REPORTING PROGRESS ON THE USE OF THE WHO 2009 DENGUE CASE CLASSIFICATION: A REVIEW

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Abstract. This review reports on the progress in the use of the WHO 2009 dengue case classification—dengue and severe dengue—following up on a previous review (Horstick *et al*, 2012). The previous review detailed Steps 1 - 5 in developing the 2009 WHO case classification. As a further step, a systematic review of published studies comparing the two classifications has been published with 12 studies and a further 10 expert opinion papers that recommend the use of the 2009 WHO dengue case classification for clinical management, epidemiology, and clinical research. Furthermore, a formal expert consensus was reached in La Habana, Cuba in 2013 with dengue experts from the Americas, sharing experiences that applied the 2009 WHO dengue case classification. The expert panel recommended to 1) update ICD10, 2) include the 2009 WHO case classification in country epidemiological reports globally, and 3) implement studies improving sensitivity/specificity of the dengue case definition.

Keywords: 2009 WHO dengue case classification, dengue and severe dengue, evidence

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 (WHO/TDR, 2009), including the 2009 WHO dengue case classification: dengue and severe dengue (D/SD). Warning signs (WS) have been established for triage, to help clinicians with symptomatic cases in need of closer surveillance and/or hospitalization [dengue with warning signs (D+WS)].

Historically, the DF/DHF/DSS case classification of dengue (dengue hemorrhagic fever and dengue shock syndrome) was developed in 1975 by expert consensus, based on studies on Thai children in the 1950´s and 1960´s, with modifications in 1986 and 1997 (Bandyopadhyay *et al*, 2006). In the last modification of 1997 four grades of DHF were defined (DHF 1, 2, 3, 4) with 1, 2 being DHF and 3, 4 being DSS (WHO, 1997).

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This review was presented at the 2014 Conference on Adult Dengue. Bangkok: The Infectious Disease Association of Thailand (IDAT) in collaboration with the Pediatric Infectious Disease Society of Thailand (PIDST), 2014.

This article refers in the following to the dengue case classification recommended by WHO in 2009 (D/SD) as the "2009 WHO case classification" and to DF/DHF/DSS as the "1997 WHO case classification".

The reasons for developing the 2009 WHO case classification were the shortcomings of the 1997 WHO case classification that were established in many studies. Based on the largest prospective multicenter dengue study, the Dengue and Control (DENCO) study (Alexander *et al*, 2011), the 2009 WHO case classification describes dengue as it currently occurs globally; focusing on severe dengue, defined as plasma leakage (shock or fluid accumulation with respiratory distress, which includes the former dengue shock syndrome), severe bleeding, or severe organ manifestation.

With the improved description of dengue cases, case reporting is facilitated. Warning signs have been empirically validated to some extent in the DENCO study. This review has the objective to report on the further evidence that has been reported on the use of the 2009 WHO case classification globally, because after its publication in 2009, a discussion evolved internationally on the usefulness and applicability of the 2009 WHO case classification compared to the 1997 WHO case classification.

METHODS

This article reports the process of the development and on further published evidence for or against the use of the 2009 WHO case classification, after a previous review in 2012 (Horstick *et al*, 2012). Additionally implementation aspects derived from the individual were analyzed, with a view towards practical public health recommendations.

RESULTS

In the previous review (Horstick *et al*, 2012), the steps were published for the development of the 2009 WHO dengue case classification . These steps included:

Step 1: A systematic literature review that highlighted the shortcomings of the 1997 WHO case classification, which were (1) difficulties in applying the criteria for DHF/DSS, (2) the tourniquet test has a low sensitivity for distinguishing between DHF and DF, and (3) most DHF criteria had a large variability in the frequency of occurrence (Bandhyopadhyay *et al*, 2006).

Step 2: An analysis of regional and national dengue guidelines and their application in the clinical practice showed a need to re-evaluate and standardize guidelines because the actual ones showed a large variation of definitions, an inconsistent application by medical staff, and a lack of diagnostic facilities necessary for the DHF diagnosis in frontline services (Santamaria *et al*, 2009).

Step 3: A prospective cohort study in seven countries that confirmed the difficulties in applying the criteria of the 1997 WHO case classification, even in tertiary care hospitals; that this classification does not represent levels of disease severity; and that a clear distinction between severe dengue (defined by plasma leakage and/or severe hemorrhage, and/or organ failure), and (non-severe) dengue can be made using highly sensitive and specific criteria. In contrast, the sub-grouping of (non-severe) dengue into two further severity levels was

only possible with criteria that gave approximately 70% sensitivity and specificity (Alexander *et al*, 2011).

Step 4: Three regional expert consensus groups in the Americas and Asia concluded that "dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome" (Horstick *et al*, 2012), and that revising the results of Step 3, the 1997 WHO case classification is not related to disease severity (unpublished meeting proceedings in La Habana, Cuba and Kuala Lumpur, Malaysia 2007 and Heidelberg, Germany 2008).

Step 5: In a global expert consensus meeting at WHO in Geneva, the evidence collected in Steps 1-4 was reviewed, and a revised scheme was developed and accepted (unpublished meeting proceedings 2008); thereby distinguishing between: dengue with or without warning signs and severe dengue (D/D+WS/SD). Further field-testing and acquisition of further prospective evidence of the revised scheme was recommended.

Step 6: In 18 countries, the usefulness and applicability of the 2009 WHO case classification compared to the 1997 WHO case classification were tested showing clear results in favor of the former (Barniol *et al*, 2011).

In a further step (Step 7), a systematic review of the published studies comparing the two classifications has been published (Horstick *et al*, 2014a). These studies were performed after the publication of the 2009 WHO case classification, and most of the 12 studies included (prospective, post hoc analysis of existing datasets or reviewing existing medical charts, any qualitative design) were performed in Asia (Basuki *et al*, 2010; Chaterji *et al*, 2011; Kalayanarooj, 2011; Jayaratne *et al*, 2012; Van de Weg *et al*, 2012; Gan *et al*, 2013; Prasad *et al*, 2013; Thein *et al*, 2013; Tsai *et al*, 2013), with the exception of three studies: one which included 18 study sites worldwide (Barniol *et al*, 2011), one study from Nicaragua (Narvaez *et al*, 2011) and one study from Peru (Siles *et al*, 2013). Ten expert opinion articles were used for discussion (Srikiatkhachorn *et al*, 2011; Akbar *et al*, 2012; Hadinegoro, 2012; Halstead, 2012; Horstick *et al*, 2012; Farrar *et al*, 2013; Halstead, 2013; Horstick *et al*, 2013; Lin *et al*, 2013; Wiwantikit, 2013).

For the 2009 WHO case classification, studies show that : 1) determining severe dengue: sensitivity was measured between 59%-98% (88% and 98% for the two prospective studies), specificity 41%-99% (99% for the prospective study). When comparing the 1997 WHO classification, the sensitivity was lower with 24.8%-89.9% (24.8% and 74% for the prospective studies). Specificity for the 1997 WHO case classification was 25% and 100% (100% from the prospective study); 2) application of the 2009 WHO case classification is easy; 3) for (non-severe) dengue as defined in the 2009 WHO case classification, there may be a risk of monitoring increased case numbers of dengue cases; and 4) warning sign validation studies are needed to further validate the warning signs.

For epidemiological purposes and pathogenesis research, the following has been referenced (the information is derived only from the expert opinion papers): easy application, increased sensitivity (severe dengue), international comparability of the 2009 WHO case classification are advan-

tageous; the 3 SD criteria (severe plasma leakage, severe bleeding and severe organ manifestation) are useful research endpoints.

The 2009 WHO dengue case classification has been especially applied in the Americas and within the member states of the Pan American Health Organization (PAHO).

In a further study (Step 8), a formal expert consensus has been held as a side event of the biannual dengue course at the Instituto Pedro Kouri (IPK), La Habana, Cuba in 2013 (Horstick, *et al* 2014b). The two day expert consensus meeting aimed to 1) share experiences from PAHO member states applying the 2009 WHO case classification, 2) present national/local data using the 2009 WHO case classification, 3) agree - with a formal consensus group - on recommendations for/or against using the 2009 WHO case classification.

In this context, eight key questions were discussed, concluding that the 2009 WHO case classification: 1) is useful describing disease progression because it considers the dynamic nature of the disease; 2) helps defining dengue cases correctly for clinical studies because it defines more precisely disease severity and allows evaluating dynamically the progression of cases; and 3) describes correctly all clinical forms of severe dengue. Further standards need to be developed regionally, especially related to severe organ involvement. 4) the 2009 WHO case classification allows for pathophysiological research identifying—in a sequential manner—the clinical manifestations of dengue related to pathophysiological events; 5) the warning signs help identify early cases at risk of shock (children and adults; the pathophysiology of the warning signs deserves further study); 6) helps treating individual dengue cases and also the reorganization of health care services for outbreak management; 7) helps diagnosing dengue, in presumptive diagnosis and following-up of the disease, because of its high sensitivity and high negative predictive value; and, 8) there is currently no update of the International Disease Classification 10 (ICD10) to include the 2009 WHO dengue case classification; therefore, there are not enough experiences of epidemiological reporting.

Once it has been implemented in epidemiological surveillance, it allows 1) identifying the severity of dengue cases in real time, for any decision-making on action; 2) measuring and comparing morbidity and mortality in countries, but 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.

CONSLUSIONS AND RECOMMENDATIONS

Based on the extensive work on the dengue case classifications, a list of recommendations can be drawn. These need to be seen firstly in the light of the limitations of this review. Limitations include publication bias; however, the inclusion of the systematic literature review (Step 7) on this issue should limit this bias. Experiences in practice may not be recorded, but the authors consulted extensively experts in the field, and especially Step 8, with the inclusion of more than 30 dengue experts, is a good example for this process.

Looking at the eight steps of a process encompassing more than ten years, the following practical recommendations can be

made, further to the recommendations in the previous review (Horstick *et al*, 2012).

• The systematic literature review indicated that the 2009 WHO case classification has clear advantages for clinical use; use in epidemiology is promising and research use may at least not be disadvantageous.

• When the experts in La Habana revised the evidence and complemented this evidence with their own experiences, the expert panel recommended to 1) update ICD10, 2), include the 2009 WHO case classification in country epidemiological reports globally, and 3) to implement studies improving sensitivity/specificity of the dengue case definition.

• Adaptations to this process may arise as further knowledge develops; especially the questions of the evidence base of the case definitions and warning signs have to be considered. Large prospective cohort studies are currently under way to strengthen the knowledge on these issues, and should be available in the near future (Jaenisch *et al,* 2013).

• The development for further elements of national capacity training for clinical management including the 2009 WHO case classification is recommended.

• Studies should attempt to include measuring dengue epidemiological data when considering the use of the 2009 WHO case classification and the related clinical algorithms.

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