WHO Dengue Case Classification 2009 and its usefulness in practice: an expert consensus in the Americas

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Introduction: In 2009, the new World Health Organization (WHO) dengue case classification – dengue/severe dengue (D/SD) – was introduced, replacing the 1997 WHO dengue case classification: dengue fever/dengue haemorrhagic fever/dengue shock syndrome (DF/DHF/DSS).
Methods: A 2-day expert consensus meeting in La Habana/Cuba aimed to (1) share the experiences from Pan American Health Organization (PAHO) member states when applying D/SD, (2) present national and local data using D/SD, and (3) agree with the presented evidence on a list of recommendations for or against the use of D/SD for PAHO, and also globally.
Results: Eight key questions were discussed, concluding: (1) D/SD is useful describing disease progression because it considers the dynamic nature of the disease, (2) D/SD helps defining dengue cases correctly for clinical studies, because it defines more precisely disease severity and allows evaluating dynamically the progression of cases, (3) D/SD describes correctly all clinical forms of severe dengue. Further standards need to be developed regionally, especially related to severe organ involvement, (4) D/SD allows for pathophysiological research identifying – in a sequential manner – the clinical manifestations of dengue related to pathophysiological events, (5) the warning signs help identifying early cases at risk of shock (children and adults), pathophysiology of the warning signs deserves further studies, (6) D/SD helps treating individual dengue cases and also the reorganization of health-care services for outbreak management, (7) D/SD helps diagnosing dengue, in presumptive diagnosis and follow-up of the disease, because of its high sensitivity and high negative predictive value (NPV), and (8) there is currently no update of the International Disease Classification10 (ICD10) to include the new classification of dengue (D/SD); therefore, there are not enough experiences of epidemiological reporting. Once D/SD has been implemented in epidemiological surveillance, D/SD allows to (1) identify severity of dengue cases in real time, for any decision-making on actions, (2) measure and compare morbidity and mortality in countries, and also globally, and (3) trigger contingency plans early, not only based on the number of reported cases but also on the reported severity of cases.
Conclusion: The expert panel recommends to (1) update ICD10, (2) include D/SD in country epidemiological reports, and (3) implement studies improving sensitivity/specificity of the dengue case definition.

Keywords: Dengue case classification, WHO 2009 dengue case classification, WHO 1997 dengue case classification, Expert consensus

Introduction

The World Health Organization (WHO) with its Special Programme for Research and Training in Tropical Diseases (WHO/TDR) issued new dengue guidelines in 2009,[1] including the 2009 WHO dengue case classification: dengue/severe dengue (D/SD) – replacing the 1997 WHO dengue case classification:[2] dengue fever/dengue haemorrhagic fever/dengue shock syndrome (DF/DHF/DSS).

The advantages of D/SD have been shown in many studies, summarized in a systematic review including prospective clinical studies comparing the two different classifications.[3]

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In Latin America and the Caribbean (LAC), the Pan American Health Organization (PAHO) has introduced D/SD in many countries, for surveillance purposes, but especially for clinical use.[4]

This process has been implemented with regional capacity training in workshops that were attended by health professionals coming from all LAC countries, including the distribution of the new dengue guidelines and the adaptation of the guidelines for PAHO. A further updated edition is under elaboration.

To further the knowledge of the usefulness of D/SD, compared to DF/DHF/DSS, a formal expert consensus meeting, with a defined methodology, has been convened by PAHO in La Havana during the 13th International Dengue Course in August 2013 at the Instituto Pedro Kouri (IPK). The aims of the expert consensus meeting were to (1) share the experiences from the PAHO member states when applying D/SD, (2) present national and local data using D/SD, and (3) agree with the presented evidence on a list of recommendations for or against the use of D/SD for PAHO, and also globally.

Methods

The expert consensus panel followed broadly the nominal group technique,[5] already adapted and used in similar exercises by WHO;[6] however, the group composition was larger because of the representativeness of PAHO member states with 14 members, one chair, two facilitators, and several observers from PAHO and Cuba.

The PAHO member states represented were Bolivia, Brazil, Colombia, Cuba, Ecuador, El Salvador, Mexico, Nicaragua, Paraguay, and Peru – countries affected by dengue in the tropics and subtropics. The experts were invited by PAHO using a purposive sampling method, since experts needed to be familiar with both dengue classifications and needed experience in applying both dengue classifications to identify and diagnose clinical dengue cases, not only in routine dengue control but also in outbreak situations. Furthermore, the expert panel represented, according to the study question, expertise in clinical dengue, hospital management, dengue surveillance/outbreak management, both basic and operational/implementation research, and public health. Prior to the involvement in the entire process, all experts declared their conflicts of interests in writing and no conflict of interest was stated, following the rules of PAHO.

For the expert consensus, the following steps have been undertaken:

Step 1: Prioritization exercise with a final list of eight key questions for discussion (e-mail consultation).

Step 2: Systematic review of globally published studies comparing the two dengue case classifications (the systematic review has been published separately,[3] and the results are only referred to in the following reporting).

Step 3: The 14 participants of the expert consensus meeting were asked to prepare their local experiences – both with formal local studies and/or if not available their expert opinion – with the two case classifications. No specifications were made for the study type in order not to limit the potential contributions; however, the definitions for the clinical observations were standardized by using the case definitions of the two case classifications.

Step 4: One expert consensus meeting (two days duration – 15/16.08.2013, with representation of PAHO), considering steps 2 and 3, to discuss all aspects of using the two dengue case classifications.

Step 5: Consensus on the key questions, prior to anonymous ranking, voting, and iteration.

Furthermore, a detailed agreement on the wording of the recommendations was also reached during the panel meeting by consensus, considering health services, data collection, and analysis for epidemiology and implications for research – basic, clinical, and operational/implementation research. A second round of voting was planned in case of disagreement; however, no voting was needed since the consensus was reached on all questions unanimously.

Results

The following key questions were identified in the process described in the methodology (step 1). Question 1a was added by the expert panel. During the expert panel, 11 globally available studies were presented (step 2) and 17 presentations from 10 countries were made (step 3), before discussing, final vote and agreement (steps 4–5).

1. Dengue/severe dengue helps to identify clinical cases of dengue?

1a. Dengue/severe dengue helps to identify clinical cases according to the distinctive phase of disease progression (febrile, critical, recuperation)?

Local studies presented by the experts on the panel (Brazil, El Salvador, Nicaragua, Peru) showed the following:

Nicaragua (Instituto de Ciencias Sostenibles, Managua): using data from an ongoing prospectively collected pediatric cohort study, the two case classifications were compared to detect disease severity ($n = 544$): D/SD shows a high sensitivity (92.1%) for the detection of severe cases with a specificity of 78.5%. The sensitivity DF/DHF/DSS for the detection of severe cases is low (39.0%), and the specificity is 75.5%. Dengue/severe dengue is easier to use and interpret for the practicing physician, showing a higher agreement between clinicians to classify dengue (Kappa 0.62, CI 95%: 0.53–0.71, $P = 0.001$) in

comparison with DF/DHF/DSS (Kappa 0.46, CI 95%: 0.38–0.55, $P = 0.001$).

In Brazil (Instituto de Pesquisa Clinica Evandro Chagas, FIOCRUZ, Rio de Janeiro), an analysis of data from a dataset of hospital-based dengue cases ($n = 183$) showed a sensitivity of 86.8% for the detection of severe cases for D/SD, compared to 62.3% using DF/DHF/DSS ($P < 0.001$, CI 95%: 0.12–0.31). The specificity is 79% for D/SD (DF/DHF/DSS: 94%). The negative predictive value (NPV) for D/SD is 91.7% [positive predictive value (PPV) 61.6%] and for DF/DHF/DSS is 83.2% (PPV 82.6%) (This study has been accepted separately for publication for PLOS ONE).

In El Salvador (Hospital Nacional de Niños Benjamin Bloom, San Salvador), also using data from hospital-based dengue cases (retrospective case review, $n = 361$), sensitivity is 100% and specificity is 89.89% for D/SD. The NPV was 100% (PPV 43.42%).

In Peru (Hospital Regional de Loreto, Iquitos), using data from an outbreak in 2010/11 (retrospective case review, $n = 92$), DF/DHF/DSS and D/SD have a sensitivity of 56 and 100%, a specificity of 76 and 48%, an NPV of 65 and 100%, and a PPV of 79 and 69%.

The globally reported studies[7–11] showed very similar results.[3] Considering all available information, the expert panel agreed that D/SD defines very well a group of symptoms, signs, and laboratory findings that detect (with good sensitivity) the majority of cases with dengue, supported by epidemiological criteria. Confirmation of cases is supported by laboratory diagnostics.

2. Dengue/severe dengue helps to define cases of dengue correctly for clinical research?

No formal studies were presented by the group of experts. Globally available studies[12,13] show that DF/DHF/DSS has well-documented and serious shortcomings to describe dengue cases, thus limiting its usefulness for clinical research. Considering their expert opinion in this field, especially clinical research, the expert panel agreed that D/SD helps clinical research, especially since the clinical picture of severe dengue is much better described (key questions 1 and 1a).

3. Dengue/severe dengue helps to identify the clinical presentations of severe dengue?

Local studies were available from Bolivia and Paraguay.

In Asuncion, Paraguay, during a dengue outbreak in 2011, 123 children (11 years on average ±3 years) with confirmed dengue were admitted to the Instituto de Medicina Tropical. Using D/SD, 119 cases (97%) were those that needed treatment with intravenous fluids. Eighty-nine cases (75%) had warning signs and 30 (25%) had severe dengue. Using DF/DHF/DSS, only 67 cases (54%) would have received fluid therapy ($P = 0.01$); 13 of those would have been classified as DHF grade III/IV. Severe cases not detected with DF/DHF/DSS included 11 cases (9%) with hemoconcentration and four cases (3%) with major organ involvement (encephalitis/hepatitis). The study concluded that D/SD detects earlier and describes better cases of severe dengue, with improved outcomes.

In Santa Cruz, Bolivia – in a before and after study at the Hospital San Juan de Dios (comparing two epidemics in 2009 and 2011) – prior to the outbreak of 2011 (1) D/SD was introduced, (2) clinical training related to D/SD was held, and subsequently, (3) D/SD was applied as a case classification with related treatment algorithms in the epidemic of 2011: there was a marked reduction in case fatality rates, from 0.21 deaths/1000 cases in 2009 to 0.11 deaths/1000 cases in 2011. It has been discussed if this reduction of case fatality rates is directly related to the improved identification of severe cases and/or introduction of case management algorithms.

Globally published studies[13–15] underline that DF/DHF/DSS fails to classify dengue cases correctly, with misclassifications when comparing to disease severity. The expert panel agreed that D/SD describes the clinical presentations of dengue and severe dengue much better than DF/DHF/DSS. The improved identification of severe dengue cases should help to reduce dengue mortality.

4. Dengue/severe dengue helps to identify cases of dengue correctly for pathophysiological research?

The local studies showed the following:

In Rio De Janeiro, Brazil (prospectively collected dataset of clinical pediatric cases of dengue, admitted to Intensive Care Unit (ICU) of Hospital Municipal Jesus, during the 2008 and 2011 epidemics), 654 children were hospitalized to the Intermediate Unit, of which 60 were admitted to the ICU. Applying D/SD for these severe cases showed a good pathophysiological correlation between the classification of D/SD, the cases presenting with severe plasma leakage (100%) and 69% with organ dysfunction.

In two studies performed at the University Hospital of Neiva, Colombia (one prospective study of dengue cases 2009–2010, $n = 930$, 105 cases of severe dengue; another prospective study of dengue cases 2011–2012, $n = 179$, 59 severe cases), organ failure was very prominent (20% of severe cases in the first study, 30% in the second study). It has been discussed that this study highlights that organ failure (mainly hepatitis and myocarditis, and also encephalitis) is not necessarily associated to important plasma leakage and can be the primary cause of dengue severity.

No formal study has been published globally on this key question; however, the expert panel

concluded, based on studies from Brazil and Colombia that D/SD classifies better dengue cases, especially considering the documented large proportion of dengue cases with organ involvement, with manifestations that are associated – or are not associated – to important plasma leakage. Dengue/severe dengue offers new opportunities to better correlate pathophysiological factors that determine these clinical pictures.

5. Dengue/severe dengue including the warning signs helps to identify cases of dengue with a risk of progression to shock?

The local studies showed that in Cuba, of 81 adult hospitalized cases at the IPK in an outbreak in 2012, 44 cases showed at least one warning sign, linking the warning signs strongly to the identification of progression to severe disease. Severe or maintained abdominal pain has been observed in 20 cases (22.9%), fainting in 19 cases (23.4%), bleeding of the mucosa in 19 cases (23.4%) and general deterioration in 12 cases (14.8%). All cases identified with warning signs received crystalloid fluids intravenously, 8 proceeded to dengue shock, but no deaths were reported. Of the cases with dengue shock, 75% presented during the critical period of the illness (72 hours of illness), i.e. the same day when the fever was falling, or 24 hours before or after defervescence. A large proportion of the documented warning signs occurred in the same time period (fainting: 84.2%, severe abdominal pain: 75%, rapid deterioration 66.6%, severe effusions: 66.6%, and repeated vomiting: 57%), which also supports the explanation that the warning signs are expression of plasma leakage, which is the pathophysiological phase preceding shock (key question 4). It was observed that intravenous rehydration at this early stage avoids severe hypovolemia. One of the advantages of D/SD is that it does not depend exclusively on laboratory for fundamental decisions, so it is applicable at all levels of care.

In another longitudinal study in Cuba (2008–2012), those children admitted to the Hospital Angel A. Aballí presenting with warning signs had abdominal pain in 62.5% of the cases, 37.5% had repetitive vomiting, 34.4% showed some kind of disturbance of consciousness (lethargy or irritability), 19.1% had bleeding from mucous membranes, and 16% had drowsiness. A total of 60.5% of cases with warning signs presented with those at the day of defervescence or up to 24 hours after and 39.0% did so at the end of the febrile period, or in the 24 hours before this period. For the cases with warning signs, there was also some evidence of plasma leakage, such as pleural effusion, ascites, hepatomegaly, increased thickness of the gallbladder wall, presence of perivesicular fluid, or peri- or para-renal fluids. The presence of warning signs was successfully used to treat affected children early.

In the above mentioned study in Rio de Janeiro, Brazil (key question 4) of the 60 cases referred to the ICU, 96% presented with at least one warning sign, intense and persistent abdominal pain, continuous vomiting, bleeding of mucous membranes, and irritability were the most frequent warning signs, drowsiness being less common. All cases presented as well with fluid accumulation, documented by ultrasound or radiology. The fall of platelets was not associated with severity. The warning signs preceded other signs and symptoms of early shock and severe plasma leakage, such as oliguria, postural hypotension, and difficulty breathing. Therefore, the warning signs were considered as particularly helpful to identify cases of dengue progression to severe disease.

Globally published studies investigating warning signs conclude with different aspects:

(1) For the prospective studies, the DENCO study provided limited evidence on three warning signs (severe abdominal pain, lethargy, and mucosal bleeding), all predicting severity within 24 hours in advance;[16] also, the combination of five warning signs is a very good predictor of severe disease;[17]

2) Retrospective studies on this issue have limited value;[18] however, studies examining the warning signs included the following results: no warning sign alone or combined had a sensitivity of more than 64% in predicting severe disease in one study;[19] however, when warning signs were used for criteria for admission, these were good indicators for severity;[20] ascites, mucosal bleeding, hematemesis, and thrombocytopaenia were identified as good indicators for warning signs;[21] and abdominal pain and hematemesis were identified for the same purpose in another study.[22]

The expert panel agreed that D/SD can be used very effectively to identify both pediatric and adult cases of dengue with a risk of progression to shock, specially based on the use of warning signs. However, further quantitative studies are needed to improve knowledge on single but also combinations of warning signs. These studies need to be prospective.

6. Dengue/severe dengue helps the treatment of cases of dengue?

An outbreak report from the NorthEast of Brazil presented retrospectively analyzed data of dengue cases. It became clear that the improved classification of cases could help the management and treatment of cases in outbreak situations – this study was subsequently published in 2014.[23] Globally published studies[9,13] regarding the ease of application and the acceptance of D/SD show very good results. The expert panel agreed that D/SD clearly helps the treatment of cases of dengue, perhaps even to reduce

case fatality rates and/or to reduce the onset of severity.

7. Dengue/severe dengue helps diagnosing dengue?

Local studies are available from Ecuador and Mexico:

In Guayaquil, Ecuador at the Hospital Luis Vernaza, a qualitative study with questionnaires and focus groups has shown that nurses and doctors preferred to use D/SD. Dengue/severe dengue is much easier to apply, practical and didactic, adjusting to the changes in the epidemiological characteristic of the disease – including older populations, including dengue in pregnancy and with comorbidities. Clinical decision-making is improved and reflects disease severity, is less dependent on laboratory, requiring fewer resources, and helps to improve dengue surveillance with improved notifications. But there is a need for dissemination and clinical training. Also, it was perceived that there should be further evaluations of the application of D/SD.

This was also shown in Mexico, in a case study of introducing D/SD until 2013, where the use of D/SD was also seen as superior to DF/DHF/DSS, but clinical training is needed, in both routine and outbreak operations; furthermore, the clinical training needs to be sustained.

Only one globally published study looked at case classifications and the ability to diagnose dengue with the given case definitions for dengue.[24] This study acknowledges that D/SD was not primarily designed for detecting dengue: DF compared to SD has a sensitivity of 95.4% compared to 79.9%, specificities are 36 and 57%, respectively.

The expert panel concluded that D/SD helps diagnosing dengue, especially with its ease of application; however, further studies are warranted and continuous medical training is necessary.

8. Dengue/severe dengue is helpful to improve dengue surveillance?

No local or globally published study compared D/SD and its usefulness in dengue surveillance. The expert panel considered that especially the improved discrimination between dengue and severe dengue, when applied in clinical practice, should allow for improved data collection and also international comparability. Also several studies presented in key questions 1–7 concluded similarly; however, no study presented during the expert consensus examined specifically this question. The expert panel recommended the use of D/SD for surveillance, with the above mentioned reasons, however, also suggested to initiate research on this issue.

Discussion

The expert panel agreed that D/SD describes severe dengue correctly, sensitivity and NPV increase and specificity decreases. Dengue/severe dengue describes better the different phases of dengue, this facilitates the therapeutic intervention and the prediction/early detection of severe dengue. These characteristics of D/SD help particularly during outbreaks and contribute to a reduction of mortality. Although in LAC overall case fatality rates of dengue are perceived to be low.

However, there is a need for improving definitions, such as the criteria for severe organ damage (severe hepatitis has been discussed and early signs of plasma leakage), since the classification does not fully define the clinical pictures.

For the case definition of dengue, it has been concluded that further quantitative studies are needed to define better the cardinal signs of dengue (D), such as fever, headache, retro-ocular pain, exanthema, arthralgia, and myalgia.

The warning signs have been discussed, especially that further quantitative studies should be conducted, to better describe the value of each – but also combinations – of warning signs. The expert panel agreed that plasma leakage documented by ultrasound or radiology could be useful as a further warning sign, as shown in different outbreak reports. Nevertheless, applying clinical warning signs has helped to prevent deaths in the Americas, especially since warning signs are a clear announcement of imminent shock.

Mucosal bleeding has been discussed further, needing more definitions, especially if nose and mouth bleeds should be considered the same as stomach or bowel bleeds. More details are needed to the frequency of vomiting, more definitions about the characteristics of severe abdominal pain. Thickening of the gallbladder wall could be added to the list of warning signs, although it involves further technology for its detection and cannot be applied in all health centers. Fluid balance has also been discussed as a further element to detect plasma leakage.

The expert panel discussed and agreed that certainly there is good acceptability of the warning signs by health professionals who work with dengue and that they are applicable at all levels of care; however, continuous training is required for the use of warning signs.

The expert panel was clearly in favor of D/SD for all fields of research, since experts highlighted the fact that D/SD describes all the clinical pictures of dengue as they occur and that helps for pathophysiological studies, to determine the different processes leading to different clinical pictures. More research is needed to describe the different processes (apoptosis, autoimmunity, T-lymphocyte functions) operating in the endothelium, platelets, liver, myocardium, brain, and others.[25,26]

The expert panel discussed and agreed that D/SD is well accepted by clinicians, but implementation needs training in each country, including all levels of health professionals involved in dengue control. In addition – and especially in outbreaks – a reorganization of health services is needed to attend a surge in dengue cases. Good links to epidemiological surveillance and laboratory are required.

Discussion of Limitations

An expert consensus group has its limitations with potential biases, especially related to the group composition. This bias has been reduced by including specialists from many different countries and subfields, the group composition was gender balanced (6 of 14 members being female). Participants were asked to document their conflict of interest; no interests were declared. Participants were not paid for their advice, and peer influencing of opinions was limited by anonymous voting.

The results are partly derived from studies from the Americas. However, since for each of the key questions a presentation was made of the published studies on the particular key question, global aspects were included.

Also, the published studies allowed for another comparison, not only relying on the potentially biassed views of the single experts.

Further limitations are areas where the expert panel had to rely more on conclusions derived from the results, not related to the results themselves, as for example the questions around the usefulness of D/SD in research or epidemiological surveillance. However, the expert panel answered to this potential limitation with a more careful consideration of their recommendation and including a need for further studies.

Ideally, a comparison of the use of a clinical case definition and related case classifications should be measuring against a 'gold standard.' In the absence of such an agreed standard for dengue, this study compares the two classifications against each other.

Also, with the amount of data visited, the expert consensus panel had to be limited to the predefined key questions, and other important areas, like the etiology and pathophysiology of the different clinical pictures where not discussed in detail, or for example the relation between dengue severity and comorbidities. These questions need addressing in further studies.

Conclusion

Concluding, the expert panel stated the following in an agreed statement by all members, following the key questions:

1. For identifying clinical cases of dengue, the expert panel agreed that 'D/SD is useful, especially to describe each phase of disease progression, because it considers the dynamic nature of the disease.'
2. 'Dengue/severe dengue helps to define dengue cases correctly for clinical studies, because it defines more precisely the different levels of disease severity, and also as it allows to evaluate dynamically the progression of the cases.'
3. 'Dengue/severe dengue describes correctly all clinical forms of severe dengue. Further standards need to be developed regionally, especially related to severe organ involvement.'
4. For pathophysiological research, 'D/SD allows identifying – in a sequential manner – the clinical manifestations of dengue related to pathophysiological events, as cases experience these during the course of illness.'
5. 'Dengue/severe dengue helps with the warning signs to identify early cases at risk of shock. The pathophysiology of the warning signs deserves further studies.'
6. 'Dengue/severe dengue helps treating individual dengue cases and also for the reorganization of healthcare services for outbreak management.'
7. Dengue/severe dengue helps diagnosing dengue, because 'D/SD helps initially in the presumptive diagnosis and follow-up of the disease in its various stages and clinical presentations, because of its high sensitivity and high NPV.'
8. As for dengue surveillance, 'there is currently no update of the International Disease Classification 10 (ICD 10) to include the new classification of dengue (D/SD); therefore, there are not enough experiences of epidemiological reports. Once D/SD has been implemented in epidemiological surveillance, D/SD allows to (1) identify the severity of dengue cases in real time, for any decision-making on actions, (2) measure and compare morbidity and mortality in countries, and also globally, and (3) trigger contingency plans early, not only based on the number of reported cases but also on the reported severity of cases.'

The expert panel recommends therefore to (1) update the ICD 10, (2) include the use of D/SD in country epidemiological reports, and (3) implement studies to improve sensitivity and specificity of the dengue case definition.

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Disclaimer Statements

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