DISCUSSION PAPERS ON CHILD HEALTH

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Dengue, Dengue Haemorrhagic Fever and Dengue Shock Syndrome in the Context of the Integrated Management of Childhood Illness

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List of abbreviations

AFR	WHO African Region
AMR	WHO/PAHO Americas Region
DF	dengue fever
DHF	dengue haemorrhagic fever
DSS	dengue shock syndrome
IMCI	Integrated Management of Childhood Illness
ORS	Oral Rehydration Solution
PAHO	Pan-American Health Organization
SEAR	WHO South-East Asian Region
TT	Tourniquet test
WHO	World Health Organization
WPR	WHO Western Pacific Region

Executive summary

Dengue is not included in the generic Integrated Management of Childhood Illness (IMCI) algorithm but it is an important differential diagnosis of fever in children presenting to first-level health facilities in tropical Asia and Latin America. There has been no previous summary of existing dengue guidelines to explore their usefulness in the context of IMCI and to identify questions for research.

This review summarises the virology, transmission and pathogenesis of dengue, its significance by region, and its epidemiologic, demographic, and clinical features; assesses existing diagnostic guidelines; evaluates the evidence-base for current treatment guidelines; examines IMCI adaptations of dengue algorithms; and discusses experience with home management of dengue and recognition of specific clinical signs and symptoms by caretakers. The studies included in this review were identified by a search on PubMed of the scientific literature published in English from 1966 to the present.

Based on this review, further development of dengue algorithms is suggested, followed by recommendations for necessary research and for country-specific adaptations.

Introduction

Dengue is an important differential diagnosis of fever in children presenting to first-level health facilities in tropical Asia and Latin America. Dengue is not included in the generic Integrated Management of Childhood Illness (IMCI) algorithm, but due to its importance, it was incorporated in several Asian and Latin American IMCI adaptations. Most of these adaptations have not been tested for their performance.

Prior to and in parallel with IMCI, there have been guidelines developed on the management of dengue. The "Guidelines for Treatment of Dengue Fever/Dengue Hemorrhagic Fever in Small Hospitals" developed by the WHO Regional Office is widely used (1).There has been no previous summary of existing dengue guidelines to explore their usefulness in the context of IMCI and to identify questions for research. The objectives of this review are:

- to summarise the virology, transmission and pathogenesis of dengue, its significance by region, and its epidemiologic, demographic, and clinical features;
- to assess existing diagnostic guidelines;
- to evaluate the evidence-base for current treatment guidelines;
- to examine IMCI adaptations of dengue algorithms;
- to search the literature for experience with home management of dengue and recognition of specific clinical signs and symptoms by caretakers; and
- to make suggestions for how to proceed in terms of further development of dengue algorithms, research, and country-specific adaptations.

The studies included in this review were identified by a search on PubMed of the relevant scientific literature published in English from 1966 to the present. Dengue was linked with the following key words: virology, antibody, transmission, pathogenesis, incidence, prevalence, distribution, burden, epidemiology, diagnosis, haemorrhage, shock, treatment, algorithms, home care, treatment seeking, and IMCI. Other material was obtained from various sources (e.g. WHO website and unpublished reports).

Background

VIROLOGY, TRANSMISSION, AND PATHOGENESIS

Dengue is caused by infection with one of four dengue virus serotypes, i.e. dengue 1-4. Infection with one serotype provides life-long immunity against reinfection by that same serotype, but not against the other serotypes. The vast majority of dengue infections are asymptomatic but a proportion manifest as a non-specific febrile illness or progress to severe disease.

Aedes aegypti is the principal mosquito vector of dengue. Adult mosquitoes shelter indoors and bite during the daytime. They are adapted to breed around human dwellings, in water containers, vases, cans, old tyres and other discarded objects (2). The secondary vector for dengue virus is *Ae albopictus*, which contributes significantly to transmission in Asia and whose presence is spreading in Latin American countries. Dengue outbreaks have also been attributed to *Ae polynesiensis* and *Ae scutellaris*, but to a lesser extent.

Uninfected mosquitoes acquire the virus when they feed on a viraemic individual. The virus develops in the mosquito for 1 to 2 weeks and once it reaches the salivary glands, it can be transmitted to humans during feeding attempts, which may occur several times a day over the rest of the mosquito's lifetime of 1 to 4 weeks (total). The virus can have a significant transmission potential (Ro) in certain areas (3). After an infectious mosquito bite, the virus replicates in local lymph nodes and within 2 to 3 days disseminates via the blood to various tissues. The virus circulates in the blood typically for 4 to 5 days during the febrile phase and is cleared within a day of defervescence (4).

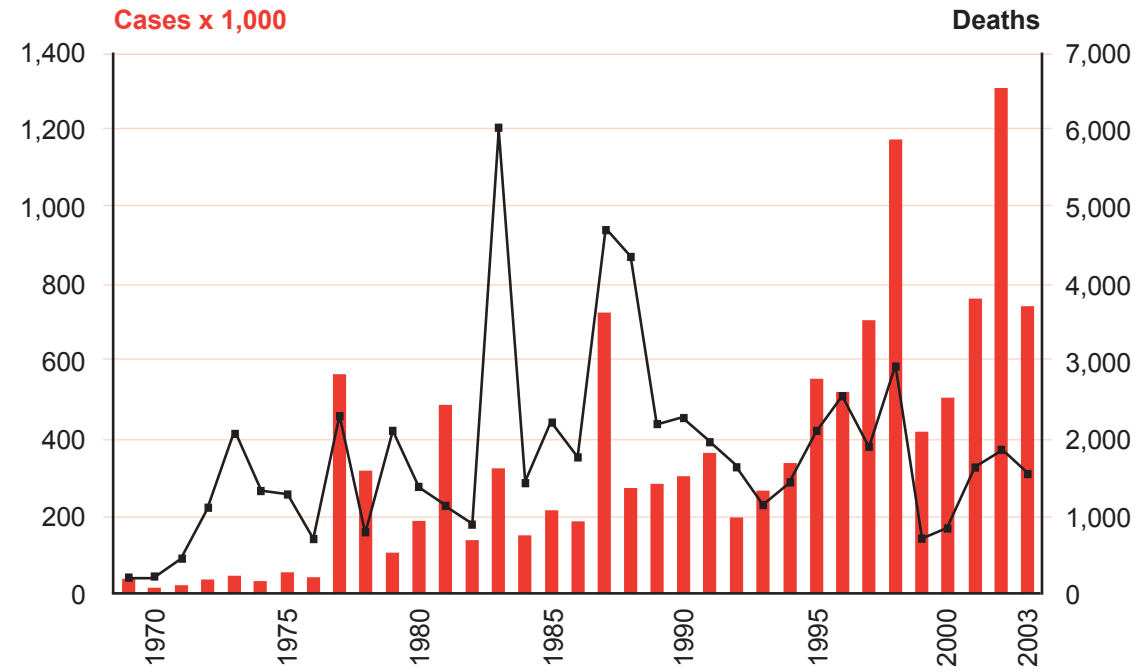
The pathogenesis of severe dengue is not well understood. It has been observed that the risk of severe disease is increased at least 15-fold during repeat (secondary) compared to primary dengue infections (5). Various mechanisms have been suggested, including antibody-dependent enhancement or ADE (6, 7), complement activation by virus-antibody complexes (8, 9) and T-cell mediated immunopathology (10). Differences in virulence of viral genotypes have also been suggested to explain the pathogenesis of severe dengue (11-13).

The dominant hypothesis, ADE, postulates that during secondary infection, pre-existing non-neutralising antibodies opsonise the virus and enhance its uptake and replication in macrophages. Secondary infections have been shown to lead to higher viral loads and the manifestations of severe dengue are believed to be due to virus replication which induces infected monocytes to release vasoactive mediators (14-16). ADE may not completely explain the pathogenesis of severe dengue but it seems clear that immune potentiation plays a pivotal role. More recently, investigators have speculated that profound T-cell activation and death may contribute to the systemic disturbances leading to severe dengue, and original antigenic sin in the T-cell responses may suppress or delay viral elimination, leading to higher viral loads and increased immunopathology (17).

SIGNIFICANCE OF THE PROBLEM

An estimated 500,000 cases of severe dengue require hospitalisation each year, of which a very large proportion is in children. At least 2.5% of cases die, although case fatality could be twice as high (18). The figure below shows the rise in the annual number of dengue cases worldwide reported to WHO.

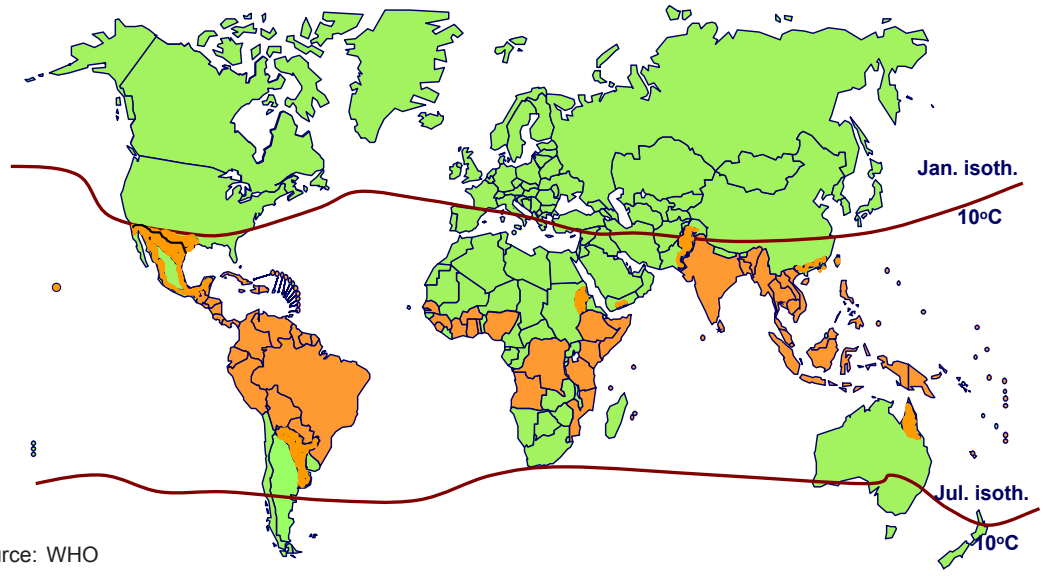
Figure 1. Annual number of DF/DHF cases and deaths reported to WHO, 1969-2003



Source: WHO

Although mild dengue infections have been recognised for years, the first epidemic of severe dengue was reported in the Philippines in 1953. This rapidly spread to Thailand, Viet Nam, Indonesia, and other Asian countries, becoming endemic and epidemic in several of them. Before 1970 only nine countries had experienced severe dengue epidemics, a number that had increased more than four-fold by 1995 (18). The burden of disease is greatest in Asia, where in many countries dengue is a leading cause of paediatric hospitalisation. The figure below shows the global distribution of dengue.

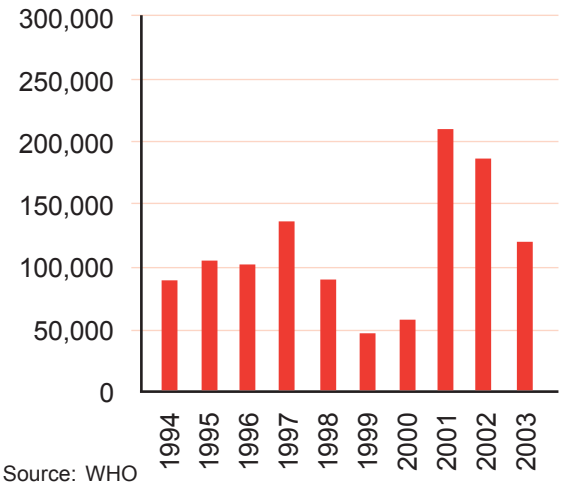
Figure 2. Worldwide distribution of dengue, 1975-1996



Source: WHO

The countries belonging to the WHO South-East Asian Region (SEAR) are stratified in terms of dengue endemicity (19). In Indonesia, Myanmar and Thailand, epidemics have been caused by all four virus serotypes during the past 20 years. In addition, multiple virus serotypes are circulating, there is high morbidity in children, and epidemics occur in urban centres every 3 to 5 years. In Bangladesh, India, Maldives and Sri Lanka, dengue is an emerging disease, epidemics are becoming more frequent, multiple virus serotypes are circulating, and the disease is spreading within countries. In Bhutan and Nepal, there are no reported cases and endemicity is uncertain. Overall reported cases of dengue from 1994 to 2003 are shown in the figure below.

Figure 2. Reported cases of DF/DHF, 1994-2003 (South-East Asia Region)



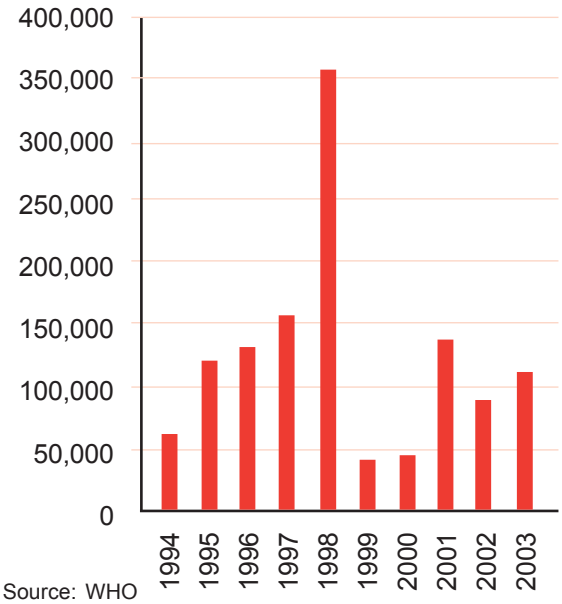
Source: WHO

Countries included in this WHO region

Bangladesh
Bhutan
Democratic People's Republic of Korea
India
Indonesia
Maldives
Myanmar
Nepal
Sri Lanka
Thailand

Thirty-three of the 37 countries belonging to the WHO Western Pacific Region (WPR) have epidemic dengue (20). Reported cases from 1994 to 2003 are shown in the figure below. Singapore has been the one country in the

Figure 3. Reported cases of DF/DHF, 1994-2003 (Western Pacific Region)



Source: WHO

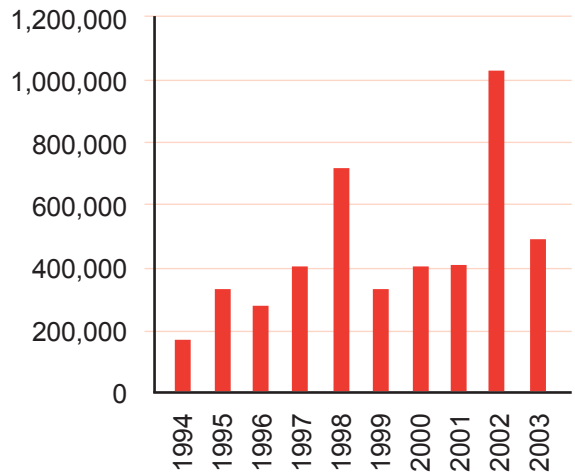
Countries included in this WHO region

Australia
Brunei Darussalam
Cambodia
China
Cook Islands
Fiji
Japan
Kiribati
Korea, Republic of
LaoPDR
Malaysia
Marshall Islands
Micronesia, Fed.States
Mongolia
Nauru
New Zealand
Niue
Palau
Papua New Guinea
Philippines
Singapore
Solomon Islands
Tokelau
Tonga
Tuvalu
Vanuatu
Vietnam
Western Samoa

region, which has been able to maintain a low incidence of dengue through an integrated mosquito control programme incorporating source reduction, health education and law enforcement implemented since 1969 (21,22). However, it has been recently shown that a very high degree of elimination of the vector in dengue-prone areas needs to be achieved and sustained in order to control transmission (23).

The first epidemic of severe dengue in the Americas occurred in Cuba in 1981 and subsequently 24 other countries in the region have reported severe dengue (24). The figure below shows the cases reported by the WHO/PAHO Americas Region (AMR) from 1994 to 2003. In 2002, widespread epidemics of severe dengue were reported in Brazil, Colombia, Cuba, Ecuador, El Salvador, Honduras, Peru, and Venezuela (25, 26).

Figure 4. Reported cases of DF/DHF, 1994-2003 (Americas Region)



Source: WHO

Countries included in this WHO region

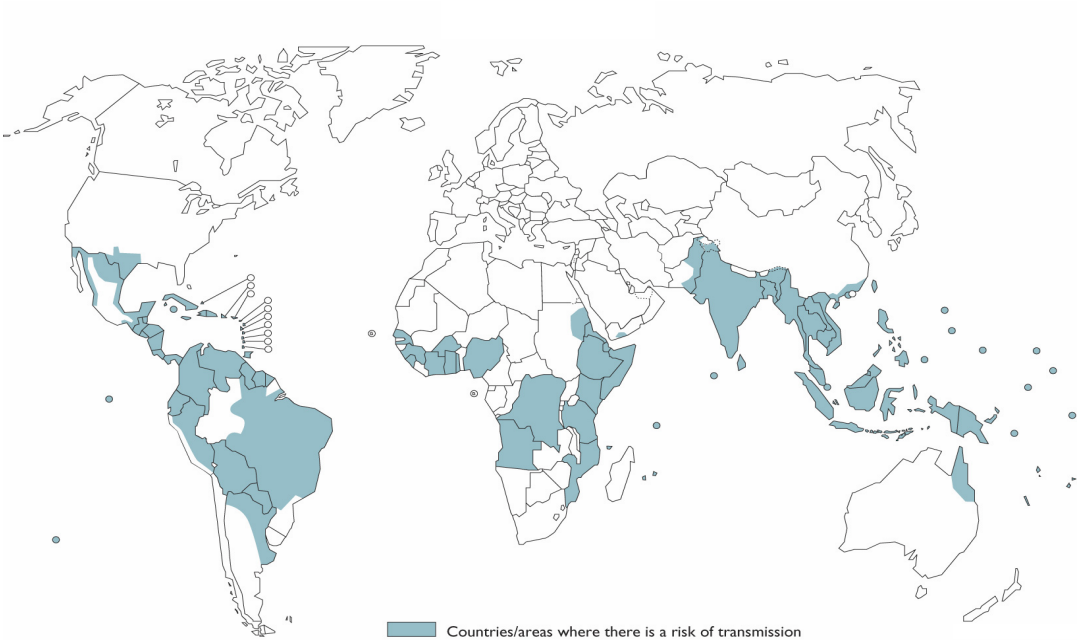
Antigua and Barbuda
Argentina
Bahamas
Barbados
Belize
Bermuda
Bolivia
Brazil
Canada
Chile
Colombia
Costa Rica
Cuba
Dominica
Dominican Rep.
Ecuador
El Salvador
Grenada
Guatemala
Guyana
Haiti
Honduras
Jamaica
Mexico
Nicaragua
Panama
Paraguay
Puerto Rico
Peru
St Kitts and St.Christopher/ Nevis
St Lucia
St. Vincent and Grenadines
Suriname
Trinidad and Tobago
United States of America
Uruguay
Venezuela

The bar graphs from the three regions, which are based on routine national reporting systems, provide some insight into the burden of dengue but their shortcomings need to be appreciated. Dengue is difficult to diagnose. Some countries report severe dengue cases only; others report all dengue cases. Some countries report only laboratory-confirmed cases whereas others report suspected cases as well. Problems of over- and under-diagnosis, incomplete reporting, and delays also weaken the data (27). To overcome some of these problems, the WHO has recently developed and piloted “DengueNet”, an internet-based reporting system for dengue.

Other than tropical Asia, Latin America and the Caribbean, there are areas of the world (infested with *Ae aegypti*) that have the potential for dengue transmission, as shown in the map below (28). In the WHO African Region (AFR), the dengue viruses circulate and infections occur but severe dengue is not reported (29, 30). This observation and findings in Haiti have led to the hypothesis of a dengue resistance gene in black populations (31).

This review will focus on tropical Asia and Latin America and the Caribbean.

Figure 6. Areas infested with *Aedes aegypti* and with dengue epidemic activity, 2003



Source: WHO

EPIDEMIOLOGIC AND DEMOGRAPHIC PARAMETERS

The age-specific incidence of symptomatic dengue infections varies between regions. The IMCI algorithm is for children less than five years of age. Thus, the burden of dengue in this age group should determine whether it should be included in the algorithm. The incidence of symptomatic disease by age group is discussed below.

a) In hyper-endemic Asian countries where there is concurrent transmission of multiple serotypes and cyclical epidemics, primary dengue infection usually occurs in young children and produces few symptoms. Occasionally, severe dengue is noted in infants less than one year of age and is attributed to the presence of maternal antibody (32). In general, symptomatic dengue and severe disease, associated with secondary or repeat infections, occur in older children (33-38). As tabulated below, 25 to 37% of symptomatic dengue requiring hospitalization is reported in children 5 to 9 years of age. The data from Children's Hospital No 1 in Ho Chi Minh shown below is unusual in having a relatively disproportionate amount of cases among children less than five years of age but this may simply be because proportions are skewed by the exclusion of those over 15 years of age (who are not admitted to this hospital).

Table 1. Age distribution of dengue cases from hospital-based studies in hyper-endemic Asian countries

Hospital and year	Diagnosis and number (n)	Percentage of cases by age group			
		Less than 5 years	5 to 9 years	10 to 14 years	Over 15 years
San Lazaro Hospital, Manila, Philippines, 1983-1984 (39)	Laboratory-confirmed dengue cases, n = 517	15%	36%	26%	23%
Children's Hospital No 1, Ho Chi Minh City, Viet Nam, 1996 (40)	Clinically suspected dengue cases, n = 4,011	34%	37%	29%	N/A
M Hoesin Hospital and Charitas Hospital, Palembang, South Sumatra, Indonesia, 1998 (41)	Clinically suspected dengue cases n = 1772	16%	25%	59%	

Population-based prospective studies focusing on children beyond infancy have shown that the incidence of dengue varies geographically and from year to year, as shown below.

Table 2. Incidence of laboratory-confirmed symptomatic dengue from population-based prospective studies in hyper-endemic Asian countries

Study site	Population size	Age range	Study period	Incidence
Yangon, Myanmar (38)	~ 12489	1 to 9 years	1984 to 1988	0.3% (hospitalised dengue cases/year)
Bangkok, Thailand (33)	1757	4 to 16 years	June 1980 to January 1981	0.7% (symptomatic dengue cases over 1 season)
Yogyakarta, Indonesia (35)	1837	4 to 9 years	1995 to 1996	0.6% (symptomatic dengue cases/year)
Kamphaeng Phet, Thailand (42)	2119	7 to 11 years	June 1998 to November 1998	3.6% (symptomatic dengue cases over 1 season)
	1928		June 1999 to November 1999	3.3% (symptomatic dengue cases over 1 season)
	1713		June 2000 to November 2000	0.8% (symptomatic dengue cases over 1 season)

In some countries a gradual shift in peak attack rate towards older age groups has been noted (43). This is most dramatically seen in Singapore where there has been a decade of successful mosquito control. In a recent report, less than 1% of children 10 months to 5 years old and only 7% of those 6 to 10 years of age were

found to have dengue antibodies (21) and the peak dengue mortality has moved from children to adults (44). In Bangkok, the median age of hospitalised dengue cases has increased progressively from 3 years and 10 months in the sixties, to 5 years and 7 months in the seventies, 7 years and 5 months in the eighties (45) and to a mean of 8 years in the nineties (46). Economic development with improvements in housing and sanitation and the resulting decreased exposure of young children to the mosquito vector is perhaps responsible for this shift.

b) In Asian countries where dengue is an emerging disease, outbreak investigations report dengue in all ages but adults appear to be more affected, as presented in a report from India and Bangladesh below.

Table 3. Age distribution of hospitalized dengue cases during outbreaks in Asian countries where dengue is an emerging disease

Location, year, and number (n)	Percentage of cases by age group			
	Less than 5 years	5 to 10 years	11 to 20 years	21 years and older
Lucknow, India, 1996, n = 206 (47)	9%	12%	23%	56%
Dhaka, Bangladesh, 2000, n = 176 (48)	~ 6%		~ 94% (82% in adults 18 years and older)	

c) In Latin American and Caribbean countries, the incidence of dengue has grown rapidly during the past two decades and circulating virus serotypes have gone from none to single to multiple. However, case fatality rates are still lower than those in tropical Asia, as shown below (49) and this is probably due to the lower ratio of severe to mild disease but there may be other explanations.

Table 4. Dengue case fatality rate (%), by region, 1998-2000

	1998	1999	2000
SEAR	1.4	1.0	0.3
WPR	0.4	0.2	N/A
AMR	N/A	0.03	0.02

In contrast to hyper-endemic Asian countries where severe dengue is considered a children's disease, in Latin American and Caribbean countries, severe dengue affects both children and adults and there have been epidemics affecting only adults (50). A comparison of clinical manifestations of severe dengue in children and adults as reported in five different studies from Cuba, Puerto Rico, India and Thailand showed variability in the frequency of certain manifestations including rash, abdominal pain, and hepatomegaly (50).

CLINICAL FEATURES

Classic dengue or "break bone fever" is characterized by a sudden onset of high-grade fever, severe headache, pain behind the eyes, nausea, vomiting, rash and a low total white blood cell count. Although thrombocytopaenia and bleeding of varying severity are features of severe dengue, these may also occur in milder disease (51). Classic dengue fever is usually self-limiting.

The hallmark of progression to severe dengue is increased vascular permeability and consequent plasma leakage (14, 52). Plasma leakage may become severe enough to cause circulatory compromise and shock. If shock occurs, it usually takes place after 2 to 5 days of fever. Patients with severe dengue have coagulation abnormalities but these are not severe enough to cause major bleeding. When major bleeding does occur, it is almost invariably associated with profound shock since this, in combination with thrombocytopaenia, hypoxia, and acidosis, can lead to multiple organ failure and disseminated intravascular coagulation (53-57). In an analysis of 77 patients with severe dengue in Kuala Lumpur, Malaysia, the factor that most determined outcome was duration of hypovolaemic shock (58). In Cebu, Philippines, increased risk for death in children with severe dengue was associated with late presentation to hospital (59). Severe dengue may also be characterised by unusual manifestations where the risk of death is high. These include hepatic damage, cardiomyopathy, encephalopathy, and encephalitis (60-62).

Hospital-based studies on the risk of shock and death in severe dengue in tropical Asian countries were reviewed. The percentage of admitted cases who developed shock ranged from 9 to 60% with in-hospital case fatality rates ranging from 0.2 to over 9%.

Table 5. Hospital-based, descriptive studies on severe dengue in Asia

Authors	Study period	Type of study	Location	Severe dengue	With shock	Died
Manaloto CR, et al (63)	1983-1984	prospective	Hospital of Infant Jesus, Manila, Philippines	379 (laboratory confirmed)	9%	2%
Samsi TK et all (64)	1987- 1988	prospective	Sumber Waras Hospital, West Jakarta, Indonesia	151 (laboratory-confirmed)	15%	1.8%
Chairulfatah A, et al (65)	1991- 1993	prospective	Dr Hassan Sadikin General Hospital, Bandung, Indonesia	128 (laboratory-confirmed)	19%	0.7%
Aggarwal A, et al (66)	1996	retrospective	Kalawati Saran Children's Hospital, New Delhi, India	134 (clinically-suspected)	31%	6.0%
Kabra SK, et al (67)	1996		All India Institute of Medical Sciences, New Delhi, India	193 (clinically-suspected)	59%	9.3%
Chansiriwongs V, et al (46)	1995-1999	retrospective	Children's Hospital, Bangkok, Thailand	3721 (laboratory-confirmed)	31%	0.2%

The risk of shock and death from these hospital-based studies is affected by several factors including: admission policies (hospitals with more lenient admission policies are likely to have a lower proportion of severe dengue), referral patterns (tertiary hospitals are likely to receive the sicker patients), and case management (patients with prompt and better management are less likely to progress to shock).

The risk for severe dengue is better quantified through population-based prospective studies. As shown below, there is great variation in the incidence of dengue infection, symptomatic dengue, and severe dengue. Although some of this variation may be due to differences in study methodology (i.e. varying age groups under surveillance, diagnostic criteria for infection, and degree of completeness of detection of cases), there appear to be real temporal and geographic differences in incidence.

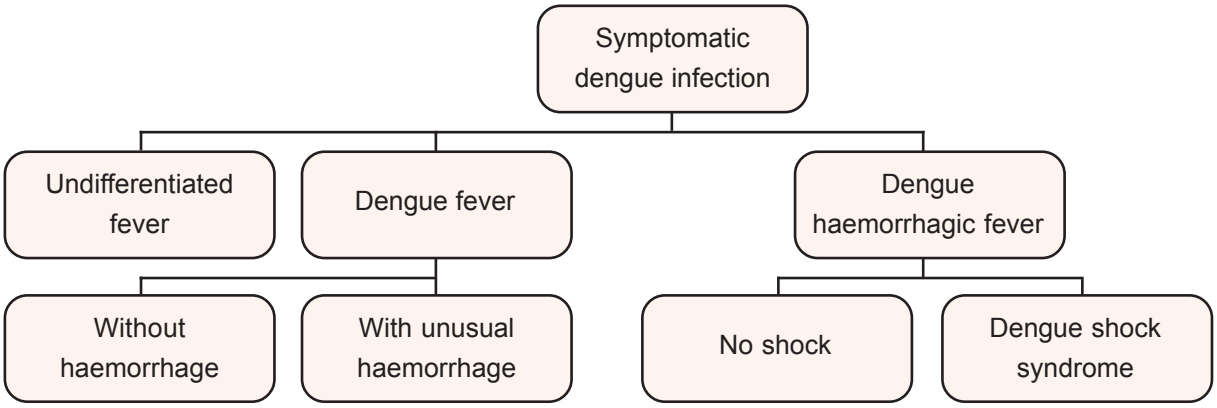
Table 6. Incidence of dengue infection and disease from prospective, population-based studies in hyper-endemic Asian countries

Study site	Population size	Age range	Study period	Incidence (cases/year)				
				Dengue infection	Sympto-matic dengue	Hospita-lised dengue	Severe dengue	Deaths
Yangon, Myanmar (38)	~ 12489	1 to 9 years	1984 to 1988	10.6%		0.3%	0.2%	
Bangkok, Thailand (33)	1757	4 to 16 years	June 1980 to January 1981	5.9%	0.7%	0.4%	0.4%	
Yogyakarta, Indonesia (35)	1837	4 to 9 years	1995 to 1996	29.2%	0.6%	0.4%	0.4%	0.05%
Kamphaeng Phet, Thailand (42)	2119	7 to 11 years	June 1998 to November 1998	7.9%	3.6%	0.7%	0.4%	
	1928		June 1999 to November 1999	6.5%	3.4%	0.8%	0.5%	
	1713		June 2000 to November 2000	2.2%	0.8%	0.1%	0.1%	

Diagnosis and management

THE WHO CLASSIFICATION AND CASE DEFINITIONS

The WHO guidelines propose the following classification for symptomatic dengue infection (68):



The WHO case definitions of dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS) are described below. Given the variability in the clinical illness associated with dengue infection, the WHO guidelines emphasize the need for laboratory confirmation (68).

Probable DF is an acute febrile illness with *two or more* of the following manifestations:

- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia
- Rash
- Haemorrhagic manifestations
- Leukopaenia;

  and
- Supportive serology;

  or
- Occurrence at the same location and time as other confirmed cases of dengue

Confirmed DF is a case confirmed by laboratory criteria (isolation of the dengue virus, fourfold or greater change in antibody titres, demonstration of the dengue virus antigen or genomic sequence).

To fulfil the WHO case definition for DHF, the following must *all* be present:

- Fever or history of acute fever, lasting 2-7 days, occasionally biphasic.
- Bleeding (haemorrhagic tendencies), evidenced by at least one of the following:
  - a positive tourniquet test (TT)
  - petechiae, ecchymosis, or purpura
  - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
  - haematemesis or melena
- Thrombocytopaenia (100,000 cells per mm^3 or less)
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - a rise in the haematocrit equal or greater than 20% above average for age, sex and population
  - a drop in the haematocrit following volume-replacement treatment equal to or greater than 20% of baseline
  - signs of plasma leakage such as pleural effusion, ascites, and hypoproteinaemia.

To fulfil the case definition for DSS, the four criteria above for DHF (fever, haemorrhagic tendencies, thrombocytopaenia, and plasma leakage) must *all* be present *plus* evidence of circulatory failure manifested as:

- Rapid and weak pulse
- Narrow pulse pressure (<20 mm Hg)

  or
- Hypotension for age (this is defined as systolic pressure < 80 mmHg for those less than five years of age, or < 90 mmHg for those five years of age and older.)
- Cold clammy skin and restlessness.

In the WHO guidelines, DHF is also classified according to severity. Grade I is defined as fever and non-specific constitutional signs and symptoms; the only haemorrhagic manifestation is a positive TT and/or easy bruising. Grade II is the same as grade I but includes spontaneous bleeding, usually in the form of skin or other haemorrhages. Grade III is circulatory failure manifested by a rapid, weak pulse and narrowing of the pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness. Grade IV is profound shock with undetectable blood pressure or pulse. Grades III and IV define DSS (68).

In addition, the guidelines list indicators that may be used to guide the diagnosis of DHF/DSS. These indicators may help clinicians to establish an early diagnosis, ideally before the onset of shock but are not intended to be substitutes for the case definitions. The listed indicators of DHF/DSS are: high fever of acute onset, haemorrhagic manifestations (at least a positive TT), hepatomegaly, shock, thrombocytopaenia, and haemoconcentration. The first two clinical observations, plus one of the laboratory findings establishes a provisional diagnosis of DHF. The presence of shock in a patient with a provisional diagnosis of DHF supports the diagnosis of DSS (68).

ASSESSMENT OF THE WHO CLASSIFICATION AND CASE DEFINITIONS

There is little hard evidence for the WHO classification of DF, DHF and DSS, but instead considerable clinical experience, which is difficult to quantify. Recently, a study evaluated the usefulness of the WHO classification system in the context of a busy paediatric practice in a dengue endemic area (69). Of the four criteria recommended by the WHO to indicate a diagnosis of DHF, two (bleeding and thrombocytopaenia) occurred almost as frequently in the children with DF as those with DHF, and were also relatively common in children with other febrile illnesses. 18% of children with DSS failed to meet all four of the necessary criteria for DHF. Thus, not only were bleeding and thrombocytopaenia common in children without apparent DHF but these features were also absent in some children with true DHF (69).

Investigators have reported inconsistencies and difficulties using the WHO classification system and some have found it necessary to define new categories to reflect patterns of disease more accurately (67, 70-71). A symposium on "Severe Dengue: The Application of Case Definitions to Surveillance, Clinical Care, and Research" was held during the 52nd annual meeting of the American Society of Tropical Medicine and Hygiene in December 2003, where the shortcomings of the WHO classification system and potentially more appropriate case definitions were discussed.

In the context of the IMCI, the WHO classification is inappropriate for the following reasons:

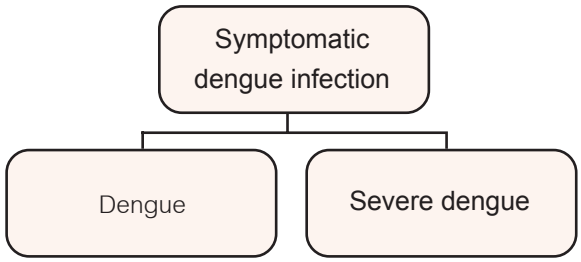
a) **There is a great deal of overlap between DF and DHF:** The WHO case definition differentiates between DF and DHF grades 1 to 4, where DSS is DHF grades 3 and 4. There is no evidence that DF and DHF/DSS are distinct clinical entities rather than manifestations of a spectrum of disease. Thrombocytopaenia and bleeding are features of DHF/DSS, but these may also occur in DF leading to additional categories of DF without bleeding and DF with unusual bleeding.

b) **The four requirements in the WHO case definition of DHF (fever, thrombocytopaenia, haemorrhage, and signs of plasma leakage) are difficult to fulfill or may not always be fulfilled:** A single platelet count may not always reveal thrombocytopaenia. To detect thrombocytopaenia and early plasma leakage requires laboratory tests, often not available in primary care centres in impoverished dengue-endemic countries. Haemorrhagic manifestations may not always be present in severe dengue, particularly during the early phase.

c) **The term "DHF" puts undue emphasis on haemorrhage:** The hallmark of severe dengue (and the manifestation that should be watched for) is not haemorrhage but vascular permeability leading to plasma leakage. Haemorrhage may or may not be present in severe dengue and conversely may occur in children with otherwise uncomplicated dengue. When life-threatening haemorrhage does occur in severe dengue, it is almost invariably a late manifestation and associated with profound or prolonged shock as discussed above.

d) **The classification is too complicated for use in the context of IMCI:** Assessment and classification of children into DF or DHF would, in the vast majority of cases, not be possible in first-level referral centres. Even in tertiary centres with available laboratory tests, the current case definitions cause confusion when patients are suspected to have DHF but do not fulfil all four requirements or have otherwise uncomplicated DF with minor haemorrhagic manifestation.

It may probably be better to use the terms dengue and severe dengue as shown below, with no emphasis on bleeding or on a specific platelet count cut-off:



In this simplified classification system, vascular permeability resulting in plasma leakage would be the hallmark of severe dengue. Early signs of plasma leakage would include haemoconcentration, pleural effusions or ascites. Danger signs of severe dengue would include circulatory compromise or shock (cold extremities, weak radial pulse, prolonged capillary refill), altered sensorium (unconscious, lethargic, combative), mucosal bleeding (haematemesis, melena, or bleeding from the nose or gums) and unusual manifestations (hepatic damage, cardiomyopathy, encephalopathy, and encephalitis).

OTHER OUT-PATIENT ASSESSMENT PROTOCOLS FOR DHF

Other than the more detailed WHO guidelines (1, 68), a number of brief and more prescriptive protocols for the clinical assessment of dengue have been developed in various countries (72-74). The protocols are based on the WHO case definitions with additional components such as follow-up, indications for admission, and instructions for those not hospitalised. The main features of some published protocols are shown below:

Table 7. Protocols for the clinical assessment of dengue

	Criteria for clinical diagnosis	Follow-up of suspected dengue cases	Indications for admission	Instructions if not hospitalised
Standardized clinical management, Children's Hospital, Bangkok, Thailand, 1999 (72)	- high continuous fever for 2-7 days - haemorrhagic manifestations (at least a positive TT) - hepatomegaly - circulatory disturbance - thrombocytopaenia - haemoconcentration	Follow-up all suspected dengue patients closely every day starting day 3 of illness Perform a complete blood count every day	- weakness - bleeding - thrombocytopaenia (<100,000 /cu mm) - rising haematocrit - clinical deterioration at defervescence - acute severe abdominal pain - shock / signs of circulatory compromise - sensorial changes - parental anxiety or lives far away from hospital	Advise caretakers of warning signs
Out-patient management of dengue illness in young adults, University Hospital, Kuala Lumpur, Malaysia, 1993 (73)		Patients not admitted should be monitored daily	- bleeding - BP < 90/60 mm Hg - platelets <50,000 cells/cu mm - haematocrit > 50%	Symptomatic treatment
DHF: Current Approaches to Management, Singapore General Hospital, Singapore 1980 (74)	- high continuous fever for 2-7 days - haemorrhagic manifestations (at least a positive TT) - hepatomegaly - circulatory disturbance - thrombocytopaenia - haemoconcentration		All patients suspected of having DHF should be admitted to hospital for observation, especially from the 3rd to the 7th day of the febrile period when shock frequently occurs	

TOURNIQUET TEST

One of the criteria for diagnosis included in the WHO case definition and in published protocols is the tourniquet test (TT), which is a measure of capillary fragility and thrombocytopaenia. The WHO guidelines stipulate that a blood pressure cuff should be inflated on the upper arm to a point midway between the systolic and diastolic pressures for five minutes, and then the number of resulting petechiae in an area 6.25 cm^2 (2.5 x 2.5 cm) should be counted. The TT is considered positive when 20 or more petechiae are observed within the square (1, 68).

Table 8. Results of the tourniquet test (TT) from various studies

Study location and number of subjects (n)	Age group	% with positive TT				
		Laboratory-confirmed dengue infections				Other viral infections
		DF	DF with bleeding	DHF	DSS	
Delhi, India, n = 240 dengue cases (67)	4 months to 13 years	40%	18%	62%	64%	
Bangkok and Kamphaeng Phet, Thailand, n = 51 dengue cases and n= 108 other viral infection cases (75)	6 months to 14 years	36% 64%*		52% 65%*		21% 39%*
Bangkok and Kamphaeng Phet, Thailand, n = 318 dengue cases and n= 331 other viral infection cases (76)	6 months to 15 years	88%*		91%* (grade 1) 95%* (grade 2)	91%* (grade 3 , 4= DSS)	52%*
Dong Nai Province, Viet Nam, n = 598 dengue cases, n = 236 who were unclassifiable and n= 71 without dengue (77)	1 month to 15 years	38%		45%		6%

* Criteria for positivity modified to 10 petechiae within the square

The table above shows how poorly the TT differentiates between mild and severe dengue and thus cannot be relied upon for decisions regarding hospital admission. Non-dengue infections may also manifest with a possitive TT. For the diagnosis of dengue infection in general, the sensitivity, specificity, positive predictive value, and negative predictive values of the TT are presented below.

Table 9. Results of the tourniquet test (TT) from various studies

Study location and number of subjects (n)	Sensitivity for dengue infection	Specificity for dengue infection	Positive predictive value	Negative predictive value
Bangkok and Kamphaeng Phet, Thailand, n=51 dengue cases and n=108 other viral infection cases (75)			49% 44%*	75% 79%*
Bangkok and Kamphaeng Phet, Thailand, n=318 dengue cases and n= 331 other viral infection cases (76)	90%	48%	62%	83%
Dong Nai Province, Viet Nam, n=598 dengue cases, n=236 who were unclassifiable and n=71 without dengue (77)	42% 29%**	94% 97%**	98% 98%**	17% 15%**

* Criteria for positivity modified to 10 petechiae within the square
** Modified TT using a simple elastic tourniquet applied at maximum stretch around the midpoint of the upper arm for five minutes

The results above are widely divergent and probably reflect inter-observer variability as well as the day of illness when the TT was done. For example, among the dengue patients in one of the studies above, the modified TT was positive in 46% four days, 56% three days, 67% two days, and 78% one day before defervescence and in 90% on the day of defervescence (76).

If the TT is positive it can be helpful, but there is almost always some evidence of bleeding already, and if negative it may not mean anything. As shown by the Dong Nai study (77), if the TT is positive there are almost always petechiae present and the test only contributes additional information in 5% of cases. The TT does not help to differentiate between DF and DHF, it takes equipment (sphygmomanometer and various cuff sizes for children) and some time to perform, and is uncomfortable for the patient. Thus, many health workers in developing countries assessing children for dengue do not use the TT.

DIAGNOSTIC KITS

A number of kits for dengue diagnosis (e.g. MRL Dengue IgM ELISA™, PanBio Dengue Duo IgM and IgG capture ELISA™, Venture Technologies Dengue IgM and IgG Dot Blot assay™) are now commercially available. In more affluent treatment settings, they are used to confirm dengue and to distinguish between primary and secondary infections (78). The question is whether these kits could be useful in the context of IMCI. It is doubtful that exclusion of secondary dengue infection in febrile children attending primary health care facilities in developing countries would rule out progression to DHF. There are also the practical issues of feasibility and sustainability. Also, most of the kits are not reliably positive until at least the fifth day of illness, which is too late to be useful for IMCI.

At the moment, the rapid tests that are commercially available are sold at a price that makes them inaccessible to most developing world health systems. However, low-cost rapid tests for dengue are being developed, and will be useful when available. Antigen as well as antibody detection will be important, because patients often report initially during the viraemic phase prior to seroconversion.

DIAGNOSIS IN THE CONTEXT OF INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS

The risk of death underscores the importance of early detection of severe dengue. Unfortunately, it is often not possible to predict whether a patient with dengue will progress to severe disease (79). The hallmark of progression is increased vascular permeability but its detection prior to the onset of shock is often difficult. Early signs of plasma leakage cannot be discerned on physical examination; clinical detection of pleural effusions or ascites is unreliable unless the volumes of fluid are large. Repeated X-rays may be necessary but often not available in small hospitals. Sonography has been advocated as a useful diagnostic tool for early identification of pleural effusion, ascites, or gallbladder wall thickening but require equipment and technical expertise. Thus, documentation of haemoconcentration by serial haematocrit determinations, although not without problems, is the most readily available surrogate measure of plasma leakage. When a patient's history and physical examination suggest dengue infection, a rising haematocrit is probably the optimal method to diagnose progression to severe dengue. Even this simple test is often not available in first-level health care facilities.

Thus, in first-level health care facilities, the critical decision as to whether it is safe to send home a child during the first few days of fever or whether referral to hospital is necessary often cannot be made. Criteria for admission should include danger signs (i.e. signs of circulatory compromise, change in sensorium, and bleeding) but

should probably include early signs as well (i.e. haemoconcentration). When measurement of haematocrit is not possible, current practice is to refer all patients to larger hospitals for assessment, complete blood count, and possible hospitalization. The need for evaluation of many febrile children overwhelms the clinical and laboratory capacity of referral centres during the dengue season, particularly during outbreaks that occur every three to four years. Lenient admission policies improve outcome but require increased health resources, which are often not available. If the early determinants of disease severity were understood in detail, more effective and less costly case management might be devised.

TREATMENT

Guidelines for the treatment of dengue were developed by Nimmannitya and others in Bangkok, and these later evolved into the WHO guidelines of 1974, updated in 1986, 1994, and 1997 (68). The general introduction of these guidelines, particularly intensive fluid replacement and monitoring, have reduced case fatality rates from around 20% to less than 1% in hospitals with facilities for monitoring and intravenous resuscitation (72). The guidelines have since been modified and placed in a format easier to use by health workers in small hospitals in developing countries (1).

The guidelines recommend that patients suspected or confirmed to have non-severe dengue be managed at home with bed rest, paracetamol, oral fluids and follow-up haematocrit and platelet counts.

Those with signs of plasma leakage may be followed closely at the out-patient department or admitted to hospital to receive intravenous fluids (5% dextrose in normal saline solution) at 6ml/kg/hour for 3 hours, reduced to 3ml/kg/hour with improvement and discontinued after 24 hours. If the patient fails to improve or worsens, intravenous fluid rate should be gradually increased from 6 to 10ml/kg/hour then changed to colloid (if haemocrit is rising) or blood (if haematocrit falls and bleeding is suspected). Once improvement is noted, intravenous fluid rate should be gradually decreased from 10 to 6 to 3ml/kg/hour and discontinued after 24 to 48 hours. The trend in the haematocrit (stable or gradually decreasing) in conjunction with the clinical signs (stable pulse rate and blood pressure, and increasing urine output), should be used to assess for improvement. It has sometimes been suggested to continue or even increase intravenous fluids until the haematocrit decreases or to achieve a particular number. This puts the patient at risk of fluid overload particularly in the later stages of the illness. Many patients who die, do so of fluid overload rather than intractable shock.

Patients with signs of circulatory compromise should immediately receive rapid volume replacement with 10-20 ml/kg/hour of crystalloid solution. If no improvement is noted, oxygen should be administered and the crystalloid solution should be replaced with colloid (if haematocrit is rising) or blood (if haematocrit falls). Again, once improvement is noted, intravenous fluid rate should be gradually decreased from 10 to 6 to 3ml/kg/hour and discontinued after 24 to 48 hours (1).

As described above, the cornerstone of management of severe dengue is fluid replacement. When circulatory compromise is noted, the recommended strategy is to rapidly administer crystalloids (normal saline or lactated Ringer's solution) while actively monitoring the haematocrit level and reserving colloids for refractory or recurrent shock. The crystalloid solution must be isotonic and the volume just sufficient to maintain effective circulation during the period of plasma leakage. Excessive or prolonged intravenous fluid administration may result in fluid overload. The guidelines advise that fluid rates should be reviewed every 1 to 3 hours, depending on the condition of the patient (1).

These guidelines have been widely accepted and in use for many years but until recently, there had been no randomised comparisons to assess the optimal fluid. The immediate administration of colloids for dengue patients with shock, was investigated in a randomised, double-blind trial in 1995 (80) and 1996 to 1997 (81). The investigators found that the more severely ill children with very narrow pulse pressures (less than 10 mm Hg) improved significantly more quickly if they immediately received a colloid solution. For children with circulatory compromise but higher pulse pressures (between 10 and 20 mm Hg), there was no difference in outcome between the groups that immediately received crystalloid or colloid.

Studies of ancillary treatment modalities in dengue have been reported. One compared oxygen mask treatment versus nasal continuous positive airway pressure in dengue shock syndrome (82). Although the number of subjects was small and the results were not statistically significant, the results suggested that nasal continuous positive airway pressure seemed to be more effective. Studies evaluating steroids to prevent shock (83-84) in DHF has so far indicated no benefit from their use. Details in the intensive care monitoring of DSS such as the blood gas and central venous pressure monitoring, the use of inotropes, sodium bicarbonate, and blood products, and the management of complications are not included in the scope of this review.

Dengue in the Integrated Management of Childhood Illness

INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS DENGUE ALGORITHMS

The Integrated Management of Childhood Illness (IMCI) is a strategy to assist health workers at first-level facilities in developing countries on the out-patient management of children less than five years of age (85). In the generic IMCI guidelines, there is an initial assessment for General Danger Signs (unable to drink or breastfeed, vomits everything, convulsions, lethargy or unconsciousness). This is followed by the assessment, classification, and treatment of acute respiratory infection, diarrhoeal disease, malaria, measles, ear problems, malnutrition, and the sick young infant. The IMCI algorithms for each of the conditions follow a colour-coded scheme: green for mild illness (e.g. simple cold or diarrhoea with no dehydration), yellow for moderate illness (e.g. pneumonia requiring an oral antibiotic or diarrhoea with some dehydration requiring oral rehydration therapy), and red for severe illness requiring urgent referral to hospital (e.g. severe pneumonia or diarrhoea with severe dehydration).

Due to the recognition of dengue as a significant health problem, 13 countries from three WHO regions have included the disease into their IMCI adaptations (86). There is wide variation in the DF/DHF country-adapted algorithms. Below follows a tabulation of the countries and the five variants of DF/DHF algorithms.

Table 10. Variations in the dengue IMCI adaptations

Variant	Countries
4 classifications: Fever-DHF unlikely, DHF, severe DHF, DSS	- Viet Nam
3 classifications: Fever-DHF unlikely, DHF possible, DHF	- Cambodia - Guatemala - Indonesia - Myanmar
3 classifications: Suspected DF, Suspected DHF, Very severe febrile disease	- El Salvador
2 classifications: DF, Severe DHF	- Colombia - Dominican Republic - Paraguay - Venezuela
2 classifications: Fever-DHF unlikely, Severe DHF	- Philippines
1 classification: Suspected DHF	- Honduras - Nicaragua

In these algorithms, the recommended treatment for those requiring urgent referral varies from ORS to IV fluids and some algorithms included oxygen, antipyretics (no aspirin), antibiotics, and measures against hypoglycaemia.

Home treatments for the classification not requiring referral consists mainly of oral fluids and antipyretics (no aspirin). Follow-up is recommended until the child is afebrile (1 country) and until afebrile for 2 days (2 countries).

To complement the IMCI outpatient guidelines, a manual entitled "Management of the child with a serious infection or severe malnutrition: Guidelines for care at the first referral level in developing countries" (also known as the Referral Care Manual) was developed (87). The manual describes a sequential process for managing sick children with conditions that require admission to hospital. Dengue is discussed briefly in the referral care manual. More recently, a pocket book based on the Referral Care Manual has been developed (88). Management of dengue fever and severe dengue are described in the pocketbook.

AN EVALUATION OF DENGUE ALGORITHMS IN ASIA

From 1996 to 1998, a study of dengue algorithms in Asian countries was conducted by Dr Eric Simoes in collaboration with staff from the Department of Paediatrics, Dr. Soetomo Hospital, Surabaya, Indonesia, the Centre for Tropical Disease, Ho Chi Minh City, Viet Nam, and the University of Oxford, United Kingdom (89). During the time of the study, Indonesia, the Philippines, and Viet Nam had included dengue in their IMCI adaptations. The objective of the study was to evaluate the sensitivity, specificity, and predictive value of simple clinical signs and symptoms in the diagnosis of dengue hemorrhagic fever.

Table 11. Sensitivity, specificity, and predictive value of two lists of signs

List-1	
- shock - altered sensorium - mucosal bleeding - petechiae	Sensitivity = 63% Specificity = 92% Positive predictive value = 32% Negative predictive value = 98%
List-2	
- shock - altered sensorium - mucosal bleeding - petechiae - vomiting	Sensitivity = 79% Specificity = 64% Positive predictive value = 12% Negative predictive value = 98%

In the first part of the study, a list of signs and symptoms from the three country IMCI adaptations were evaluated among hospitalised Indonesian and Vietnamese children less than 15 years of age. This initial evaluation resulted in two lists of signs that in children less than five years of age with presence and/or a history of fever would indicate severe dengue. The signs in list-1 and list-2 consist of signs of shock (cold extremities, weak radial pulse, or prolonged capillary refill time), altered sensorium (unconscious, lethargic, or combativeness), mucosal bleeding (haematemesis, melena, or bleeding from the nose or gums), petechiae, and vomiting. List-2 is the same as list-1, with the addition of one more sign. A comparison of the performance of the two lists is shown in the table 11. The addition of vomiting increased the sensitivity but decreased the specificity and the positive predictive value.

In the second part of the study, list-1, list-2 and the lists from the three country IMCI adaptations were evaluated among children attending the Dong Nai Hospital outpatient department. The results among children less than five years of age are shown in the table below:

Table 12. Sensitivity, specificity, and predictive value of the various lists of signs and symptoms when applied to children less than five years of age

	True positive	False positive	True negative	False negative	Sensitivity	Specificity	Positive predictive value	Negative predictive value
LIST-1	30	63	748	18	63	92	32	98
LIST-2	38	291	520	10	79	64	12	98
Indonesia	38	303	508	10	79	63	11	98
Philippines	38	297	514	10	79	63	11	98
Viet Nam	30	68	743	18	63	92	31	98

The study concluded that in children less than five years of age (the target age of IMCI), list-2 and the lists from Indonesia and the Philippines had the highest sensitivity of 79%, with an acceptable specificity of 63 to 64%. The advantage of list-2 is that it contains less than half the number of signs and symptoms compared to the lists from Indonesia and the Philippines. The addition of other signs such as headache, abdominal pain and tenderness, high fever for three or more days, and the tourniquet test did not add significant sensitivity to the algorithm. The scope of the study did not include the role of simple laboratory tests (haematocrit and platelet count). Several possible colour-coded "dengue box" of list-2 could be developed, including the two discussed below.

a) From the study, the author concluded that shock, altered sensorium, history of bleeding, and petechiae should be placed in the red box. The yellow classification should include only vomiting, in the absence of any of the above. Children without the above symptoms/signs should be in the green classification.

If the child (>2 months to five years) has fever, ask the following:

Does the child have fever or history of fever > 3 and < 8 days and any one of the following signs? - shock - altered sensorium - mucosal bleeding - petechiae	Refer immediately
Does the child have fever or history of fever > 3 and < 8 days and vomiting?	?
Does the child have fever or history of fever > 3 and < 8 days but none of the above signs?	Instructions for: - home care - follow-up - danger signs

This algorithm raises the question of how should children in the yellow box, if indeed a yellow box is included, be managed. Because of the progressive nature of dengue, perhaps the green colour sends the wrong message; particularly during the first few days of fever, the child may not have any of the signs in the red or yellow box but still need to be carefully followed-up.

b) Perhaps it would be more logical to have only a pink and yellow box. Shock, altered sensorium and mucosal bleeding (with or without the addition of petechiae and vomiting) should go into the red box. Children without these signs should be considered to fall under the yellow box and be reviewed daily, as shown below.

If the child (>2 months to 5years) in a dengue endemic area has fever, ask the following:

Does the child have fever or history of fever > 3 and < 8 days and any one of the following signs? - shock - altered sensorium - mucosal bleeding - (petechiae) - (vomiting)	DHF → refer immediately
Does the child have fever or history of fever > 3 days but none of the above signs?	Instructions for: - daily out-patient follow-up - home care - danger signs

There are several issues with these classification schemes:

- The first question is whether the signs of shock could already be picked up by the assessment for General Danger Signs early in the IMCI assessment flow. Similarly, altered sensorium and vomiting everything are already General Danger Signs, thus there may be no need to repeat these signs in the dengue box.
- Can health workers pick up the many signs of shock (cold extremities, weak radial pulse, or prolonged capillary refill time) or should one sign be specifically chosen?
- A potential drawback is over-referral if even just mild petechiae is included in the red box.
- Guidelines on how the follow-up should be done and what should be the specific danger signs that caretakers should watch for should be developed. Qualitative studies should be undertaken to determine whether these signs can be recognised at home.
- Many countries may wish to include physical examination findings such as hepatomegaly or abdominal tenderness in the algorithm.

The generic dengue box deemed to be most appropriate would need to be elaborated to include classification, treatment and follow-up, then validated in various countries. Also, the role of simple laboratory tests (haematocrit more than platelet count) in IMCI would need to be assessed. It may be feasible to determine hematocrit values even at primary care facilities, using either standard blood draws or microcapillaries drawing blood from a fingerprick. This test is low-cost and requires minimal equipment and technical skill. Finally, the dengue algorithm may be made separate from the IMCI and used for both young and older children above five years of age.

FIELD-TESTING OF AN IMCI ALGORITHM MODIFIED TO INCLUDE DENGUE INFECTION

To determine whether nurses, using an IMCI algorithm modified to include dengue infection, satisfactorily classified children in an area endemic for DHF, a study was carried out at the Dong Nai Paediatric Centre in southern Viet Nam (90). The relevant portions of the modified algorithm that was tested are shown below:

Table 13. Diagnostic classification by a modified IMCI algorithm (90)

General Danger Signs	History of being unable to drink or breastfeed, vomits everything or convulsions. Child is lethargic or unconscious.
Fever	By history or feels hot or axillary temperature > 37.5°C
Dengue Risk	Child > 6 months and lives in a dengue risk area or has been in a dengue risk area in the last two weeks - DSS - Cold, clammy extremities or pulse not detectable or weak and fast pulse - Severe DHF - Lethargic or restless or right upper abdominal tenderness or nose bleeding or gum bleeding or black vomit or black stools - DHF - Petechiae or skin haemorrhages or high continuous fever for three days or more - DHF unlikely

Nurses assessed and classified a systematic sample of 1,250 children aged 2 months to 10 years presenting to the outpatient department. Their classification was compared with that of a paediatrician blind to the result of the nurses' assessment and which could be modified in the light of simple investigations including dengue serology. In 859 children aged 2 to 59 months, the nurses were able to classify the presenting illness in >99% of children and found more than one classification in 70%. For the children with pneumonia, diarrhoea, DSS, severe DHF, and severe disease requiring urgent admission, the nurse's classification was >60% sensitive and >85% specific compared with that of the paediatrician.

For the nurses' classification of DHF, the specificity was 50-55% for the children <5 years and in children with a definitive serology. Among children 2 months to 10 years, nurses classified five times as many children as having DHF using the modified IMCI chart as the paediatrician. Alterations in the DHF algorithm improved specificity at the expense of sensitivity.

The nurses classified correctly all 20 children with DSS on admission. However, 3 of another 20 children who developed DSS during the course of their hospitalization were classified by the nurses at the time of admission as unlikely to have DHF. These three children presented with fever on day 2 of their illness and developed skin petechiae on day 3 or 4, and shock on day 4 or 5.

The authors concluded that using the modified IMCI chart, the nurses classified appropriately many of the major clinical problems in sick children <5 years old in southern Viet Nam but further modifications will be required in the dengue section (90).

COMPARISON OF DENGUE ALGORITHMS IN ASIAN AND LATIN AMERICAN COUNTRIES

The signs for urgent referral in the seven Latin American and five Asian country dengue algorithms (86) were grouped into these classifications: shock, altered sensorium, bleeding, and vomiting. The number of countries that include a manifestation of shock, altered sensorium, bleeding, and vomiting as an indicator for urgent referral is shown in the table below:

Table 14. Number of countries that include the sign as an criteria for urgent referral

Major signs in list-1 and list-2	Asian (n=5)	Latin American (n=7)
Shock (cold and clammy extremities, prolonged capillary refill time, cold hands and feet, weak pulse)	5	0
Altered sensorium (drowsy, lethargic, difficult to wake, abnormally sleepy)	3	1
Bleeding (haematemesis, melena, bleeding from the nose or gums, gastrointestinal bleeding, petechiae, ecchymosis, spontaneous or provoked bleeding, and any bleeding)	5	5
Vomiting	2	1

It is interesting to note that all the Asian country algorithms include a manifestation of shock or poor perfusion as a criterion for urgent referral, whereas none of the Latin American algorithms do. Of the seven Latin American countries, five included bleeding and none included shock as a criterion for urgent referral. Altered sensorium was also more commonly included in the Asian compared to the Latin American algorithms. The differences may be a reflection of the variation in epidemiologic and clinical characteristics of dengue between the two regions (as discussed above). But the non-inclusion of shock in the Latin American algorithms also raises the question of whether this has resulted from the undue emphasis on haemorrhage in the term DHF.

HOME MANAGEMENT AND THE RECOGNITION OF SPECIFIC SIGNS AND SYMPTOMS

There have been no randomised trials of the most optimal home management for dengue fever. In any case, not many treatment options exist. Various IMCI and non-IMCI protocols mainly recommend oral fluids and antipyretics (no aspirin). In a hospital and health centre-based study in Nicaragua, fluid intake during the 24 hours before being seen by a clinician was statistically associated with decreased risk for hospitalization of dengue fever patients (91). Similar results were obtained for children <15 years of age, older adolescents, and adults in independent analyses. The most common liquids ingested were water, fruit juices, oral rehydration solution (ORS), and tea.

More important is instructing caretakers regarding close follow-up and the signs and symptoms that should be watched for at home. Caretakers should be made aware of the risk of progression from dengue fever to severe

disease. Defervescence with clinical deterioration, bleeding, acute and severe abdominal pain and vomiting, weakness or drowsiness, refusing to eat, restlessness, changes in behaviour, cold and clammy skin, no passage of urine for 4 to 6 hours are signs that have been recommended for caretakers to watch for (68). In the dengue algorithms described above, nine countries included signs and symptoms to indicate that the child should be brought back immediately to the health facility (86). These included various manifestations of bleeding, shock, abdominal/epigastric pain and vomiting. The ability of mothers to recognise these warning signs and symptoms has not been verified.

Conclusions

FURTHER DEVELOPMENT OF DENGUE ALGORITHMS

a) Evaluation of the TT shows that the test is inadequate for differentiating between DF and DHF. Considering these results plus the equipment, skill, and time needed to perform the test, it would probably be inappropriate to implement the TT in first-level health care facilities in developing countries. The test should probably not be included in the IMCI algorithm.

b) The current WHO classification and case definitions are misleading and put undue emphasis on haemorrhage as the complication to watch for, rather than plasma leakage. For the IMCI algorithm, it may be more useful to utilise the terms “dengue” and “severe dengue”. Trying to classify children into DF and DHF based on early clinical signs would, in the vast majority of cases, not be possible in first-level referral centres. The IMCI dengue algorithm should be simple and address the main issue of whether the child should be referred or not and if not, what instructions should be given to the mother or care-giver.

c) Due to the progressive nature of DHF that cannot be ameliorated by medication or home treatment, the final generic algorithm should include close follow-up/repeat evaluations starting from the third to the seventh day of fever until the patient is afebrile for at least 24 hours. The algorithm should include guidelines for children presenting before day 3 of illness.

d) Since the dengue algorithm would be useful in all age groups, consideration should be given for development of guidelines separate from IMCI that would be applicable for older children and adults. In countries where DHF is not common in children under five years of age, dengue would not be included in IMCI.

SUGGESTIONS FOR NECESSARY RESEARCH

a) There is a critical need to reassess the current WHO classification of DF, DHF and DSS. The simpler classification of dengue and severe dengue suggested will need to be tested in multicentric studies.

b) Dr Simoes’ study was an important first step in the development of generic IMCI DF/DHF guidelines and follow-up studies should be done to validate the finalised algorithm.

c) From previous and experience, a collation of signs included in the various country IMCI adaptations, and the results from Dr Simoes’ study, the major signs requiring urgent referral are shock, altered sensorium, and bleeding. The specific indicators of shock (cold and clammy extremities, prolonged capillary refill time, cold extremities, and weak pulse), altered sensorium (drowsiness, lethargy, difficult to wake, abnormally sleepy), and bleeding (haematemesis, melena, bleeding from the nose or gums, gastrointestinal bleeding, petechiae, ecchymosis, spontaneous or provoked bleeding, and any bleeding) that occur early enough and can be recognised by health workers in first-level referral centres need to be determined through health centre-based research.

d) The question of whether we can rely on clinical manifestations alone in referral decisions of children with fever in dengue-endemic areas remains unanswered. Studies of the feasibility of including of the measurement of haematocrit in the IMCI guidelines are needed. Haematocrit measurements are very important and even if this test is not available in every health centre, it may be possible to organise communal local facilities shared by different groups.

e) A qualitative study to determine the messages to be included in the counselling of signs to watch out for and the need for close follow-up would greatly assist in the development of effective messages. In dengue-endemic countries, these messages could be included in the IMCI "mother's card."

f) The clinical studies from Dr Jeremy Farrar's group in Ho Chi Minh have began to clarify many issues in the treatment of DHF and many more such studies should be undertaken to evaluate various modalities of treatment (e.g. on the value of ORS in DF and early DHF, the use of inotropes, management of pleural effusion, and other issues). The clinical studies should be randomised and whenever possible blind, be large enough to show important clinical differences, and be well conducted with formal Data Safety Monitoring Committees and appropriate statistical analysis.

RECOMMENDATIONS FOR COUNTRY-SPECIFIC ADAPTATIONS

a) Due to the variation in epidemiology of dengue, the decision to incorporate dengue into IMCI rests on whether the disease is a significant problem in children under five years of age in a specific region or country. Each country should determine and monitor the modal age of symptomatic dengue by investigating age-specific seroepidemiology and the age-specific hospitalization rates. Country- or at least region-specific analyses would have to be performed to define the age stratification of disease burden. This should be reassessed periodically as dengue becomes more endemic in an area or the epidemiological profile changes.

b) Each country/area should probably also determine baseline haematocrit data for the population of children of different age groups. An area- and age-specific haematocrit value may help in the early detection of plasma leakage (92-93). To look for a significant rise in an individual child, population data could be helpful with the caveat that some children with haemoconcentration will not achieve haematocrit levels above whatever cut-off is chosen.

c) Dengue algorithms, whether they are included within IMCI or are separate, would need region or country-specific validation.

d) Dengue/DHF programmes in dengue-endemic countries should emphasize early health seeking behaviour when fever occurs and recognition of danger signs. Due to the variability of timing of circulatory compromise, the number of days of fever cannot be used to exactly predict the onset of shock. Effective public health messages could go a long way in correcting apprehensions and wrong information about dengue.

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