

# The WHO dengue classification and case definitions: time for a reassessment

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Dengue is the most prevalent mosquito-borne viral disease in people. It is caused by four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), of the genus *Flavivirus*, and transmitted by *Aedes aegypti* mosquitoes. Infection provides life-long immunity against the infecting viral serotype, but not against the other serotypes. Although most of the estimated 100 million dengue virus infections each year do not come to the attention of medical staff, of those that do, the most common clinical manifestation is non-specific febrile illness or classic dengue fever. About 250 000–500 000 patients developing more severe disease. The risk of severe disease is several times higher in sequential than in primary dengue virus infections.<sup>1</sup> Despite the large numbers of people infected with the virus each year, the existing WHO dengue classification scheme and case definitions have some drawbacks. In addition, the widely used guidelines are not always reproducible in different countries—a quality that is crucial to effective surveillance and reporting as well as global disease comparisons. And, as dengue disease spreads to different parts of the globe, several investigators have reported difficulties in using the system, and some have had to create new categories or new case definitions to represent the observed patterns of disease more accurately.<sup>2,3</sup>

Dengue fever is characterised by a sudden onset of high-grade fever with non-specific constitutional symptoms, and most cases resolve without specific treatment. The pathognomonic feature of severe dengue (which WHO classifies as dengue haemorrhagic fever [DHF]) is a transient increase in vascular permeability resulting in plasma leakage. In severe cases, circulation is compromised and the patient can go into hypovolaemic shock, and even die without appropriate management.<sup>4</sup> Patients with DHF can also have abnormal blood coagulation, but major haemorrhage is unusual except in association with profound or prolonged shock.<sup>5–7</sup> Severe dengue can also be characterised by hepatic damage, cardiomyopathy, encephalopathy, and encephalitis—although these manifestations are rare—and the risk of death in such cases is high.<sup>8,9</sup>

Dengue is most prevalent in tropical Asia, Latin America, and the Caribbean, and health-care workers need to be able to diagnose it in patients presenting with fever. Early detection and management of severe disease are essential to prevent death. Recommendations for the classification and management of DHF were developed following key findings in Bangkok in the 1960s. In particular, in a 1964 study of 123 Thai children admitted to hospital with dengue, researchers identified that clinically important loss of fluid from the vascular

compartment was indicated by a 20% increase in packed-cell volume.<sup>10</sup> The recommendations evolved into the WHO guidelines of 1974, updated in 1986, 1994, and 1997.<sup>11</sup> The recommendations for intensive but judicious fluid replacement successfully reduced case-fatality rates to less than 1% (untreated, up to 40% of severe cases die) in hospitals equipped for appropriate monitoring and intravenous resuscitation.<sup>12</sup> Although the guidelines have since been adapted by each region,<sup>13,14</sup> and are widely used in clinical practice and training, they have never been formally validated. Each country has developed its own clinical training programme largely based on the WHO guidelines, but no standard training materials or methods exist.

Ideally, a good dengue classification scheme would allow appropriate triage of patients, guide clinical management, facilitate the assessment of potential interventions (such as intravenous fluids, new antiviral treatments, and vaccines), and, through careful definition of the clinical phenotype, aid in the investigation of the underlying pathogenesis. It would be greatly advantageous if such a scheme could identify, through early recognition of key warning signs, patients who are likely to progress to severe disease. A scheme that fulfilled these requirements would also facilitate epidemiological surveillance and reporting as well as global disease comparisons. However, to be effective, a scheme needs to be simple and reproducible, user-friendly, and applicable throughout the health-care systems of the countries where it is to be used. Here, we review the magnitude of the burden of dengue disease in endemic areas, highlight the limitations of the current WHO dengue classification scheme, and propose a solution for developing a more robust system.

## The burden of disease

In hyperendemic Asian countries, where there is concurrent transmission of several serotypes, primary dengue virus infections are seen in young children, whereas symptomatic dengue generally occurs during secondary dengue virus infections in school-age children or young adults.<sup>15–19</sup> Prospective, population-based studies in several Asian countries have shown geographic and temporal variation in the incidence of dengue virus infection and disease in children (table 1).<sup>16–19</sup> The burden of dengue in these hyperendemic countries is substantial, with 22–292 per 1000 children infected each year, and 1–8 per 1000 children admitted to hospital per year.

In the Latin American and Caribbean region, the threat to public health from dengue has grown rapidly in the

	Study period	Population size	Age range (years)	Incidence (cases per 1000 children per year)			
				Dengue infection	Symptomatic dengue	Hospitalised dengue	Dengue with plasma leakage
Bangkok, Thailand <sup>16</sup>	1980–81	1757	4–16	59	7	4	4
Yangon, Myanmar (Burma) <sup>17</sup>	1984–88	~ 12 500	1–9	106	..	3	2
Yogyakarta, Indonesia <sup>18</sup>	1995–96	1837	4–9	292	6	4	4
Kamphaeng Phet, Thailand <sup>19</sup>	1998	2119	7–11	79	36	7	4
	1999	1928		65	34	8	5
	2000	1713		22	8	1	1

Table 1: Prospective, population-based studies in hyperendemic Asian countries showing the incidence of dengue infection and disease

past two decades along with an increase in the number of concurrent circulating dengue virus serotypes. The burden of dengue in the region also varies by country. For example, from 1996 to 1997 (two non-epidemic years) the laboratory-based surveillance system in Puerto Rico detected 0·71 cases per 1000 children aged 2–18 years.<sup>20</sup> By contrast, prospective cohort studies in Managua, Nicaragua, recorded 60–180 infections per 1000 children from 2001 to 2003, and 4·6 confirmed cases per 1000 children aged 2–9 years during a non-epidemic dengue year from 2004 to 2005 (Hammond SN, Balmaseda A, Kuan G, and Harris E, unpublished).

Children with severe dengue are particularly susceptible to shock, with the highest mortality in infants. In children admitted to hospital, case-fatality rates can be as high as 4% depending on the age of the population and disease severity (table 2).<sup>20–28</sup> True case-fatality rates are probably higher because hospitals that confirm the diagnosis and publish their findings are more likely to practise better case management than hospitals without basic diagnostic tools. A review of case-fatality rates that included clinically diagnosed cases showed variation in mortality figures between regions and between hospitals, from less than 1% to 13%.<sup>29</sup>

### Limitations of the WHO classification scheme and case definitions

The WHO scheme classifies symptomatic dengue virus infections into three categories; undifferentiated fever, dengue fever, and DHF (figure).<sup>11</sup> Dengue fever is clinically defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, or leucopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. A case must meet all four of the following criteria to be defined as DHF: fever or history of fever lasting 2–7 days; a haemorrhagic tendency shown by a positive tourniquet test or spontaneous bleeding; thrombocytopenia (platelet count  $100+10^9/L$  or less); and evidence of plasma leakage shown either by haemoconcentration with substantial changes in serial measurements of packed-cell volume, or by the development of pleural effusions or ascites, or both.

DHF is further classified into four severity grades according to the presence or absence of spontaneous bleeding and the severity of plasma leakage.<sup>11</sup> The term dengue shock syndrome (DSS) refers to DHF grades III and IV, in which shock is present as well as all four DHF-defining criteria. Moderate shock, identified by narrowing of the pulse pressure or hypotension for age, is present in grade III DHF, whereas profound shock with no detectable pulse or blood pressure is present in grade IV DHF.

	Study period	n	Age range	Number with shock	Number of deaths
<b>Asia</b>					
Manila, Philippines <sup>21</sup>	1983–84	517	0–47 years	2 (0.4%)	0
Bangkok, Thailand <sup>22</sup>	1994	60	6 months to 14 years	9 (15%)	0
Bangkok, Thailand <sup>23</sup>	1995–99	4743		1186 (25%)	95 (0.2%)
Chonburi, Thailand <sup>24</sup>	2001	347	0–66 years	40 (12%)	1 (0.3%)
Ho Chi Minh City, Vietnam <sup>25</sup>	1998–2002	107	0–11 months	22 (20.5%)	4 (3.7%)
Ho Chi Minh City, Vietnam <sup>26</sup>	1999–2004	641	6 months to 15 years	641(100%)	1 (0.2%)
Dhaka, Bangladesh <sup>27</sup>	2000	176	any age	1 (1%)	2 (1%)
<b>Latin America</b>					
Puerto Rico <sup>20</sup>	1994–99	1757	any age	17 (1%)	20 (1%)
Managua and Leon, Nicaragua <sup>2</sup>	1998	328	any age	37 (11%)	1 (0.3%)
Managua and Leon, Nicaragua <sup>28</sup>	1999–2001	114	0–11 months	46 (40%)	13 (1%)
		1211	1–14 years	419 (35%)	
		346	15 years or older	40 (12%)	

Table 2: Proportion of shock and death in patients with laboratory-confirmed dengue admitted to hospital

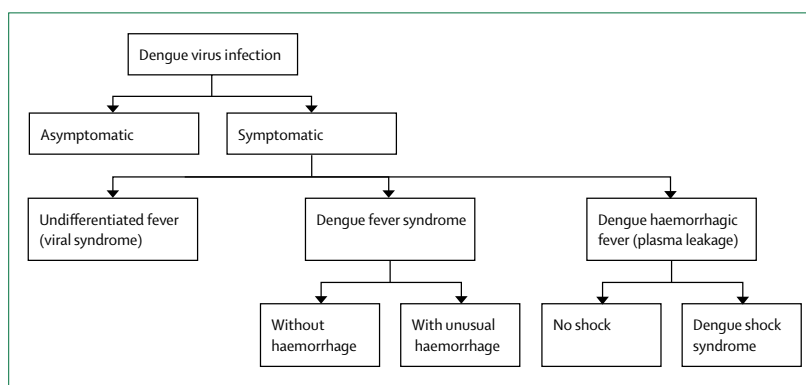


Figure: WHO classification of symptomatic dengue infection

The WHO classification scheme and case definitions are based on substantial clinical experience mainly from Thailand, which, although valuable, is difficult to quantify and might not represent findings in other countries. Undoubtedly, widespread adoption of the WHO system, together with implementation of the accompanying management guidelines, contributed to the striking initial fall in case-fatality rates. However, after the recent global expansion in dengue disease, several investigators have reported difficulties in using the system, with some finding they have to create new categories or altogether new case definitions to represent the observed patterns of disease more accurately.<sup>2,3</sup> As a result, the terms “dengue fever with unusual haemorrhage” and “dengue with signs associated with shock” have been introduced.

In a study<sup>30</sup> of 30 virologically confirmed dengue deaths in Jakarta, Indonesia, nine (30%) people had gastrointestinal bleeding before the onset of shock with no evidence of haemoconcentration during the hospital stay, so they did not meet the WHO criteria for DHF. In a study in Vietnam, bleeding and thrombocytopenia were almost as common in the 312 children classified as having dengue fever as in the 319 classified as having DHF. In addition, of the 310 children with shock and laboratory-confirmed dengue, 57 (18%) did not meet all four WHO criteria for DHF.<sup>31</sup> In a study in Nicaragua, 20 (61%) of 33 infants, 194 (69%) of 283 children, and 20 (77%) of 26 adults with shock and laboratory-confirmed dengue did not fulfil the WHO criteria for DHF.<sup>32</sup> Thus, not only are bleeding and thrombocytopenia common in children without apparent DHF, but these features, and sometimes definitive evidence of plasma leakage, are also absent in some children with “true” DHF.

Several groups have also investigated the usefulness of the tourniquet test—said to be a measure of capillary fragility and thrombocytopenia—for the diagnosis of DHF (table 3).<sup>22,33,34</sup> The findings show that the test differentiates poorly between dengue fever and DHF, and that many children with non-dengue febrile illnesses also have positive tests. And since health-care workers must have the appropriate equipment and enough time to do the test, and because it is uncomfortable for the patient, many choose not to use it, yet the test remains an integral part of the existing scheme.

Our assessment suggests that the WHO classification system and case definitions could be improved. First, the scheme distinguishes rigorously between dengue fever, DHF, and DSS, but there is much overlap between the three. Possibly, as previously suggested,<sup>35</sup> dengue disease exists as a continuous range rather than as distinct clinical entities. Second, all four requirements for the WHO definition of DHF (fever, haemorrhage, thrombocytopenia, and signs of plasma leakage) might not always be fulfilled or detected. Frequently, assessment and classification are not possible in first-level referral centres, primarily because basic measurements such as packed-cell volume and platelet counts cannot be done. Even in tertiary centres, the WHO definitions cause confusion when patients with otherwise uncomplicated dengue fever have severe thrombocytopenia or when patients suspected clinically to have DHF do not meet all four WHO criteria. Third, the DHF/DSS classification excludes severe dengue disease associated with “unusual manifestations”. Finally, the term DHF places undue emphasis on haemorrhage when the danger sign that should be watched for and managed is plasma leakage leading to shock. We believe these issues lead to difficulties not only in clinical management but also in clearly defining the clinical phenotype for studies of the underlying pathogenesis.

### Potential solution

Few prospective data support the WHO classification scheme for dengue. A large multicentre descriptive study is needed to obtain the evidence to establish a robust dengue classification scheme for use by clinicians, epidemiologists, public-health authorities, vaccine specialists, and scientists involved in dengue pathogenesis research. Dengue case definitions derived in this way might prove more useful for presumptive diagnosis, management, and final diagnosis, than the existing scheme.

In such a study, clinical data should be obtained systematically for large numbers of patients of all ages, presenting to all levels of the health-care system, from all regions of the world, and covering the full range of symptomatic disease. Ideally, patients should be recruited during the first few days of illness and receive standard care, with clinical manifestations recorded in detail daily

	Age range	Number with positive tourniquet test/total			Ability of the tourniquet test to diagnose dengue infection			
		Dengue fever*	Dengue haemorrhagic fever*	Other febrile illness	Sensitivity	Specificity	PPV	NPV
Bangkok and Kamphaeng Phet, Thailand <sup>22</sup>	6 months to 14 years	10/28 (36%)	12/23 (52%)	23/108 (21%)	..	..	49%	75%
		18/28 (64%)†	15/23 (65%)†	42/108 (39%)†	..	..	44%†	79%†
Bangkok and Kamphaeng Phet, Thailand <sup>33</sup>	6 months to 15 years	154/176 (88%)†	132/142 (93%)†	172/331 (52%)†	90%†	48%†	62%†	83%†
Dong Nai Province, Vietnam <sup>34</sup>	1 month to 15 years	119/312 (38%)	129/286 (45%)	4/71 (6%)	42%	94%	98%	17%

\*Classified according to WHO criteria. †Criteria for positivity modified to ten petechiae within the square.

Table 3: Studies of the tourniquet test in the diagnosis of laboratory-confirmed dengue

until symptoms resolve. The development of shock, altered consciousness, severe bleeding, unusual manifestations, or death would be considered as an indication of severe dengue, the main outcome, and the data might then be used to construct an algorithm to predict this outcome.

The findings not only would allow the current scheme to be formally assessed, but also might suggest useful modifications to it, or indeed form the basis for the development of an alternative system that could more accurately represent the different clinical syndromes seen and be simpler to apply. It is crucial that a broad consensus of all stakeholders is achieved, and that any new or modified system is properly validated if it is to prove useful in the long term. Although the focus should be on common disease manifestations, such studies might also help to identify the true frequency of the so-called 'unusual manifestations' of dengue and clarify the differences in clinical presentation between children and adults. In view of the growing incidence of dengue virus infections throughout much of the tropical world and the continued spread of the disease, everyone involved in clinical management or dengue research must engage with these issues to ensure we provide clear evidence on which to base guidelines for good clinical practice.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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