

## Perspective Piece

### Dogma in Classifying Dengue Disease

Jeremy J. Farrar,\* Tran T. Hien, Olaf Horstick, Nguyen T. Hung, Thomas Jaenisch, Thomas Junghanns, Axel Kroeger, Ida S. Laksono, Lucy Lum, Eric Martinez, Cameron P. Simmons, Adriana Tami, Kay M. Tomashek, and Bridget A. Wills  
*Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland; Institute of Public Health, University of Heidelberg, Heidelberg, Germany; Children's Hospital Number 1, Ho Chi Minh City, Vietnam; Department of Infectious Diseases, Section of Clinical Tropical Medicine, Heidelberg University Hospital, Heidelberg, Germany; Liverpool School of Tropical Medicine, Liverpool, United Kingdom; Department of Paediatrics, The Gadjah Mada University and Dr. Sardjito Teaching Hospital, Yogyakarta, Indonesia; Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; Instituto de Medicina Tropical Pedro Kouri, Havana, Cuba; Department of Medical Parasitology, Faculty of Health Sciences, University of Carabobo, Valencia, Venezuela; Department of Medical Microbiology, Molecular Virology Section, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; Dengue Branch, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, San Juan, Puerto Rico*

In his recent perspective entitled *Dengue: the Syndromic Basis to Pathogenesis Research, Inutility of the 2009 WHO Case Definition*, Halstead expresses concern that adoption of the 2009 World Health Organization (WHO) classification scheme will compromise the “analytic clarity needed to understand mechanisms underlying dengue pathophysiology, pathogenesis, treatment, and therapeutics.”<sup>1</sup> Leaving aside the important issue of how best to resolve the long running and convoluted debate on dengue case definitions and classification, two important misconceptions need to be addressed.

First, rather than being a research tool, the 2009 WHO dengue classification scheme is primarily intended to be used by clinicians and public health specialists engaged in dealing with the ever-expanding global pandemic of dengue disease.<sup>2,3</sup> The main objectives of the classification scheme are to improve case management by timely identification of severe or potentially severe cases, and to ensure that scarce resources are directed towards those most in need. The simplicity and sensitivity of the classification scheme should enable the complete clinical spectrum of dengue to be captured by surveillance systems and enhance the comparability of epidemiologic data gathered over time from different countries and regions. If, in addition, the new system provides a valid framework for scientific research on dengue pathogenesis, this feature should be regarded as a bonus.

The limitations of the 1997 WHO classification scheme of dengue fever (DF) and dengue hemorrhagic fever (DHF) grades I, II, III, and IV (grades III and IV being referred to collectively as dengue shock syndrome [DSS]) with respect to clinical case management have long been a focus of discussion.<sup>4–7</sup> One established dogma has been that DHF/DSS equates to severe dengue disease, and DF is mild. However, from a number of studies, it has become clear that a significant proportion of clinically severe cases, including patients with hypovolemic shock caused by plasma leakage, fall within the DF classification.<sup>8–11</sup> The complex nature of the 1997 classification system, the need for frequent laboratory testing of hematologic parameters, the requirement for all four DHF criteria to be fulfilled even if shock is present, and the fact

that the supporting evidence for DHF is often identified only during the recovery phase of the illness are among the factors contributing to this paradox. Conversely, many cases that fulfill all the requirements for a diagnosis of DHF can be conservatively managed and require little or no intervention.<sup>9</sup> Recognizing these difficulties, a number of countries developed local adaptations to the 1997 case classification, introducing novel categories that were deemed to reflect clinical disease patterns not captured by the scheme.<sup>12–14</sup> Consequently, the classification of dengue became fragmented and epidemiologic comparisons within and between countries became almost impossible.

As acknowledged in his perspective, the new 2009 classification presents significant improvements over the DF/DHF/DSS system in two key areas: 1) it reflects disease severity in real time, and 2) it enables identification of a higher proportion of clinically severe cases.<sup>15–18</sup> However, as is also pointed out, concerns have been raised regarding the possibility that the recommendation to admit all patients with dengue with warning signs might increase the total volume of admissions and adversely affect the quality of care given to hospitalized case-patients.<sup>19</sup> In fact, although the warning signs included in the 2009 scheme were primarily derived from recommendations by an expert panel of experienced clinicians, rather than resulting directly from a formal evidence base,<sup>20</sup> it is unlikely that many doctors working in dengue-endemic areas would be comfortable managing dengue patients with persistent vomiting, pleural effusions or ascites, and mucosal bleeding at home. Additionally, many of the warning signs recommended as criteria for hospital admission were already present in the 1997 guidelines (acute abdominal pain, restlessness or lethargy, a decrease in the platelet count concurrent with an increase in the hematocrit).<sup>21</sup> However, after introduction of any new system, it is important that on-going review and evaluation are integrated into the structure of change. Several large multicenter and multinational studies are in progress and are looking at warning signs that may be associated with development of severe disease or may predict the need for hospitalization (ClinicalTrials.gov: NCT01421732 and NCT01550016), with the eventual aim to introduce amendments to the 2009 classification if supported by evidence from these prospective studies.

Second, Halstead indicates that the DF/DHF/DSS classification system remains useful in the context of current dengue

\*Address correspondence to Jeremy J. Farrar, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. E-mail: jfarrar@oucru.org

research to understand disease pathogenesis and pathophysiology. Undoubtedly, significant scientific advances were made in the 1960s and 1970s after recognition of dengue virus infection as the cause of the severe new disease that emerged across several major cities in Asia at that time; much of our current understanding of pathogenesis in primary and secondary dengue infections stems from that early pioneering work.<sup>22–27</sup> Unfortunately, however, we must also recognize that we are no nearer to elucidating the mechanisms responsible for the microvascular derangements that are the hallmark of severe disease,<sup>28–30</sup> or to understanding the immune correlates of protection,<sup>31</sup> than we were more than 40 years ago. Another long-established dogma that may have contributed to this lack of progress is the belief that DF and DHF are two separate disease entities with distinct clinical characteristics. Careful observational studies now suggest that the major clinical manifestations (altered vascular permeability, thrombocytopenia, coagulation derangements, hepatic dysfunction) show considerable overlap between the two syndromes, and indicate that dengue virus infection disrupts a number of different physiologic systems to varying degrees in individual patients, influenced by host and viral factors, with the relative prominence of the resulting abnormalities determining the final clinical phenotype.<sup>8,32–35</sup> Thus, a spectrum of disease exists rather than two distinct entities, and it is crucial that this spectrum is recognized if pathogenesis research is to move forward in the 21st century.

Halstead is concerned that “if in the future pathogenesis research is based upon clinical responses included in severe dengue such patients will exhibit an admixture of dengue disease syndromes.” We share his concern that great care is needed when defining clinical groups for comparisons in pathogenesis studies. However, we would argue that although patients fulfilling the necessary criteria for DHF or DSS form reasonably well-defined groups, the DF category is heterogeneous and includes patients with significant vascular leakage and/or bleeding who fail to fulfill all criteria for DHF and are therefore classified as having DF by default.<sup>8,9</sup> The resulting diagnostic categories are not mutually exclusive and interpretation of experimental data is compromised. In addition, because factors (viral or host) that contribute to the final phenotype may be different for particular characteristics such as vascular leakage, bleeding, or liver dysfunction, it is only by using much stricter definitions of these phenotypes that we are likely to be successful in teasing out the underlying mechanisms.

Although designed primarily for use as a clinical tool, the WHO 2009 classification does enable severe dengue cases to be differentiated into three specific sub-categories (severe vascular leakage, severe bleeding, and severe organ dysfunction) to look at pathogenesis in a more focused way. Two novel susceptibility loci associated with DSS have already been identified by use of this method.<sup>36</sup> However, further refinement is needed, and we strongly advocate that the dengue research community should work together to develop international standards for the detailed discrimination of clinical phenotypes for use in pathogenesis studies and/or therapeutic intervention trials. For example, an internationally agreed system that defines the minimum dataset required to make an informed evaluation of the severity of vascular leakage in an individual patient, potentially enabling a score to be assigned to facilitate comparisons within and between

research studies, would be invaluable to the research community. Similarly development of a systematic approach to defining the etiology and severity of bleeding manifestations or hepatic dysfunction would be a major step forward. To reduce the selection and information bias inherent in retrospective data collection, we also urge that pathogenesis studies should be designed to collect data prospectively from well-defined study populations comprising the full spectrum of dengue disease, rather than relying on potentially incomplete information extracted from the clinical medical records of selected patient groups.

Finally, it is important to stress that case definition and case classification serve different purposes and should not be conflated into a single concept. Typically, a case definition is used for discovery, epidemiologic, or diagnostic purposes, usually in the absence of confirmatory laboratory tests, but case classification separates patients into different disease categories based on predefined criteria. In the WHO 2009 guidelines, the criteria for making a clinical diagnosis of dengue remain virtually unchanged, with only minor modifications from those used to define DF in the 1997 guidelines, but classification into disease categories has been substantially revised and is now based on clinical severity rather than a syndromic approach.

In conclusion, dengue is a complex disease. Establishing change is always difficult, but the need for a clinically relevant, easy to apply case classification is beyond question. Such a classification scheme needs to reflect the contemporary epidemiology of the disease, be able to assess severity in real time, and be globally harmonized. The 1997 WHO scheme was too complicated to use in clinical or public health settings, yet was not sufficiently precise for detailed pathogenesis studies. The 2009 WHO classification, based on prospectively collected evidence and with on-going validation studies involving more than 12,000 patients in 12 countries across Asia and the Americas, brings clarity, clinical and epidemiological utility, and the potential for development of more precise definitions of clinical phenotype for pathogenesis studies.

Received March 25, 2013. Accepted for publication March 26, 2013.

Authors' addresses: Jeremy J. Farrar, Tran T. Hien, Cameron P. Simmons, and Bridget A. Wills, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam, and Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford OX3 7BN, United Kingdom, E-mails: jfarrar@oucru.org, hientt@oucru.org, csimmons@oucru.org, and bwills@oucru.org. Olaf Horstick, Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland, and Institute of Public Health, University of Heidelberg, Heidelberg, Germany, E-mail: ohorstick@yahoo.de. Nguyen T. Hung, Children's Hospital Number 1, Ho Chi Minh City, Vietnam, E-mail: drthanhhung@gmail.com. Thomas Jaenisch and Thomas Junghans, Department of Infectious Diseases, Section Clinical Tropical Medicine, Heidelberg University Hospital, Heidelberg, Germany, E-mails: Thomas.jaenisch@urz.uni-heidelberg.de and thomas.junghans@urz.uni-heidelberg.de. Axel Kroeger, Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland, and Liverpool School of Tropical Medicine, Liverpool L3 5QA, United Kingdom, E-mail: kroegera@who.int. Ida S. Laksono, Department of Paediatrics, The Gadjah Mada University, and Dr. Sardjito Teaching Hospital, Yogyakarta, Indonesia, E-mail: ida\_laksono@hotmail.com. Lucy Lum, Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, E-mail: lumcs@ummc.edu.my. Eric Martinez, Instituto de Medicina Tropical Pedro Kouri, Marianao, Havana, Cuba, E-mail: emartinez@informed.sld.cu. Adriana Tami,

Department of Medical Parasitology, Faculty of Health Sciences, University of Carabobo, Valencia, Venezuela, and Department of Medical Microbiology, Molecular Virology Section, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, E-mail: a.tami@umcg.nl. Kay M. Tomashek, Dengue Branch, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, San Juan, PR 00920, E-mail: kct9@cdc.gov.

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