An Evaluation of Modified Case Definitions for the Detection of Dengue Hemorrhagic Fever

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ABSTRACT: The case definition for dengue hemorrhagic fever (DHF) requires fever, platelets ≤100,000/mm³, any hemorrhagic manifestation, and plasma leakage evidenced by hemoconcentration ≥20%, pleural or abdominal effusions, hypoproteinemia or hypoalbuminemia. We evaluated the specificity and yield of modified DHF case definitions and the recently proposed World Health Organization criteria for a provisional diagnosis of DHF, using a data base of laboratory-positive and laboratory-negative reports of hospitalizations for suspected dengue in Puerto Rico, 1994 to 1996. By design, all modifications had 100% sensitivity. More liberal criteria for plasma leakage were examined: 1) adding as evidence a single hematocrit ≥50% (specificity 97.4%); 2) accepting hemoconcentration ≥10% (specificity 90.1%); and 3) accepting either hematocrit ≥50% or hemoconcentration ≥10% (specificity 88.8%). The new DHF cases identified by these definitions (and percent laboratory positive) were 25 (100.0%), 95 (90.5%), and 107 (91.6%), respectively. In contrast, the provisional diagnosis of DHF (fever and hemorrhage, and one or more of platelets ≤100,000/mm³, or hemoconcentration ≥20%, or at least a rising hematocrit [redefined quantitatively as a 5% or greater relative change]) showed a specificity of 66.8%, and identified 318 new DHF cases, of which 282 (88.7%) were laboratory-positive. Very small changes in the criteria may result in a large number of new cases. The modification that accepted either hematocrit ≥50% or hemoconcentration ≥10% had acceptable specificity, while doubling the detection of DHF-compatible, laboratory-positive severe cases, but "provisional diagnosis" showed even lower specificity, and may produce inflated DHF incidence figures. Modified case definitions should be prospectively evaluated with patients in a health-care facility before they are recommended for widespread use. *Key words: Dengue, Dengue hemorrhagic fever, Population surveillance, Patient selection*

Dengue hemorrhagic fever (DHF) is an acute, mosquito-transmitted viral disease, characterized by fever, thrombocytopenia, hemorrhagic manifestations, and excessive capillary permeability that may lead to shock and death (1). Any disease that cannot be precisely diagnosed by utilizing a single laboratory test, such as DHF, must be identified by the use of a clinical case definition (a set of clinical and laboratory criteria for deciding whether a person has a particular disease or other health related condition) (2). The use of a standard case definition is a mechanism to assure that every case is diagnosed in the same way, regardless of when or where it occurrs, or who identifies it (3). A simple, uniformly used case definition has great utility for research, surveillance, cost-effectiveness studies, and international comparisons when it has high specificity (so only true cases are identified). When prompt detection and treatment can save a patient's life, such as in DHF, a premium is placed on high sensitivity (so all cases are identified), even at the cost of lower specificity (treating cases that do not need such treatment).

Surveillance data for DHF are widely used as evidence of the disease's characteristics, its impact on society, the

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risk factors for transmission, and how incidence may be changing due to global processes. International reports of case ratios of DHF-to-dengue may be as disparate as 0:59,357 in Brazil and 496:137 in Colombia in 1992 (4). Without analyses of surveillance systems for DHF, it is impossible to determine if such differences are due to varying prevalence of risk factors for dengue infection and DHF in each population, or to differential application of the DHF case definition. This is not unique to DHF. A comparison of rates of cholera in Latin America, between and within countries, has also demonstrated how the use of different case definitions will result in marked discrepancies in surveillance data (5-6).

The purposes of our study were to evaluate the utility for disease surveillance of several modifications to the current DHF case definition, and to demonstrate the importance of its component requirements (the effect of small changes in the criteria in the resulting number of cases). Several studies show that surveillance for DHF must, in practice, liberalize the criteria for evidence of excessive capillary permeability, and recently the World Health Organization (WHO) published new criteria for reporting DHF with a "provisional diagnosis" (1,7-10). A useful modified definition would be one that improved the identification of patients with plasma leakage and at risk for shock among cases of laboratory-positive severe dengue.

Methods

Surveillance. The Dengue Branch, Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention (CDC), receives diagnostic specimens from government clinics, public and private hospitals, laboratories, and physicians' offices throughout Puerto Rico (population 3.5 million, 1990 census). These specimens are sent directly to CDC, or are collected locally and delivered by personnel of the Puerto Rico Department of Health. To evaluate the severity of reported cases, infection control nurses at all hospitals (n=56) are asked to provide a 40-item report of demographic and clinical information on patients discharged with a diagnosis (or consideration) of dengue fever. These nurses (organized as the Puerto Rico Association of Epidemiologists) provide the data voluntarily; therefore, some infection control nurses at large public hospitals do not participate routinely. We included patients with onsets of symptoms from 1994 to 1996, and only cases identified by our laboratory as being positive or negative by serologic or virologic criteria. Data are stored and analyzed using Epi-Info software (11). We searched for errors in data entry by reviewing a systematic 10% sample of reports, and found an error rate of 0.44%. Outliers (values that seemed abnormally high or low) were checked by calling the hospital to verify the values in the hospital record.

Clinical case definition of DHF. The WHO case definition for DHF mentions four criteria: fever, or history of acute fever; any hemorrhagic manifestation; low platelet count (100,000/mm^3 or less); and evidence of plasma leakage due to increased vascular permeability: elevated hematocrit or a drop after intravenous fluid treatment (20% or more change from baseline), pleural or abdominal effusions, or hypoalbuminemia or hypoproteinemia (1). The relative change in hematocrit (hemoconcentration) was calculated as the ratio of the difference of maximum and minimal hematocrit (or hemoglobin) values, divided by the minimal value (12-13). In consideration of the reference values used in local hospitals, hypoalbuminemia was defined as a serum albumin less than 3 g/dL. It is important to highlight that the WHO criteria for reporting DHF do not require a positive laboratory test for dengue infection.

Comparison of modifications. A computer algorithm identified cases that fulfilled WHO's criteria for DHF. Each modification was converted to an EPI Info computer program, applied to our data base of case reports, and compared to the WHO case definition. The changes explored in six modifications were selected *a priori* based on our experience with the DHF surveillance system. For many hospitalized patients, the medical history and laboratory testing are not reported in the detail necessary to fulfill the requirements of the standard case definition. In addition, patients frequently receive intravenous fluids before hematocrit or hemoglobin levels are measured. All patients with suspected dengue considered in this surveillance system were hospitalized; therefore, they all had an illness of moderate to extreme severity. In six modifications, only one of the four criteria was altered at a time. "0Fever" eliminated the requirement for fever documentation; "0platelet" disregarded the requirement for a platelet count; "platelets<150K" raised the threshold for minimum platelet count to the commonly used lower limit for normal (150,000/mm^3) (14). The criterion for excessive capillary permeability, being the most complex, was examined with three different modifications. We used the alternative of any hematocrit level at or greater than 50% ("Hcrit≥50"); we lowered the criterion for minimum hemoconcentration from 20% to 10% or more ("Hmcon≥10"); and we combined the last two changes, with a minimum 10% hemoconcentration or a hematocrit level at 50% or greater ("Hmcon ≥10Hcrit ≥50"), as additional alternatives to document hemoconcentration. As a seventh modification we tested the recent WHO criteria for a provisional diagnosis of DHF, that is, fever

and any hemorrhagic manifestation, and one or more of the following findings: platelet count ≤100,000/mm^3, or hemoconcentration ≥ 20%, or at least a rising hematocrit (1). We redefined the last item as a 5% or greater relative change in hematocrit, to establish a minimum, and to allow for the frequent situation in which the patient presents with hemoconcentration, so only a drop in hematocrit (due to intravenous fluid treatment) is observed.

The criteria used for these comparisons were specificity, yield, and the case-fatality rate among the positive additional cases identified. Sensitivity and specificity were calculated in comparison to the current DHF reporting definition, taken as the "gold standard" for surveillance reports. For all modifications, patients who fulfilled the standard criteria for DHF were still diagnosed as DHF (i.e., sensitivity was 100%) because in all seven alternatives, the changes either eliminated restrictions, or added alternatives to consider a case as DHF. Yield means the number of extra cases identified, in spite of a sensitivity of 100%, because sensitivity refers to cases diagnosed by the current DHF definition, and with the alternative definitions more cases are labeled as DHF. The case-fatality rate among the positive additional cases was examined to detect whether the alternative definitions for DHF were selecting a group of patients with less severity of illness than among the WHO-defined DHF. A similarity of rates, given laboratory positivity, would suggest that both groups of DHF cases (defined according to WHO or to an alternative definition) shared a similar underlying process.

Laboratory. The laboratory methods for dengue diagnosis at the CDC Dengue Branch have been previously described in detail. In brief, laboratory-positive cases are those whose diagnostic specimens are positive for virus isolation, anti-dengue immunoglobulin M (IgM), anti-dengue immunoglobulin G at ELISA titers ≥163,540, or antigen detection by immunohistochemistry. In specimens collected 6 or more days after onset of symptoms, the lack of significantly elevated IgM rules out the diagnosis of dengue, and the case is considered negative (15).

Results

From 1994 to 1996, the infection control nurses in Puerto Rico reported the hospitalization for suspected dengue of 915 (85.1%) laboratory positives and 160 (14.9%) negatives for dengue; of 118 that fulfilled the WHO criteria for DHF, 97 (82.2%) were laboratory positive, including five deaths. The male:female ratio, age distribution, frequency of hemorrhagic manifestations and DHF diagnosis (according to the standard definition) were similar in the laboratory-positive and laboratory-negative patients (Table 1). The laboratory-negatives showed less marked thrombocytopenia on average, but higher frequency of plasma leakage (as a general category), effusions, shock, and a higher case-fatality rate. The sub-group of laboratory-negative cases who fulfilled the WHO criteria for DHF stands out because of female predominance, higher median age, and markedly higher

Table 1. Selected findings in patients hospitalized with suspected dengue, and positive or negative laboratory results, Puerto Rico, 1994 - 1996

Patient characteristics and clinical findings	Laboratory Positive (n=915)		Laboratory Negative (n=160)	
	DHF	not DHF	DHF	not DHF
DHF status	97 (10.6%)	818 (89.4%)	21 (13.1%)	139 (86.9%)
Male:female ratio	1: 0.9	1 : 1	1 : 1.6	1:1.1
Median age in years (range)	24 (0-72)	25 (0-96)	41 (1-66)	23 (0-85)
Mean platelets /mm^3	36,000	62,000	39,000	116,000
Mean albumin g/dl	3.0	3.6	3.0	3.5
Mean hemoconcentration	32%	12%	31%	13%
Any hemorrhage	100%	329 (40.2%)	100%	49 (35.3%)
Plasma leakage	100%	88 (10.8%)	100%	20 (14.4%)
Effusions	9 (9.3%)	10 (1.2%)	3 (14.3%)	3 (2.2%)
Shock	2 (2.1%)	5 (0.6%)	6 (28.6%)	3 (2.2%)
Case-fatality rate	5 (5.2%)	10 (1.2%)	5 (23.8%)	7 (5.0%)

incidence of effusions, shock, and deaths than among the laboratory-positive DHF cases.

Table 2 shows the specificity and yield (laboratory-positive and -negative cases) of applying modified DHF case definitions to the data base of hospitalizations for suspected dengue (as indicated, all modifications had 100% sensitivity). Specificity (the proportion of true negatives identified by a test) was calculated by substracting the new DHF cases identified with each modified definition (in column 3) from 957 (the number of "true" DHF negatives, according to the standard definition) then dividing by 957 and expressing the result as a percentage. The definition that includes either a hematocrit ≥50% or hemoconcentration ≥10% among the criteria for evidence of excessive capillary permeability showed high specificity and high yield, more than doubling the detection of DHF-compatible cases and collecting mostly laboratory positives, who showed a case-fatality rate similar to standard DHF cases. In contrast, the WHO "provisional diagnosis" of DHF showed a lower specificity, tripling the detection of DHF-compatible cases.

specificity of 88.8%. It compensates for a clinical environment where patients are rehydrated promptly as part of standard care. The definition for "provisional" DHF showed lower specificity (66.8%), and may have even lower specificity when used without dengue laboratory diagnosis. The results of this evaluation of modified case definitions were probably affected by the nature of the data base (hospitalized cases, mostly laboratory positive, in a location where dengue is endemic and three serotypes had circulated for over a decade). Some of the data points may reflect transient changes or machine errors, but DHF is defined by the simultaneous presence of several abnormalities. The data were not collected prospectively with repeated measures, as for a clinical study, but were voluntarily reported by community and teaching hospitals, such as would occur in any surveillance system.

The recognition and study of emerging diseases is critically dependent on the case definition used for surveillance (16). For public health surveillance systems, evaluation of the sensitivity and specificity of case definitions is as important as the evaluation of diagnostic

Table 2. Specificity, yield (and laboratory-positive to negative cases), and deaths (and case-fatality rate in newly identified laboratory- positive cases) by modified DHF case definition.

Modifications*	Specificity**	Yield (Laboratory-Positive to Negative New Cases)	Deaths (Case-fatality Rate among New Positive Cases)
Platelets<150,000	99.7%	3 (3:0)	0
0fever	99.6	4 (1:3)	1 (100.0%)
0platelet	98.7	12 (9:3)	0
Hcrit≥50	97.4	25 (25:0)	0
Hmcon≥10	90.1	95 (86:9)	1 (1.2)
Hmcon≥10Hcrit≥50	88.8	107 (98:9)	1 (1.0)
Provisional diagnosis	66.8	318 (282:36)	3 (1.1)

*Modifications: Platelets<150,000 raised the threshold for minimum platelet count to 150,000/mm^3; 0fever eliminated the fever requirement; 0platelet disregarded the requirement for a platelet count; Hcrit≥50 added the alternative of any hematocrit at or greater than 50%; Hmcon≥10 lowered the criterion for minimum hemoconcentration from 20% to 10% or more; and Hmcon ≥10Hcrit ≥50 combined the last two changes, with a minimum 10% hemoconcentration or a hematocrit at 50% or greater; Provisional diagnosis requires fever and hemorrhage, and one or more of platelets ≤100,000/mm^3, or hemoconcentration ≥20%, or at least a 5% or greater change in hematocrit. All have 100% sensitivity.

*Specificity = ((957 - yield of new cases, in column 3)/957)) x 100

Discussion

The modified DHF definition that included either a hematocrit ≥50% or hemoconcentration ≥10% among the criteria for evidence of excessive capillary permeability doubled the number of DHF-compatible, laboratory-positive cases identified, from 98 to 196, while keeping a

methods is for clinical medicine. Dengue is an emerging infectious disease, i.e., one "whose incidence in humans has increased within the past two decades or threatens to increase in the near future" (17). DHF was first recognized as a clinical entity in the Philippines in 1953 and in Thailand in 1958 (18-19). In 1975, an advisory committee convened by WHO published criteria for the clinical

diagnosis of DHF said to result in a 90% laboratory confirmation rate, with the stated purpose to "avoid an overdiagnosis of the disease" (20). Later versions (1980, 1986, 1994, 1997) expanded the spectrum of findings used to document DHF, and eliminated ambiguities in the description of requirements (1,21-23). Nevertheless, the case definition still remained as strict as it was originally intended, for clinical diagnosis in the absence of dengue laboratory testing.

High specificity, although desirable in a case definition, may come at the expense of low sensitivity. The current definition for DHF requires an abundance of clinical and laboratory observations, and is easily misunderstood (24-25). Easier detection of DHF cases is not only necessary to improve the quality of surveillance data; more importantly, it is required for the prevention of shock, and ultimately, to save the lives of persons infected with dengue. Severe and fatal cases of laboratory-confirmed dengue may not be categorized as DHF unless all the necessary tests have been performed (history of fever; skin, urine, and stool examinations to search for evidence of bleeding; frequent hematocrits and platelet counts; well-timed chest X-rays, measurement of serum albumin or protein levels to detect excessive capillary permeability). Alternatively, only the cases with the most typical and severe presentations will be detected by surveillance systems. The gold standard for diagnosing DHF requires a combination of hospital data, facilities for dengue diagnosis, and clinical judgement (9). In 1997, WHO published a definition for cases of "provisional diagnosis" of DHF, to be reported as DHF if they also have virologic or serologic evidence of acute dengue infection, or if there is history of exposure in a dengue endemic or epidemic area (1). As in previous occasions, WHO did not provide information on the accuracy of these criteria for identifying a true case of DHF (sensitivity, specificity, positive and negative predictive value) or an estimate of their impact on DHF incidence statistics, if the new definitions for reporting are used as recommended.

AIDS offers the best-known demonstration of the effect of a change of case definition on surveillance data. A broad deliberative process and the publication of statistical projections preceded the adoption of expanded surveillance criteria that resulted in an increase, by more than 100%, in the number of cases reported in 1993 compared to 1992 (26-27). From our results, it is clear that small changes in the DHF diagnostic criteria (especially with regard to excessive capillary permeability) can produce large changes in the resulting number of cases. Before modified case definitions for DHF are recommended for widespread use, they should be examined in a prospective study in fully evaluated patients in a health-care facility, or applied retrospectively to well-examined groups, like the cohort in reference 9. In such a population, a modified definition that identified a large number of additional DHF cases and still maintained a high sensitivity and specificity compared to the final clinical diagnosis would be demonstrably more useful for clinical care and disease surveillance than the current WHO definition for DHF (28).

Resumen

La definición de caso para dengue hemorrágico (DH) exige la presencia de fiebre, plaquetas ≤100,000/mm^3, cualquier manifestación hemorrágica, y extravasación de plasma manifestada por hemoconcentración ≥20%, efusiones pleurales o abdominales, hipoproteinemia o hipoalbuminemia. Evaluamos la especificidad y rendimiento de modificaciones de la definición de caso de DH y los recién propuestos criterios de la Organización Mundial de la Salud para diagnóstico provisional de DH, usando informes de hospitalización por sospecha de dengue en Puerto Rico, de 1994 a 1996, con diagnóstico de laboratorio positivo o negativo. A propósito, todas las modificaciones tenían sensibilidad de 100%. Se examinaron criterios más liberales para extravasación de plasma: 1) añadir como evidencia un sólo hematócrito ≥50% (especificidad 97.4%); 2) aceptar hemoconcentración ≥10% (especificidad 90.1%); y 3) aceptar un hematócrito ≥50% o hemoconcentración ≥10% (especificidad 88.8%). Los nuevos casos de DH identificados por estas definiciones (y el porciento de estos positivos por laboratorio para dengue) fueron 25 (100.0%), 95 (90.5%), y 107 (91.6%), respectivamente. En cambio, el diagnóstico provisional de DH (fiebre y hemorragia, y uno o más de los siguientes: plaquetas ≤100,000/mm^3, o hemoconcentración ≥20%, o por lo menos un aumento en hematócrito [redefinido cuantitativamente como un cambio relativo de al menos 5%]) demostró una especificidad de 66.8%, e identificó 318 nuevos casos de DH, de los cuales 282 (88.7%) eran positivos por laboratorio. Leves cambios en los criterios diagnósticos pueden resultar en un gran número de nuevos casos de DH. La modificación que acepta un hematócrito ≥50% o hemoconcentración ≥10% tuvo especificidad aceptable, mientras que duplicaba la detección de casos severos compatibles con DH y positivos para dengue por laboratorio, pero el diagnóstico provisional demostró aún más baja especificidad, y puede producir cifras infladas de incidencia de DH. Las modificaciones de definiciones de caso deben ser evaluadas prospectivamente en pacientes antes de ser promulgadas para uso general.

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