clinical practice, it may be too complicated and expensive to monitor every patient this closely. Therefore, an advantage of the 2009 classification over the 1997 classification is that extensive laboratory evaluation is not needed to reach a conclusion about the condition of the patient.

Recently, a large prospective and retrospective multicenter study to investigate the usefulness and applicability of the 2009 case classification in clinical practice and surveillance was carried out under the auspices of the WHO.[12] Comparison of the outcomes of the 1997 and 2009 classifications results in data that are similar to our study. However, in our cohort, more DF cases were eventually classified as suffering from severe dengue. Moreover, the WHO study reports that it is difficult to obtain information about the occurrence of warning signs from a retrospective analysis. We encountered a similar problem in our study in which data had been collected when the 1997 classification was still commonly used.

Srikiathachorn and others[3] also tested the 1997 WHO classification with treatment intervention as an indicator of severe disease. They found a sensitivity of 62% and a specificity of 92% of the WHO case definition for DHF.[3] In our cohort, we found a higher sensitivity and a much lower specificity using the 1997 classification. The most important difference between our study and the study by Srikiathachorn and others[3] is that they had included a large group of patients with other febrile illnesses in their analysis. This addition increased the specificity in their study, because the signs and symptoms used in the 1997 WHO dengue case classification are quite specific for dengue compared with other febrile diseases. In contrast, our study is more focused on the distinction between severe and non-severe disease in a population that has already been diagnosed with DENV infection.

An important advantage of the 2009 classification is that DENV infection is clearly described as a triphasic disease. This indicator is an important clinical indicator and may also be an important fact for pathogenesis studies, because it will most probably make the comparison of patient groups more accurate. Until this time, patients were usually classified on the day of admission or day of fever, which according to the revised

TABLE 4
Characteristics of patients admitted in the febrile and critical phase

Phase at admission	Febrile (N = 21)	Critical (N = 152)
Temperature (°C)*	38.5 (38.3–38.8)	37.5 (37.2–38.0)
Hematocrit (%)*	37–3 (34.1–42.0)	42.1 (37.5–46.0)
Platelet count (/mm^3)*	120,000 (95,000–137,500)	56,500 (34,000–78,000)
Leukocyte count (×10^9/L)*	4.5 (3.5–5.1)	4.8 (3.4–7.0)

*Values in median and interquartile range.

TABLE 3
Phase in which patients classified according to the 1997 and 2009 WHO case definitions were admitted

	1997 WHO classification			2009 WHO classification			
Disease severity	DF (N = 24)	DHF (N = 83)	DSS (N = 66)	Non-severe (N = 69)	Plasma leakage or bleeding (N = 70)	Plasma leakage and bleeding (N = 18)	Organ impairment (N = 16)
Phase at admission							
Febrile (N = 21)	7	12	2	17	1	0	3
Critical (N = 152)	17	71	64	52	69	18	13

DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome.

TABLE 5
Intensive treatment intervention received by patients classified according to the 2009 and 1997 WHO case definitions

	Treatment intervention			
	FRT > baseline level	Coagulation support	Circulation support	Intensive treatment intervention
1997 WHO classification				
DF (N = 24)	11	5	1	13
DHF (N = 83)	51	19	3	56
DSS (N = 66)	53	35	17	60
2009 WHO classification				
Non-severe (N = 69)	38	6	0	38
Plasma leakage (N = 64)	43	25	4	53
Bleeding (N = 6)	4	2	0	4
Plasma leakage + bleeding (N = 18)	15	12	6	18
Organ impairment (N = 16)	15	14	11	16

DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; FRT = fluid replacement therapy.

classification, does not necessarily mean that patients are in the same phase of disease. Moreover, for clinicians, it is also important to realize that patients admitted in the febrile phase are at risk to develop severe disease and should be monitored carefully.

A major drawback of the 2009 classification compared with the 1997 classification is that the criteria are less strictly defined, leaving room for arbitrary interpretation by the clinician or researcher. For example, in the 2009 case definition, the occurrence of severe bleeding has to be evaluated by the physician. Physicians may have different opinions about what kind of bleeding is severe, and therefore, this criterion may complicate the comparison of research results from different study settings. Moreover, because it is hard to obtain information about the occurrence of warning signs retrospectively, the comparison between research before and after the revised classification will be a challenge.

Taken together, we conclude that, both in clinical and research settings, the performance of the 2009 WHO case classification proves to be an improvement over the performance of the 1997 WHO case classification, although more validated and detailed classification criteria need to be defined.

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