Tropical Medicine and International Health doi:10.1111/j.1365-3156.2012.03020.x

VOLUME 17 NO 8 PP 1023–1030 AUGUST 2012

Dengue in travellers: applicability of the 1975–1997 and the 2009 WHO classification system of dengue fever

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Abstract

OBJECTIVES The aim of this study was to assess the applicability and benefits of the new WHO dengue fever guidelines in clinical practice, for returning travellers.

METHODS We compared differences in specificity and sensitivity between the old and the new guidelines for diagnosing dengue and assessed the usefulness in predicting the clinical course of the disease. Also, we investigated whether hypertension, diabetes or allergies, ethnicity or high age influenced the course of disease.

RESULTS In our setting, the old classification, compared with the new, had a marginally higher sensitivity for diagnosing dengue. The new classification had a slightly higher specificity and was less rigid. Patients with dengue who had warning signs as postulated in the new classification were admitted more often than those who had no warning signs (RR, 8.09 [1.80–35.48]). We did not find ethnicity, age, hypertension, diabetes mellitus or allergies to be predictive of the clinical course.

CONCLUSIONS In our cohort of returned travellers, the new classification system did not differ in sensitivity and specificity from the old system to a clinically relevant degree. The guidelines did not improve identification of severe disease.

keywords dengue, classification system, WHO classification system, disease severity, travellers, dengue haemorrhagic fever

Introduction

Dengue is one of the major challenges for public health in tropical and subtropical regions, with around 2.5 billion people at risk and an estimated 50–100 million cases per year. Dengue fever is caused by the dengue virus, a mosquito-borne flavivirus, which is transferred by mosquitoes of the *Aedes* genus (Halstead 1988; Kouri *et al.* 1989). Until World War II, outbreaks of dengue were reported on almost all continents every 10–30 years, mainly taking a benign clinical course with high fever and bone and back pain (Mairuhu *et al.* 2004).

After 1945, a more severe form of dengue spread dramatically across the world, and cases complicated by haemorrhage and shock were increasingly documented in Southeast Asia (Mairuhu *et al.* 2004).

Many dengue-endemic countries are popular tourist destinations (Jelinek 2000). The disease has been diagnosed in an increasing proportion of febrile travellers, ranging from 2% in the early 1990s to 16% more recently (MacLean *et al.* 1994, Doherty *et al.* 1995; O'Brien *et al.* 2001). The incidence in returning travellers is probably underestimated because in many countries it is not a notifiable condition and because of the non-specific early clinical features of the disease (Gibbons & Vaughn 2002).

In 1974, the WHO Technical Advisory Committee formulated a dengue classification system in Manila, the Philippines, which identified dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Figure 1) (WHO 1975). This system was meant to classify the severity of the disease in endemic areas for triage and medical resource allocation. Also, it was used as an epidemiological tool. The classification was mainly based on clinical data collected in the 1950s and 1960s at the Children's Hospital, Bangkok, Thailand.

Recent research by Balmaseda *et al.* (2005) and Bandyopadhyay *et al.* (2006) suggests that the 1975 classification may not be universally applicable for clinical management, because clinical characteristics of dengue appear to differ in various geographical regions and among

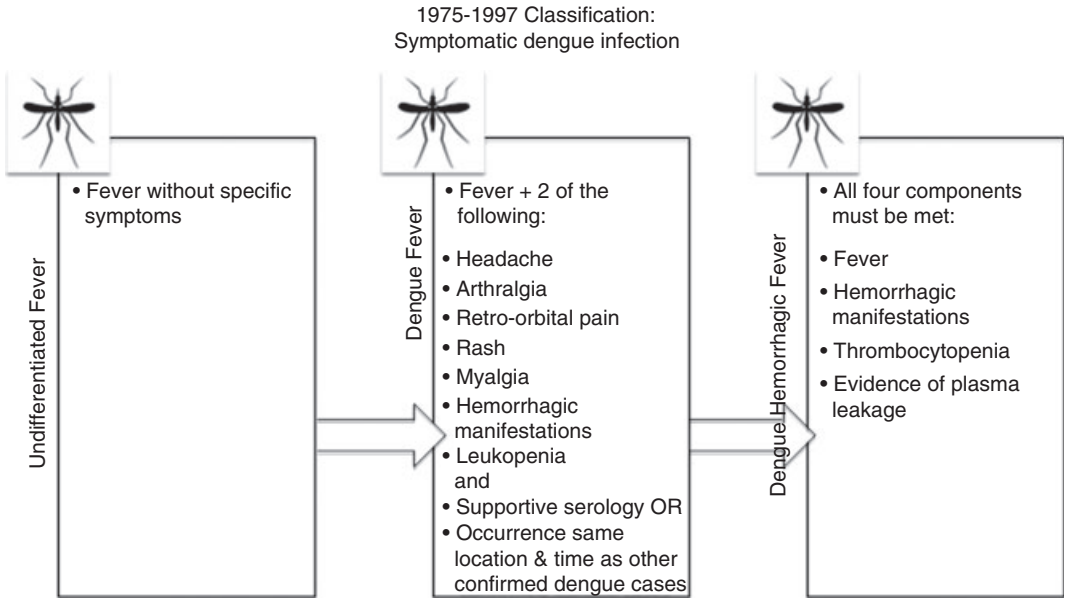

Figure 1 Dengue classification according to the World Health Organization guidelines, issued in 1975 and 1997. Dengue is classified as undifferentiated fever, dengue fever (DF) or dengue haemorrhagic fever (DHF). In addition to fever and at least two clinical findings, diagnosis of DF requires epidemiological or laboratory evidence supporting a dengue virus infection. To meet a case definition of DHF, all the four following criteria are required: (1) fever, (2) haemorrhagic manifestations, (3) thrombocytopenia (platelet count, ≤100000 platelets/mm^3) and (4) evidence of plasma leakage. Diagnosis of DHF does not require laboratory support.

different age groups. Severe clinical features also occurred in patients who did not meet the criteria for DHF, for example patients with organ failure, but without evidence of plasma leakage (Phuong *et al.* 2004; Srikiatkhachorn *et al.* 2010). In response, Alexander *et al.* (2011) developed a new dengue classification system, which is incorporated in the revised WHO guidelines of 2009 (WHO 2009). In these guidelines, a classification according to severity is outlined: dengue fever with and without warning signs, and severe dengue. From clinical data collected in numerous endemic areas worldwide, several clinical symptoms (lethargy, abdominal tenderness, mucosal bleeding, liver enlargement, persistent vomiting, haemoconcentration increase and platelet decrease) were identified as possible predictors of a severe clinical course and defined as warning signs (Figure 2).

Evaluations carried out in dengue-endemic areas have provided promising results, but have also evoked criticism. First, the new system would be too unspecific in defining severe dengue that needs close monitoring, therefore imposing a heavy workload on the health services in resource-poor countries; second, there would be too much focus on unusual dengue manifestations (Barniol *et al.* 2011; Srikiatkhachorn *et al.* 2011).

To date, the new classification had not been widely tested in returning travellers. In this population, the situation is different from permanent inhabitants of endemic areas, where only severe dengue is notified (Phuong *et al.* 2006). By contrast, travellers are inclined to seek medical attention early in the course of their disease. As a consequence, data from travellers better reflect the distribution over the different categories of severity. DHF and DSS are not reported frequently in this population. Of 483 dengue cases in the European Network on Imported Diseases, 2.7% were reported as DHF, with a 4.3 times higher risk among immigrants and travellers visiting friends and family, compared with tourists (Jelinek *et al.* 2002). DSS and death from dengue are uncommon. Two deaths were reported in a series of more than 250 cases of dengue imported into the United States between 1993 and 2000 (MMWR reported weekly Imported dengue US 1993–2000).

We compared the old and the proposed new dengue classification system in returning travellers for whom dengue serology was requested. We used clinical and laboratory characteristics of these patients to assess whether the warning signs as postulated by Alexander *et al.* (2011) apply to returning travellers, whether sensitivity and specificity of both diagnosing dengue classification systems differed, and whether clinical data currently gathered at the Academic Medical Center (AMC) were sufficient to categorise patients according to the proposed guidelines.

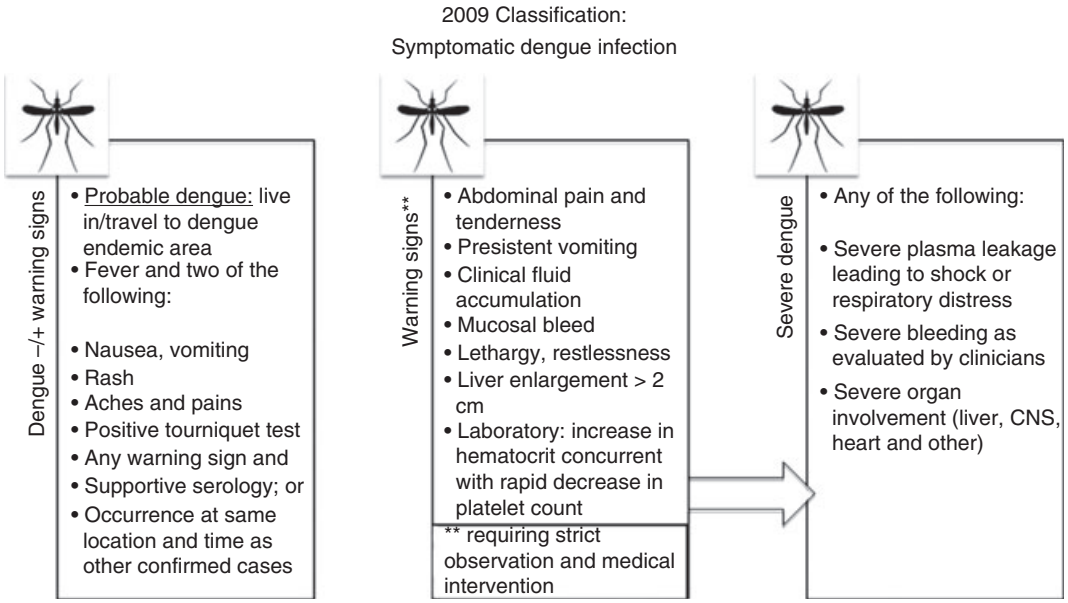

Figure 2 Dengue classification according to the World Health Organization guidelines, issued in 2009. Dengue is classified as dengue with or without warning signs and severe dengue. Diagnosis of dengue requires the presence of fever and at least two clinical findings or any warning signs. Epidemiological or laboratory evidence is required to make the diagnosis. Severe dengue is defined as dengue with any of the following: (1) severe plasma leakage leading to shock or respiratory distress, (2) severe haemorrhage or (3) any organ failure.

In the past, factors such as age, ethnicity and several chronic medical conditions (diabetes, hypertension and allergies) were described as potentially influencing severity of the disease, owing to alterations in the inflammatory response of the endothelium (Kouri *et al.* 1987; Cunha *et al.* 1999; Halstead *et al.* 2001; Lee *et al.* 2008; Figueiredo *et al.* 2010). Therefore, we analysed whether these factors influenced severity of the course of the disease.

Materials and methods

Setting

Up to 2008, around 15/1500 (1.0%) of ill returning travellers were annually diagnosed with a dengue virus infection in the AMC Amsterdam. During the dengue outbreak in 2008 in the Netherlands Antilles, these numbers rose to 50/1500 (3.3% of post-travel patients) and have remained at that level since then (data not shown).

Patient inclusion

We analysed patient data from all patients who were serologically tested for dengue at the AMC between 2006 and 2011. We removed double tests and excluded patients not treated in the AMC, missing patient files and patients who consulted the AMC more than 6 months after the onset of their symptoms and those who had not travelled.

Ethical issues

All patients attending the outpatient department of tropical and travel medicine are informed that routinely collected data may be used for scientific research, and no additional ethical clearance was needed.

Data inclusion

Information on demographic data, medical history and medication, serologic results, travel destination and travel period and duration were obtained from electronic patient files. Days of illness prior to presentation were recorded, as well as days from first day of illness to first laboratory results.

All symptoms (fever, headache, retro-orbital pain, myalgia, arthralgia, petechiae, morbilliform rash, abdominal pain/tenderness, nausea/vomiting, persistent vomiting, oedema, mucosal bleeding, lethargy/restlessness) were noted if reported by either patient or physician. Body temperature, blood pressure and liver enlargement as recorded by the physician were noted.

If physical examination was performed but symptoms were not reported, it was assumed they were not present. Lethargy was defined as extreme fatigue or through descriptions indicating extreme fatigue.

Virology

During the first 15 months of the study period, serology was performed by two different methods: immunochromatographic IgM and IgG strip assay (Dengue Duo Rapid Strip Test; PanBio, Brisbane, Australia) and ELISA (Dengue Duo IgM/IgG capture ELISA; Panbio). Because similar sensitivities and specificities for dengue IgM were observed, the use of the ELISA was discontinued after 15 months. As sensitivity of IgG of the immunochromatographic assay is low, positive IgG can be defined as a secondary infection (Blacksell *et al.* 2006). If dengue infection was highly suspected but the immunochromatographic test remained negative, samples were sent to an external laboratory for ELISA (Dengue Virus IgG and IgM Capture DxSelect; Focus Diagnostics, Cypress, CA, USA).

Definitions

Serologic confirmation of dengue was defined as seroconversion of dengue specific IgM or at least a fourfold increase in DEN specific IgG, if the ELISA test was applied (World Health Organization 1975, 2009). If possible, two serologic samples were tested from each patient: one in the initial phase and one in the convalescent phase.

Often only one sample was available. As the WHO guidelines use a cut-off of 5 days after the initiation of symptoms for IgM rapid tests and IgM ELISA to be usable (World Health Organization 2009), we defined one-sample outcomes as follows: *positive serology* – samples with positive IgM or IgG obtained >5 days after onset of symptoms, samples with positive/borderline IgM or IgG obtained ≤5 days after onset of symptoms; *indeterminate serology* – samples with borderline positive IgM obtained >5 days after onset of symptoms and borderline/negative IgG, samples with negative IgM and IgG obtained ≤5 days after onset of symptoms; *negative serology* – samples with borderline/negative IgG and negative IgM obtained >5 days after the onset of symptoms.

Dengue diagnosis was defined as both serologic confirmation and an epidemiological and clinical picture of dengue. No dengue was defined as negative serology and no clinical picture of dengue. All others were classified as indeterminate.

Thrombocytopenia was classified into ≤150 000 platelets/mm^3 and ≤100 000 platelets/mm^3. Leucocytopenia was defined as <4000/mm^3. Leucocytes and thrombocytes measured more than 28 days after onset of symptoms were considered irrelevant.

Haematocrit was frequently determined, but baseline measurements were often not available. We therefore determined haemoconcentration as a rise of haematocrit >20% above the maximum normal range stratified for sex.

Patients were classified according to the old and the new classification system. Rates of 'probable dengue' according to the old 1997 WHO definition (Figure 1) and the new 2009 classification system (Figure 2) were determined. Patients were classified as having DHF if they had all four symptoms as described in the 1997 WHO definition. Patients were defined as having dengue with warning signs if they had probable dengue and one of the warning signs as defined by the WHO in 2009.

Travel destinations were recorded as described by Freedman *et al.* (2006). If travellers visited more than one continent, their journey was defined as a world trip.

Analysis

Statistical analysis was performed using the PASW statistics 18 software package (IBM, Chicago, IL, USA). For patients with dengue, we compared the number of patients that met criteria for 'probable dengue' in the old vs. the new classification system. Specificity and sensitivity of the old and the new classification were determined, with 'probable dengue' as an outcome measure and diagnosed dengue as gold standard, excluding indeterminate results.

We compared hospital admissions in patients with and without warning signs, using a chi-square test. We determined whether age, ethnicity, hypertension, allergies and diabetes were associated with hospitalisation and warning signs in those diagnosed with dengue using Pearson's chi-square test or Fisher's exact test.

Results

In total, 1124 tests were obtained. After exclusion of those treated outside the AMC (200), double tests (285), missing files (31), onset of symptoms >6 months prior to consultation (14) and not having travelled (13), 581 patients remained.

Of these patients, 132 (22.7%) were diagnosed with dengue, 277 (47.7%) were diagnosed with no dengue, and 172 (29.6%) had indeterminate results (Table 1). In 17 indeterminate cases, serology and antigen tests were negative, but the clinical and epidemiological presentation was highly suggestive for dengue. In 31 indeterminate cases, serology was positive, but there was no clinical and epidemiological presentation typical of dengue. In 124

Table 1 Characteristics of study population

	Dengue	No Dengue	Indeterminate	Total
Total	132	277	172	581
Male (%)	63 (47.7)	132 (47.6)	72 (41.9)	267 (46.0)
European ethnicity (%)	91 (68.9)	173 (62.5)	117 (68.0)	381 (65.6)
Age				
Median	36	36	33	36
Interquartile range	28.0–51.3	27.0–47.0	26.0–48.0	27.0–47.0
Hospital admissions (%)	10 (7.6)	36 (13.0)	25 (14.5)	71 (12.2)
Probable dengue 1975 scheme (%) Sensitivity old scheme: 84.1% Specificity old scheme: 43.3%	111 (84.1)	157 (56.7)	98 (57.0)	366 (63.0)
Probable dengue 2009 scheme (%) Sensitivity new scheme: 81.1% Specificity new scheme: 46.2%	107 (81.1)	149 (53.8)	90 (52.3)	346 (59.6)
Dengue with warning signs (%)	44 (33.3)	59 (21.3)	35 (20.3)	138 (23.8)

'indeterminate' cases, serology was indeterminate without clinical suspicion of dengue.

In 449/581 (77.3%) cases, one serologic sample was available; for 132 (22.7%) cases, samples in the initial and convalescent phase were collected. In 61/132 (46.2%) confirmed cases, serologic diagnosis was based on positive IgM in one sample.

Clinical symptoms and travel destinations

Symptoms and travel destinations of the 132 confirmed dengue patients are recorded in Tables 2 and 3. A total of 111 of 132 patients fulfilled the criteria of probable dengue, and 120 of 277 patients not diagnosed with dengue were negative according to the old system (sensitivity, 84.1%; specificity, 43.3%). One hundred and seven of 132 patients fulfilled the criteria of probable dengue in the revised system, and 128 of 277 patients not diagnosed with dengue were negative according to the new system (sensitivity 81.1%, specificity 46.2%). Haemorrhagic manifestations were reported in 52 patients (8.9%) of the total population and in 22 (16.7%) of the dengue population. There were no patients who fulfilled the criteria of DHF. Dengue with warning signs was recorded in 44 patients, eight of whom were hospitalised.

Hospital admissions

In the total population, 71/581 (12.2%) were admitted versus 10/132 (7.6%) of those diagnosed with dengue. Patients with warning signs were more often admitted than those without warning signs in the total population with suspected dengue (RR, 1.43 [0.90–2.28]; $P = 0.126$). In those diagnosed with dengue, differences were significant (RR, 8.09 [1.80-35.48]; $P = 0.001$). Reasons for hospital admission in this group were high fever and severe illness (6), decreased fluid intake (2), suspicion of abdominal typhus (1) and hypotension (1). All admitted patients made a full recovery.

Risk factors, warning signs and hospital admission

Twenty-eight patients with dengue (21.2%) had a medical history, of whom 10 reported hypertension, three diabetes mellitus and five allergies. Nine of 132 patients with dengue (6.8%) were aged over 60 and 91 patients (68.9%) were of European origin. With regard to hospital admission or warning signs, no significant differences were found in those with and without a medical history in general, hypertension, allergies or diabetes mellitus (data not shown). Neither ethnicity nor age >60 were risk factors for hospital admission (data not shown).

Missing reported symptoms

Missing reported symptoms for defining 'probable dengue' were comparable in both classification systems (Table 2). The tourniquet test was never performed. To diagnose DHF, four separate symptoms are mandatory. In our data, only 14.4% of cases exhibited all four symptoms. Dengue with warning signs is diagnosed if one warning sign is present. In all cases, at least one warning sign was recorded.

Discussion

This study was carried out to assess whether the new classification system is applicable to returning travellers. The assessment was carried out by comparing the current and the proposed WHO classification scheme in their potential to identify dengue and severe cases of dengue. Also, we assessed specific risk factors for travellers heading to endemic areas.

Table 2 Clinical findings of 132 patients diagnosed with dengue on serological and clinicoepidemiological grounds

1997 Classification	Positive (%)	Negative (%)	Missing (%)
Fever*	123 (93.2)	4 (3.0)	5 (3.8)
Headache	98 (74.2)	8 (6.1)	26 (19.7)
Retro-orbital pain	44 (33.3)	15 (11.4)	73 (55.3)
Rash	88 (66.7)	22 (16.7)	22 (16.7)
Myalgia	80 (60.6)	13 (9.8)	39 (29.5)
Arthralgia	52 (39.4)	19 (14.4)	61 (46.2)
Petechiae	16 (12.1)	65 (49.2)	51 (38.6)
Leucopenia	22 (16.6)	62 (47.0)	48 (36.4)
Haemorrhagic manifestations*	6 (4.5)	98 (74.2)	28 (21.2)
Thrombocytopenia ≤100 000 platelets/mm^3*	57 (43.2)	63 (47.7)	12 (9.1)
Rise in haematocrit*	16 (12.1)	72 (54.5)	44 (33.3)
All 4 recorded in chart: 19 (14.4%)			
2009 Classification			
Fever	123 (93.2)	4 (3.0)	5 (3.8)
Nausea, vomiting	42 (31.8)	32 (24.2)	58 (43.9)
Rash	88 (66.7)	22 (16.7)	22 (16.7)
Aches and pains	122 (92.4)	10 (7.6)	0 (0)
Tourniquet test positive	0 (0)	0 (0)	132 (100)
Leucopenia	57 (43.2)	63 (47.7)	12 (9.1)
Tender abdomen†	25 (18.9)	96 (72.7)	11 (8.3)
Persistent vomiting†	0 (0)	74 (56.0)	58 (43.9)
Clinical fluid collection†	0 (0)	94 (71.2)	38 (28.8)
Mucosal bleeding†	10 (7.6)	88 (66.7)	34 (25.8)
Fatigue/lethargy†	28 (21.2)/9 (6.8)	49 (37.1)	46 (34.8)
Enlarged Liver†	6 (4.5)	98 (74.2)	28 (21.3)
Rise in Haematocrit†	1 (0.8)	66 (50.0)	65 (49.2)
At least 1 warning sign recorded in chart: 100%			

*Criteria for dengue haemorrhagic fever: (1) fever, (2) haemorrhagic manifestations, (3) thrombocytopenia (platelet count, ≤100 000 platelets/mm^3) and (4) evidence of plasma leakage (rise in haematocrit).
†Warning signs.

Table 3 Travel destinations of 132 travellers diagnosed with dengue

	Destinations N = 132 (%)
Caribbean	31 (23.4)
Central America	7 (5.3)
South America	31 (23.5)
South Central Asia	8 (6.1)
Southeast Asia	48 (36.4)
Sub-Saharan Africa	4 (3.0)
Other*	3 (2.3)

*Other destinations were North Africa, Europe, Oceania, Northeast Asia and where travellers went on a world trip.

We found that sensitivity for diagnosing probable dengue was slightly higher in the old system than in the new system, and specificity was higher in the new system than the old. The small differences we found are probably not clinically relevant.

In those diagnosed with dengue, we found that significantly more patients with warning signs were admitted than those without. There were no cases of dengue with severe haemorrhagic manifestations or shock. If we assume hospital admission to be a clear indicator of potential severe disease, we may conclude that in all returning travellers in whom there is a suspicion of dengue, the presence of warning signs should be taken into account. However, only a small percentage of those with warning signs needed hospital admission, and warning signs themselves did not seem to help in identifying those who needed intervention.

Several criteria for diagnosing DHF in the old classification system are not used in routine clinical practice in many institutions (as well as ours) as their diagnostic value is not considered as high as other clinical signs: for example, the tourniquet test, which is scarcely performed, and hypoproteinaemia, which is rarely quantified. The tourniquet test is also used in the new classification

system; however, here it is one of many warning signs and not one of the required symptoms to diagnose severe disease.

We did not find medical history, age or ethnicity to be a predictor of either clinical severity or hospital admissions, contradictory to findings of previous studies. Possibly, our small group size plays a role in this outcome. Patients diagnosed with dengue had often travelled to Southeast Asia, the Caribbean and South America.

Limitations of the study

Theoretically, patients with complications could have been missed in our retrospective cohort. Some studies recommend daily assessment (Wilder-Smith & Schwarz 2005). However, the chance that we missed admissions in other hospitals is small, as patients are routinely told to contact us in case of physical deterioration.

We did not carry out repeated measurements of haematocrit, and measurements of plasma leakage (in the form of ultrasound and chest X-rays), if it was not clinically indicated. For this reason, possibly, a certain degree of plasma leakage could have been missed in our patients. Previous studies have noted plasma leakage in a significant amount of returning travellers (Meltzer *et al.* 2012). This probably will not have much impact on the number of cases classified as DHF, but possibly would have increased the rate of those with warning signs.

Our study population only included patients for whom serology was requested. However, sensitivity and specificity may be different if a total population of travellers returning with fever would be included. We reason, however, that the sensitivity and specificity of recognizing probable dengue in this group are relevant, as these are the patients in whom dengue is featuring in the differential diagnosis and therefore those where the dengue classification system might be applied.

As a result of the high rate of indeterminate cases, our results may be biased. Seventeen patients were diagnosed with probable dengue on clinical and epidemiological grounds, without serologic confirmation and therefore were in the group of 'indeterminate' dengue. Perhaps these patients had not yet seroconverted, and no sample was taken in the convalescent phase. The rapid immunochromatographic assay has been extensively evaluated in India, Southeast Asia and the Caribbean, showing sensitivity from 45% to 100% and specificity from 57% to 100% (Blacksell *et al.* 2006). Sensitivity was highest when samples were collected later in the acute phase of infection. Another reason could be that the antigen tests were false negative in these patients or that a dengue-like illness, such as chikungunya, caused a clinical picture with negative serology in this group. A total of 155 patients had positive or indefinite serology without a clinicoepidemiological picture of dengue. This might be due to cross-reactivity with other flaviviruses such as yellow fever or Japanese encephalitis (Teles *et al.* 2005).

Conclusion

In our study, sensitivity and specificity of the old and the new classification system of dengue were comparable. We did not find any pre-existing condition to be predictive of severity. Warning signs as postulated in the new guidelines were present more often in those most ill. However, they will probably not help in the identification of those few patients with warning signs who need medical intervention. The new classification system, although more practical in use, was not superior to the old one in our traveller population. Further prospective multicentre studies are needed to establish a common understanding of the value of the current classification.

Acknowledgement

We thank all Tropencentrum patients and staff for their support.

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