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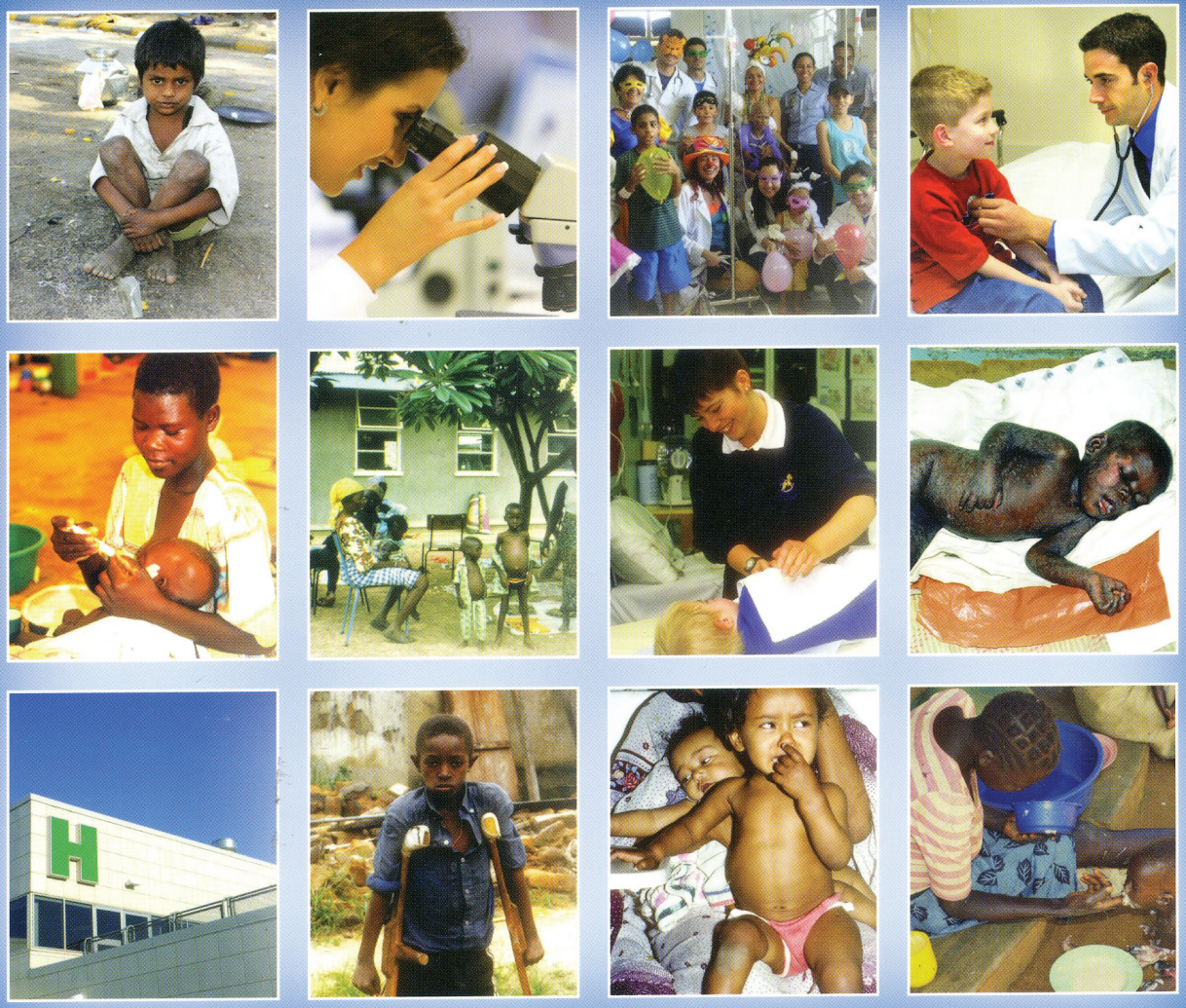

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Editorial

J. B. S. Coulter

Editor-in-Chief

Paediatrics and International Child Health (PCH) is delighted to publish eight papers representing the core of the Proceedings of the Dengue Congress at the 9th International Congress of Tropical Pediatrics in Bangkok in October 2011. These papers have been excellently summarised by Usa Thisyakorn and Krisana Pengsaa in the preface to this supplement.

The resurgence and worldwide spread of dengue means that health professionals in temperate climates as well as in tropical regions need to be aware of the condition. In the former, many patients are infected whilst travelling. In sub-Saharan Africa, dengue might be overlooked in institutions overloaded by patients with severe malaria. Medical practitioners in South-east Asia have built a fine reputation in the treatment of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), and continue to fine-tune the World Health Organization (WHO)'s dengue case classification and management. In sub-Saharan Africa, DHF might not be recognised amongst other conditions with similar clinical features, and there is a lack of experience of treating it. This is compounded by the need for serial laboratory monitoring, e.g. haematocrit and platelet count, and, in some cases, amino-transaminases. Although there is vast experience of treating diarrhoeal dehydration, it requires less judicious monitoring than when treating DHF/DSS. Conversely, the high prevalence of malnutrition and anaemic heart failure in sub-Saharan Africa means that many paediatricians are more concerned with over-hydration, even in patients with septic shock.[1] Also, even if required, colloids are unlikely to be readily available. In parts of the world where dengue is present but not well recognised, facilities will need to be made available for treatment, and medical practitioners and nurses trained in its management.

Over the years, the journal (previously known as Annals of Tropical Paediatrics) has taken a keen interest in dengue and, in the near future, will be publishing a number of papers and a commentary on the topic. The first issue of 2012 (volume 32) in February saw the journal relaunched with a new editorial board under the title Paediatrics and International Child Health (Paediatr Int Child Health). The rationale for the change of title has been outlined previously.[2] Essentially, PCH is a journal of paediatrics which publishes papers mainly from developing or low-income countries. It is considered that the word 'tropical' no longer accurately reflects the total spectrum of the journal's content as many of the countries from which submissions are received are not in tropical regions and therefore do not see 'tropical diseases', except, as evidenced above, when presented in returning travellers. The *international child health* part of the title underscores the journal's interest in the wide spectrum of topics in community child health in developing countries which need to be brought to the attention of readers. Many non-infectious diseases, e.g. obesity, are now international disorders with an alarming increase in prevalence in low-income countries.

PCH receives papers from a wide variety of countries and it is expected that the supplement will be read by paediatricians involved in the management of dengue throughout the world. The journal shall continue to take a keen interest in dengue and its development.

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Introduction

Proceedings of the Dengue Symposium at the 9th International Congress of Tropical Pediatrics

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Dengue is the most important mosquito-borne viral disease. With four different serotypes, it is a burden throughout tropical and subtropical regions and a potential threat to almost half of the world's population. Recent studies estimate that 50–100 million people are infected each year, of whom about 500,000 develop dengue haemorrhagic fever – a severe form of the disease – and 22,000 of whom die. Dengue haemorrhagic fever is also a leading cause of hospitalisation, placing tremendous pressure on strained medical resources, with an associated major economic and societal impact. Many factors have contributed to the recent dramatic rise in the number of cases of dengue fever, including increased urbanisation and travel. The heavy burden of dengue can only be lifted by strong cooperation between international institutions and agencies to create a new strategy targeting prevention of deaths, reducing morbidity and lessening the associated social and economic losses. In addition, a dengue vaccine is seen as the best way to control dengue effectively. Proper management of dengue infection, mosquito control measures as well as a candidate dengue vaccine, requires a comprehensive update of knowledge in all relevant aspects.

This parallel symposium was organised by the Thailand Chapter of the International Society of Tropical Pediatrics on 20 October 2011, in collaboration with the 9th International Congress of Tropical Pediatrics, which was held on 18–20 October 2011 in Bangkok, Thailand. The objective of the symposium was to provide the participants with a unique opportunity to share their experiences and discuss various issues relating to the pathophysiology, epidemiology, management and control of dengue. Through this symposium, participants gained knowledge and experience from invited speakers from various parts of highly endemic areas. In this context, the symposium also illustrated the importance of sharing best practice and knowledge across all regions and specialities involved in the struggle against dengue. These proceedings summarise the Parallel Symposium on Dengue held at the Queen Sirikit National Convention Center, Bangkok, Thailand, on 20 October 2011.

The supplement begins with an interesting commentary from Scott Halstead as he seeks to analyse and resolve six key controversies in dengue fever research, including the utility of the 1997 World Health Organization (WHO) case definition of dengue haemorrhagic fever and an examination of several theories of dengue infection pathogenesis. Following this, Roberto Tapia-Conyer and colleagues consider the more practical aspects of dengue fever management: community participation, structured by an integrated management strategy. It has the overall aim of improving the efficacy, cost-effectiveness, environmental impact and sustainability of vector control strategies. Tapia-Conyer and his co-authors then discuss in detail the problem of dengue fever infection in Latin America overall. They suggest various ways in which the disease could be combated, including using a vaccine or involving the community, but conclude that politics, finance and co-operation are all areas that need to be managed. A contrasting case study is then presented by Fred Were, focusing on dengue in Africa and the possible differences in the spread of the disease compared with the remainder of the dengue-endemic population. However, Were points out that it is difficult to characterise the disease in Africa owing to the poor surveillance infrastructure and under-recognition of the disease, as there is often a greater focus on malaria. Terapong Tantawichien follows this with a discussion of the increasing prevalence of dengue infection in adolescents and adults, with an in-depth analysis of its clinical manifestations and specific treatment in this age group. On a similar theme, Annelies Wilder-Smith focuses on a particular subset of the adult population

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threatened by dengue infection – travellers. Travellers are not only at risk themselves but they contribute to the spread of dengue; furthermore, they may serve to alert the international community to current epidemics. Sri Rezeki Hadinegoro considers the diagnoses of dengue fever, dengue haemorrhagic fever and dengue shock syndrome in relation to the WHO classification systems of 1997 and 2009. There has been much debate surrounding these classification criteria and Hadinegoro suggests that the evolution of dengue over past years has contributed to the limited applicability of the older case definitions. Following the DENCO study, the newer classification system was formed, but the effectiveness of this is still being debated. Finally, Nguyen Thanh Hung describes the types of intravenous solutions for treatment of children with dengue; he concludes that isotonic crystalloid solutions can be used for the majority of children, and colloids can be considered a second option.

We should like to express our sincere thanks to all of the distinguished invited speakers and resource persons for their contribution. We hope that these proceedings will prove of great interest, and help the global dengue community to improve the prevention, diagnosis and management of dengue infection.

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Controversies in dengue pathogenesis

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Research into the pathogenesis of dengue fever has exploded over the last half-century, with issues that were considered simple becoming more complex as additional data are found. This has led to the development of a number of controversies that are being studied across the globe and debated in the literature. In this paper, the following six controversies are analysed and, where possible, resolved: the 1997 World Health Organization (WHO) case definition of dengue haemorrhagic fever (DHF) is not useful; DHF is not significantly associated with secondary dengue infection; DHF results from infection with a 'virulent' dengue virus; DHF is owing to abnormal T-cell responses; DHF results from auto-immune responses; and DHF results from direct infection of endothelial cells.

Keywords: Dengue, Classification, Case definition, Virus, T cell, Auto-immune

Background

The world is in the midst of a dengue pandemic and more than 1000 papers are added each year to the literature on dengue. Clinicians and scientists attempting to understand the pathogenesis of severe dengue are confronted by six major controversies: (i) the 1997 World Health Organization (WHO) case definition of dengue haemorrhagic fever (DHF) is not useful; (ii) DHF is not significantly associated with secondary dengue infection; (iii) DHF results from infection with a 'virulent' dengue virus; (iv) DHF is caused by abnormal T-cell responses; (v) DHF results from auto-immune responses; and (vi) DHF results from direct infection of endothelial cells.

Each will be considered briefly in this article.

(i) The 1997 WHO Case Definition is Not Useful

What is the 1997 WHO case definition of DHF/DSS?

Clinical application of the 1997 WHO case definition of DHF/dengue shock syndrome (DSS) (Box 1) had several problems. Firstly, the tourniquet test and thrombocytopenia have low positive predictive values,[1–4] though the greatest problem was recognising and defining clinically significant vascular permeability. Acute dengue vasculopathy generally lasts for less than 48 hours, presenting physicians with an array of rapidly changing pathophysiological conditions.[5] The patient must have multiple haematocrit observations, and a definitive diagnosis depends on the timing of these, making nonsense of the complaint that the WHO case definition requires too many 'repeated clinical tests'.[1]

Microhaematocrit testing is critical to establishing a diagnosis of hypervolaemia owing to loss of fluid and to designing and managing fluid and colloid resuscitation.[6] In most South-east Asian countries, microhaematocrit centrifuges are on treatment wards and used by ward personnel. However, in the Americas, haematocrit determinations require venepuncture and are performed in central laboratories, resulting in serious reporting delays. Therefore, much of the perceived problem in documenting dengue vascular permeability is owing to the organisation of hospital laboratory services.[7,8]

The 2009 dengue case definition

The 2009 revised WHO case definition (Fig. 1) has, however, created serious difficulties for the clinician and research scientist.[9] This two-tiered definition consists of initial 'warning signs' and a catch-all category, 'severe dengue'. Note the failure to supply specific quantitative diagnostic criteria and the reliance on individual clinical judgment. How is one to identify 'clinical fluid accumulation', 'increase in haematocrit' or 'severe plasma leakage'? What is 'narrow pulse pressure' or 'high haematocrit'?

For the clinician, the WHO recommends that all patients with any 'warning sign' should be hospitalised.[9] Recent experience has demonstrated that compliance with this, particularly in medical communities with little prior experience of DHF, may lead to serious over-hospitalisation. This may then delay triage and recognition of patients requiring life-saving fluid resuscitation, resulting in a high case–fatality rate.[10]

While the new case definition may be useful for surveillance and reporting, there being no requirement for any laboratory studies, use of the 2009 WHO case definition to define a patient population using the term 'severe dengue' will destroy serious research on dengue pathogenesis. 'Severe dengue' substitutes a *mélange* of disease attributes, many end-stage, for the clinically unique and distinct dengue vascular permeability syndrome. Severe organ failure may result from blood loss. It is well documented that dengue fever in adults

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with peptic ulcer disease may be accompanied by severe focal gastro-intestinal (GI) bleeding, shock and death. Similarly, failure to detect and correct leaky capillaries may result in shock or compensated shock that shunts blood away from the GI tract, resulting in severe bleeding. If uncorrected, these two types of GI bleeding with different causal pathways (and completely different treatment) may result in severe shock, organ failure and encephalopathy. Furthermore, fluid accumulation with respiratory distress (owing to hypervolaemia and pulmonary oedema) is an end-stage outcome possibly resulting from mismanagement of fluid administration, i.e. too much intravenous fluid. To treat end-stage clinical observations as if they derive from a defined clinical syndrome is a serious mistake and has already led to research testing unfeasible pathophysiological hypotheses.[11] Therefore, a case definition that discriminates between primary haemorrhage and vascular permeability is necessary for robust pathological research into the spectrum of dengue syndromes.

(ii) The Correlation Between Dengue Vascular Permeability Syndrome (DHF/DSS) and a Secondary Dengue Infection is not Significant

In 1977, Rosen, an early critic of hospital-based observations of an association between a secondary-type antibody response to dengue infection and DHF/DSS, called for field-based studies to clarify the evidence.[12] Since then, a number of retrospective sero-epidemiological studies have confirmed that severe dengue disease is associated with secondary dengue infections. This includes data gathered in the 'favourable environment' of Cuba, providing unequivocal evidence that individuals circulating dengue 1 antibodies were at risk of DHF during subsequent dengue 2 or dengue 3 infections.[13–15]

However, there are often problems with data collected in a hospital rather than a study setting, with around 10–30% of hospitalised DHF cases often classified as being caused by primary dengue infection.[16] This could be owing to mis-labelling because of the retrospective nature of most of these data where

Box 1 WHO 1997 case definitions for DF, DHF and DSS[55]

DF

Probable
- An acute febrile illness with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations and leucopenia

and
- Supportive serology (a reciprocal haemagglutination-inhibition antibody titre ⩾1280, a comparable IgG enzyme-linked immunosorbent assay (ELISA, see chapter 4[55]) titre or a positive IgM antibody test on a late acute or convalescent-phase serum specimen)

or
- Occurrence at the same location and time as other DF cases

Confirmed
- A case confirmed by one of the following laboratory criteria:
  - Isolation of the dengue virus from serum/autopsy samples
  - At least a four-fold change in reciprocal IgG/IgM titres to one or more dengue virus antigens in paired samples
  - Demonstration of dengue virus antigen in autopsy tissue, serum or cerebrospinal fluid samples by immunohistochemistry, immunofluorescence or ELISA
  - Detection of dengue virus genomic sequences in autopsy tissue serum or cerebrospinal fluid samples by polymerase chain reaction (PCR)

Reportable
- Any probable or confirmed case should be reported

DHF

For a diagnosis of DHF, a case must meet all four of the following criteria:
- Fever or history of fever lasting 2–7 days, occasionally biphasic
- A haemorrhagic tendency shown by at least one of the following: a positive tourniquet test*; petechiae, ecchymoses or purpura; bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations; haematemesis or melaena
- Thrombocytopenia [⩽100,000 cells/mm^3 (100×10^9/L)]†
- Evidence of plasma leakage due to increased vascular permeability shown by: an increase in the haematocrit ⩾20% above average for age, sex and population; a decrease in the haematocrit after intervention ⩾20% of baseline; signs of plasma leakage such as pleural effusion, ascites or hypoproteinaemia

DSS

For a case of DSS, all four criteria for DHF must be met, in addition to evidence of circulatory failure manifested by:
- Rapid and weak pulse

and
- Narrow pulse pressure (<20 mmHg or 2.7 kPa)

or manifested by
- Hypotension for age

and
- Cold, clammy skin and restlessness

* The tourniquet test is performed by inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressures for 5 minutes. A test is considered positive when 20 or more petechiae per 2.5 cm^2 (1 inch) are observed. The test may be negative or mildly positive during the phase of profound shock. It usually becomes positive, sometimes strongly positive, if the test is conducted after recovery from shock.

† This number represents a direct count using a phase-contrast microscope (normal is 200,000–500,000/mm^3). In practice, for outpatients, an approximate count from a peripheral blood smear is acceptable. In normal persons, 4–10 platelets per oil-immersion field (100×; the average of the readings from 10 oil-immersion fields is recommended) indicates an adequate platelet count. An average of 3 platelets per oil-immersion field is considered low (i.e. 100,000/mm^3).

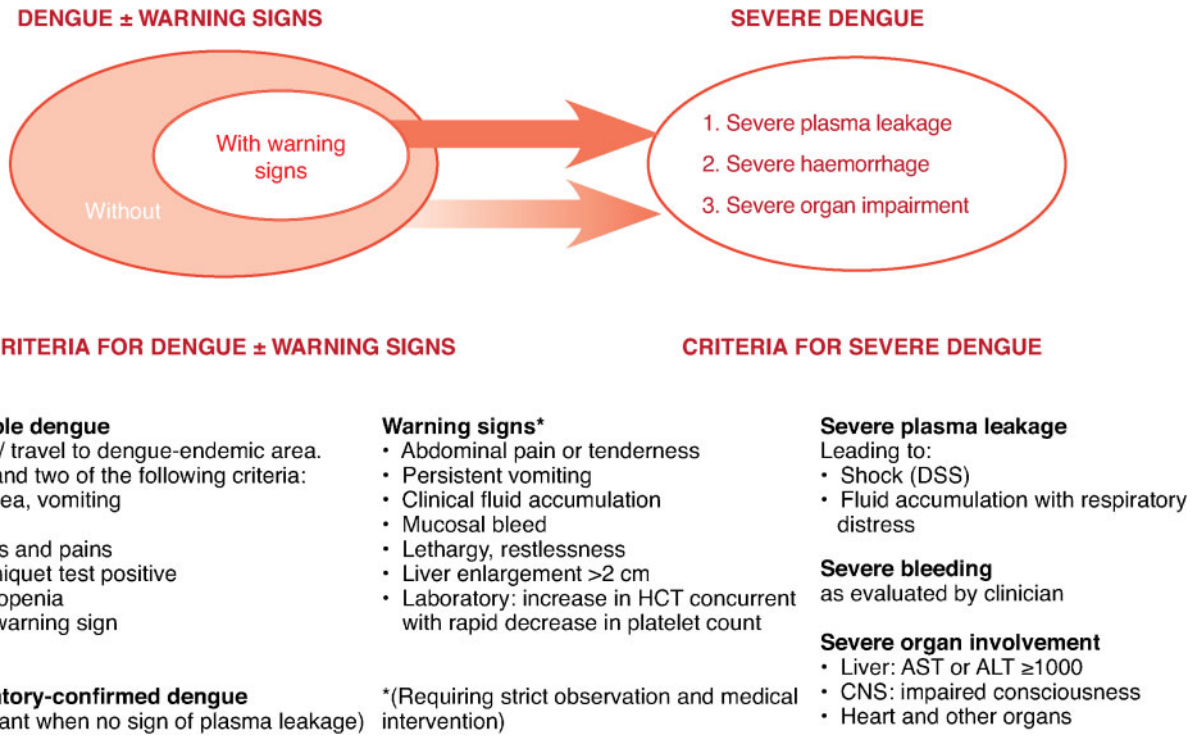

Figure 1 WHO 2009 suggested dengue case classification and levels of severity[9]

DHF may be diagnosed without evidence of vascular permeability because observers assume that it is indicated by the presence of thrombocytopenia.[16] Another explanation is serological misclassification as detection of primary and secondary antibody responses is often based on tests from a single sample of acute-phase serum.[16]

(iii) DHF/DSS is Caused by Virulent Dengue Viruses

Significant efforts have been directed to finding genetically distinct viruses that cause severe or mild dengue disease. The four dengue virus strains (DENV1–4) vary in terms of pathogenicity and virulence, though the basis for these phenotypic differences is poorly understood. Pathogenicity describes the spectrum of disease syndromes associated with dengue infection. Island epidemics and human volunteer studies provide evidence that different strains within genotypes of dengue viruses vary greatly in intrinsic pathogenicity (i.e. in naive hosts).[17,18] The ratio of DHF/DSS to total dengue infections can be measured and is referred to as virulence.

However, the relationship between second infections and dengue vasculopathy is complex. Not all sequential dengue infections result in DHF;[19] this can be affected by host factors such as ethnicity[20,21] or age[22,23] and viral aspects, including timing[24] or sequence[19] of infection, along with heterotypic cross-protection following infection.[25,26]

In patients at risk of severe disease, the severity, or virulence, of dengue infections is regulated by the antibodies (whether actively or passively acquired). Homologous antibodies can provide complete protection, while heterotypic neutralising antibodies can down-regulate disease. It has also been observed that enhancing antibodies increase the infected cell mass and disease severity. However, it is not understood how this works at the molecular level.[27]

During the 1997 Santiago de Cuba outbreak caused by DENV2 infection in patients previously exposed to DENV1, the severity of disease increased month by month. The genetic sequences of viruses collected over the course of the epidemic and the serum neutralising antibodies were analysed.[13,28] In this way, a single mutation in the non-structural genes of circulating DENV2 viruses might have contributed to viral survival or replication efficiency, thereby enhancing infection in the presence of antibodies.[28] This process was described by the researchers as 'increased viral fitness', rather than virulence, and might increase the severity of the disease during an outbreak.[28]

(iv) DHF is caused by Abnormal T-cell Responses

It has been proposed that, in dengue-infected individuals, abnormal and/or accelerated secondary T-cell responses leading to apoptosis contribute to increasing the severity of the immune elimination response.[29–33] According to this hypothesis, T-cells from a first infection are inefficient at killing target cells infected with a second virus and would attack infected macrophages, leading to increased cytokine production. These cytokines would affect the vascular endothelium, ultimately causing thrombocytopenia and altered vascular permeability.[34]

However, in patients with DHF, circulating cytokine levels are similar in infants with primary dengue infections and children of any age with secondary

dengue infection.[35] DHF/DSS in infants is attributed to antibody-dependent enhancement of dengue infections.[36–38] The ability of passively transferred dengue antibodies to enhance dengue viraemia has been demonstrated repeatedly in a monkey model.[39,40] Higher levels of dengue plasma viraemia during early disease stages were associated with increased risk of DHF in children with secondary DENV3 infection during a hospital-based prospective study.[41]

Because primary dengue infections in infants result in authentic DHF, a secondary immune response is not required to produce this syndrome. T-cell researchers need to study infant DHF/DSS to find immunological mechanisms that unify primary- and secondary-infection DHF. Clearly, if T-cell responses contribute directly to vascular permeability, T-cells responding to a first infection must be as efficient as T-cell responses to heterologous infection. However, it might be that T-cells responding to primary infections renders inefficient their response to a secondary infection.[33] Speculations that aberrant or abnormal T-cell responses cause DHF/DSS are unwarranted and unnecessary. It has long been noted that individuals with DHF are unusually healthy; surely their immune responses should be normal? Therefore, as two mechanisms cannot be responsible for the same pathology, aberrant or abnormal T-cell responses to dengue infection are not involved.

In the future, when time and effort are invested in studying the pathogenesis and immunology of infant DHF/DSS, it can be expected that a unified explanation will emerge. Meanwhile, it is important to remember that dengue infection in the presence of enhancing antibodies must produce an expanded infected-cell mass. T-cell responses, whether primary or secondary, should be proportional to this antigenic load.[42]

(v) DHF/DSS Results from an Auto-immune Process

Currently, several mechanisms are proposed to explain auto-immune responses to viral infections, including molecular mimicry.[43–45] Similarities have been observed between structural envelope and internal non-structural protein 1 (NS1) of dengue viruses and human proteins.[46,47] Furthermore, antibodies to dengue NS1 proteins have been shown to react with plasminogen and integrin,[47] platelets[48,49] and endothelial cells.[49]

However, the hypothesis that this observed structural mimicry is involved in the development of severe disease is inconsistent with the epidemiology and evolution of DHF. For example, in infant DHF, antibodies to envelope or NS1 DENV proteins are unlikely to appear earlier than the fifth day after onset of fever. However, thrombocytopenia in these infants is regularly detected on the second or third day after onset of fever, while vascular permeability occurs around day five. Crucially, thrombocytopenia and vascular permeability ease just as quickly as they begin. It is impossible to understand how NS1 antibodies can produce transient thrombocytopenia and endothelial damage as a result of an antibody response that lasts for many years. If auto-immune responses are mediated by antibodies, why does this not produce chronic vascular permeability and thrombocytopenia?[50]

(vi) DHF Results from Direct Infection of Endothelial Cells

If the hypothesis that dengue viruses replicate in endothelial cells is correct, it should be possible to observe viral antigens or virions within infected endothelial cells, as has been shown with other infections.[51] As yet, however, no unequivocal evidence of DENV infection of endothelial cells *in vivo* has been shown. Initial findings apparently showing evidence of dengue in endothelial cells was revealed to be dengue antigens on the surface of cells labelled as endothelial cells, and secondary probes showed no evidence of infection within the cells.[52]

During secondary dengue infection, DENV replication has only been observed within human hepatocytes, monocytes and macrophages.[53] Infection peaks after defervescence, with enhanced virus production resulting in a large cell mass. This attracts a massive T-cell response, leading to DSS.[54]

Conclusions

Dengue infection and the associated spectrum of syndromes are associated with a number of controversies, some of which have been empirically resolved while others require further study. In particular, a clinically and physiologically applicable case classification that will allow robust pathological research into the different levels of disease severity is a major priority.

Acknowledgments

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Community participation in the prevention and control of dengue: the *patio limpio* strategy in Mexico

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Community participation is vital to prevent and control the spread of dengue in Latin America. Initiatives such as the integrated management strategy for dengue prevention and control (IMS-Dengue) and integrated vector management (IVM) incorporate social mobilisation and behavioural change at the community level as part of a wider strategy to control dengue. These strategies aim to improve the efficacy, cost-effectiveness, environmental impact and sustainability of vector control strategies. Community empowerment is a key aspect of the strategy as it allows the local population to drive eradication of the disease in their environment. Through the *patio limpio* campaign, the concept of community participation has been employed in Mexico to raise awareness of the consequences of dengue. *Patio limpio* consists of training local people to identify, eliminate, monitor and evaluate vector breeding sites systematically in households under their supervision. A community participation programme in Guerrero State found that approximately 54% were clean and free of breeding sites. Households that were not visited and assessed had a 2.4-times higher risk of developing dengue than those that were. However, after a year, only 30% of trained households had a clean backyard. This emphasises the need for a sustainable process to encourage individuals to maintain efforts in keeping their environment free of dengue.

Keywords: Dengue, Community participation, Integrated vector management, Social mobilisation, Patio limpio

Background

In order to counter the significant public health burden of dengue in Latin America, the Pan American Health Organization (PAHO) has developed a regional initiative that utilises public participation at community level to encourage behavioural change as part of a wider strategy to control dengue.[1] The programme, known as the integrated management strategy for dengue prevention and control (IMS-Dengue), aims to promote the integration of key components to prevent and control dengue, including integrated vector management (IVM) (Fig. 1).[2,3]

This article discusses how community participation is vital to prevent and control the spread of dengue in Latin America.

Integrated Vector Management (IVM)

IVM is a global strategic framework first adopted in 2004 by the World Health Organization (WHO) for all vector-borne diseases (Fig. 2).[4] A further position statement by WHO in 2008 defined IVM as 'a rational decision-making process for the optimal use of resources for vector control'.[5] Its key elements are social mobilisation, environmental management, epidemiological and entomological surveillance, and chemical and biological control. IVM policies and strategies aim to improve the efficacy, cost-effectiveness, environmental impact and sustainability of vector control strategies in collaboration with the local community and other public and private sectors. Successful implementation of IVM strategies requires regulatory frameworks, decision-making criteria and execution of procedures that can be implemented down to the lowest administrative level.[5] This ensures that the concepts of IVM are promoted amongst relevant parties to strengthen legislation and public policy, ensure appropriate pesticide management and empower local communities.[6]

Social Mobilisation and Communication

Social mobilisation integrates different members of the community, from householders to political leaders, in order to raise awareness of dengue, deliver resources and services and ensure sustained community

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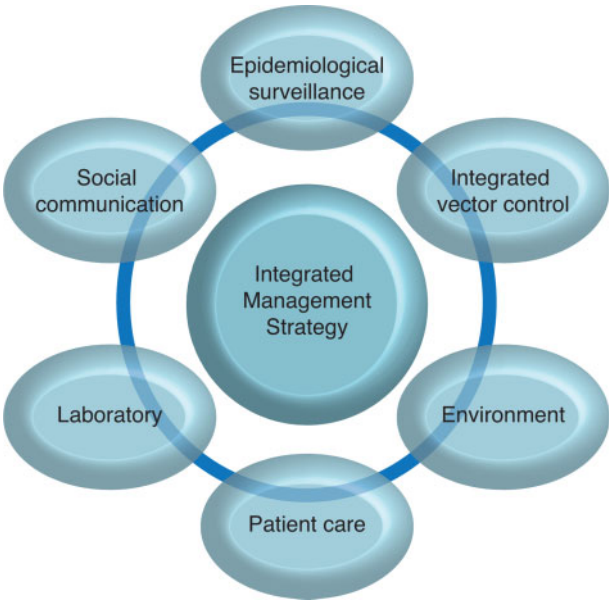

Figure 1 The integrated management strategy (IMS-Dengue) for dengue prevention and control[3]

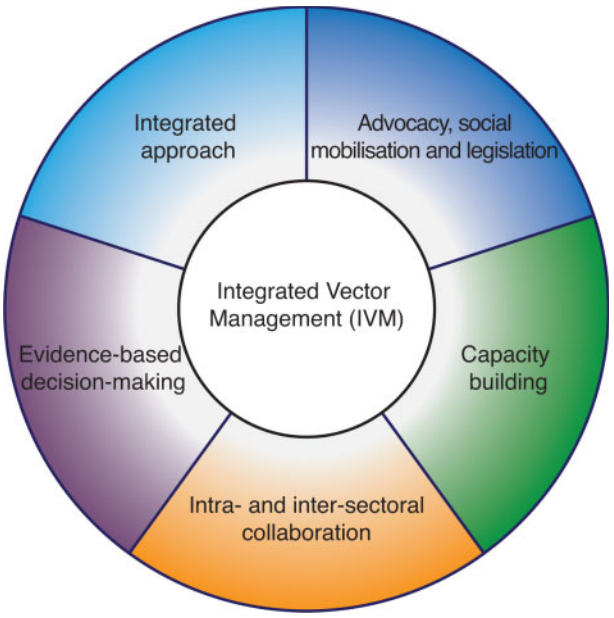

Figure 2 The components of integrated vector management (IVM)[4]

participation.[7] The concept of communication for behavioural impact (COMBI) is integral to social mobilisation and should be developed across multiple channels to ensure that information is passed throughout all levels of society.[7] The initiative aims to affect social behaviour by helping in the planning, implementation and monitoring of communicated actions which promote healthy behaviour. COMBI has been used successfully in other regions.[8]

Community empowerment is one of the most important elements of the IVM strategy, allowing the local population, who most suffer the consequences of dengue, to drive eradication of the disease in their environment.[7] Public participation is necessary at a number of stages in the local vector control strategy: in assessing the community's problems and needs, in implementing activities, and in evaluating and monitoring strategy.

Sustainable programmes and modification of individual behaviour are essential in mosquito-control initiatives. This means that individual households must accept responsibility for the control of mosquitoes in their surroundings. However, to maintain sustainability, such efforts should continue as long as the threat of dengue exists and become culturally embedded. To enable this, capacity-building and training of individuals in surveillance, laboratory diagnosis, case management and vector control are important for effective community interventions to be carried out.[7]

As part of the community mobilisation framework, leadership support from local political, religious and community heads is crucial to engage the local population. A multidisciplinary approach, for example between vector control personnel, entomologists, anthropologists, epidemiologists and social marketing experts, is also an important aspect of community mobilisation.[7]

Patio Limpio or 'Clean Backyard'

The concept of community participation as part of social mobilisation has been employed in Mexico in an attempt to raise awareness of the consequences of dengue and to explore how this can impact the risk of contracting the disease.[9] The initiative also underscores the need for hygiene in the home and instils this into local culture. The strategy, *patio limpio* in Spanish, or 'clean backyard', integrates surveillance information and vector control strategies with social mobilisation.

Patio limpio consists of training local people to identify and eliminate vector breeding sites in an organised manner. The strategy emphasises the importance of each household in the fight against dengue and the need for all households to work together with the common aim of living in a dengue-free community. The initiative relies on thorough cleaning of the home, which has benefits in addition to the creation of an environment free of dengue. These include an overall clean and presentable home, prevention of bites from other insect types as breeding sites are cleared, and the availability of the yard for recreational family activities. Furthermore, the family can work together as cleaning is an activity that can be carried out by all its members.

The implementation phase of the strategy begins with a local assembly in which the concept of group empowerment and the need for commitment from each household in keeping their surroundings clean and free of breeding sites are explained. Community leaders are identified for each block in the neighbourhood and

they are then empowered by being trained and given official identification as 'block activators'.

The role of block activators is to pass on to families in a given neighbourhood knowledge of how to identify and eliminate breeding sites and help them understand the benefits of keeping the household clean. Families are subsequently responsible for their own environment. Each block activator is responsible for visiting a number of households to train individuals in the process of vector breeding site identification and elimination. Block activators, usually women, also perform a monthly assessment of the area under their supervision and attend community assemblies. Larval indices are shared with block activators and recommendations are provided when expected outcomes are not met, which contributes to the concept of group empowerment.

Impact of Community Empowerment

The impact of community participation over 1 year (2007) on mosquito-breeding sites in Guerrero, a state in south Mexico, is shown in Table 1.[10]

More than 1000 block activators were generated and trained, with an average of approximately 15 households managed by each activator. From a sample of 5477 backyards, approximately 54% (2918) were designated as 'clean' and free of breeding sites. Further analysis revealed that households not visited and assessed by a block activator, had a 2.4-times higher risk of developing dengue, compared to those who had been trained and supervised by an activator. In addition, 80% of trained households were able to identify a breeding site and mosquito larvae at the 3-month follow-up visit. However, after a year, only 30% of trained households had a clean backyard and were conscious of the risks associated with breeding sites in their households. This emphasises the need for a sustainable process to encourage individuals to maintain efforts in keeping their environment dengue-free.

Social Communication in Guerrero

Social communication was an important element in the social mobilisation strategy employed in the State of Guerrero. The communication strategy included displaying 18 signboards and 130 posters, three daily loudspeaker transmissions in areas such as shopping centres and markets throughout the community, and distributing pamphlets to every household visited by block activators. Households already visited and trained were identified by stickers.[10]

Table 1 Results of community participation on vector breeding sites in Guerrero, Mexico, over a 12-month period (2007)[10]

Number of block activators trained	1192
Average number of households per activator	14.8
Number of backyards visited	5477
Number of clean backyards	2918
Clean backyards index (by recipients)	53.8%
Number of breeding sites identified	19,281

Vaccination and Vector Control in the Community

Even with the potential future availability of a dengue vaccine, community participation is crucial to achieving sustainable control programmes. There is a danger that, with the introduction of a vaccine, community members would regard social mobilisation and community participation as unnecessary. Further education should therefore clarify the role of a vaccine in dengue prevention and how its introduction should be combined with other aspects of vector control, such as community empowerment, in order to maintain preventive practices. The rotavirus vaccine is an example of the need to provide the public with information: communities at risk of infection had to be advised to maintain hygienic practices, despite the existence of a vaccine against rotavirus.[11]

Conclusion

Undoubtedly, dengue control programmes require a clear, integrated approach with strong community involvement, characteristics that are at the heart of the IVM and social mobilisation concepts. However, for sustained benefit, long-term behavioural modifications at an individual level are imperative. Results of the study carried out in a Mexican community demonstrate the need for community participation programmes to continue as long as dengue continues to be a threat in order to extend the benefits of such initiatives. The lack of continuity of long-term community participation programmes also results in subsequent reluctance by funding and government bodies to invest in and support such initiatives as these strategies fail to achieve desired goals and fulfil expectations. Consequently, these programmes are often relegated to serve as epidemiological projects during dengue outbreaks.

To encourage continuity of programmes, community leaders are effective channels through which to disseminate information, educate communities and catalyse behavioural change at the household level, in turn stimulating progress in the wider community.

Acknowledgments

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Dengue: an escalating public health problem in Latin America

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Dengue infection is a significant and escalating public health problem in Latin America. Its re-emergence and subsequent rise in the region over the past 50 years has largely been caused by a combination of a lack of political will, the radical growth of urban populations, migration flow and insufficient financial resources. Its increased incidence has been compounded by climate change, poor sanitation and extreme poverty, which lead to more breeding sites of the mosquito vector *Aedes aegypti*. In order to control dengue effectively, an integrated approach incorporating vector management and environmental and social solutions is required. To achieve success, these programmes require commitment and responses at both national and community level. The development of a vaccine is a vital tool in the fight against dengue. For successful introduction, those implementing vaccination need to be educated on the value of such a strategy. Effective political leadership, innovative financial mechanisms and co-operation across all disciplines, sectors and national borders are essential to eradication of the disease.

Keywords: Dengue, Latin America, Urbanisation, Vector management, Vaccine

Introduction

With more than 50 million cases reported to the World Health Organization (WHO) each year, dengue is now regarded as the world's most important mosquito-borne viral disease.[1] However, 60% of these reports are from the Americas, predominantly Latin America where the disease has re-emerged owing to re-infestation by the dengue vector *Aedes aegypti* following a period of eradication.[2]

The pattern of eradication of *A. aegypti*, its re-infestation and subsequent re-emergence of dengue in Latin America may serve as a warning of the challenges faced by other dengue-endemic regions such as South-east Asia, which has the highest dengue mortality.[2] Clinical, political and socio-economic factors have contributed to the re-emergence of the disease and integrated responses are required at national, regional and global levels. To bring about these changes, however, there will need to be significant changes in social and political attitudes.

This article discusses the increasing impact of dengue in Latin America.

The Re-emergence of Dengue in Latin America

Following the last recorded outbreak of dengue in continental USA, in 1945 in the Mississippi Delta, the Pan American Health Organization (PAHO) recommended an *A. aegypti* eradication programme in 1947.[3] This resulted in the Americas being an almost dengue-free zone from 1952 to 1965, when 19 Latin and Central American countries were certified as being free of *A. aegypti*. However, following an interruption in the vector control campaign, some countries in the region were re-infested with *A. aegypti* in 1967 and the first reports of dengue fever occurred soon after in 1968.[3]

The Spread of Dengue in Latin America

Since its re-emergence in Latin America, dengue has spread dramatically throughout the region (Fig. 1).[4] The number of dengue cases has risen from 1,033,417 in the 1980s to 2,725,405 in the 1990s, and 4,759,007 between 2000 and 2007.[5] Between 2001 and 2009, six countries accounted for more than 75% of all cases in the region: Venezuela, Brazil, Costa Rica, Colombia, Honduras and Mexico.[2] Furthermore, a change in the age-group profile of the disease was identified in the 2007 epidemic in Brazil.[6] Children were increasingly affected with severe dengue, more closely resembling the epidemiological profile in South-east Asia.

The Current Situation in Latin America

Table 1 shows the number of cases of dengue fever and severe dengue as well as the incidence rate of dengue

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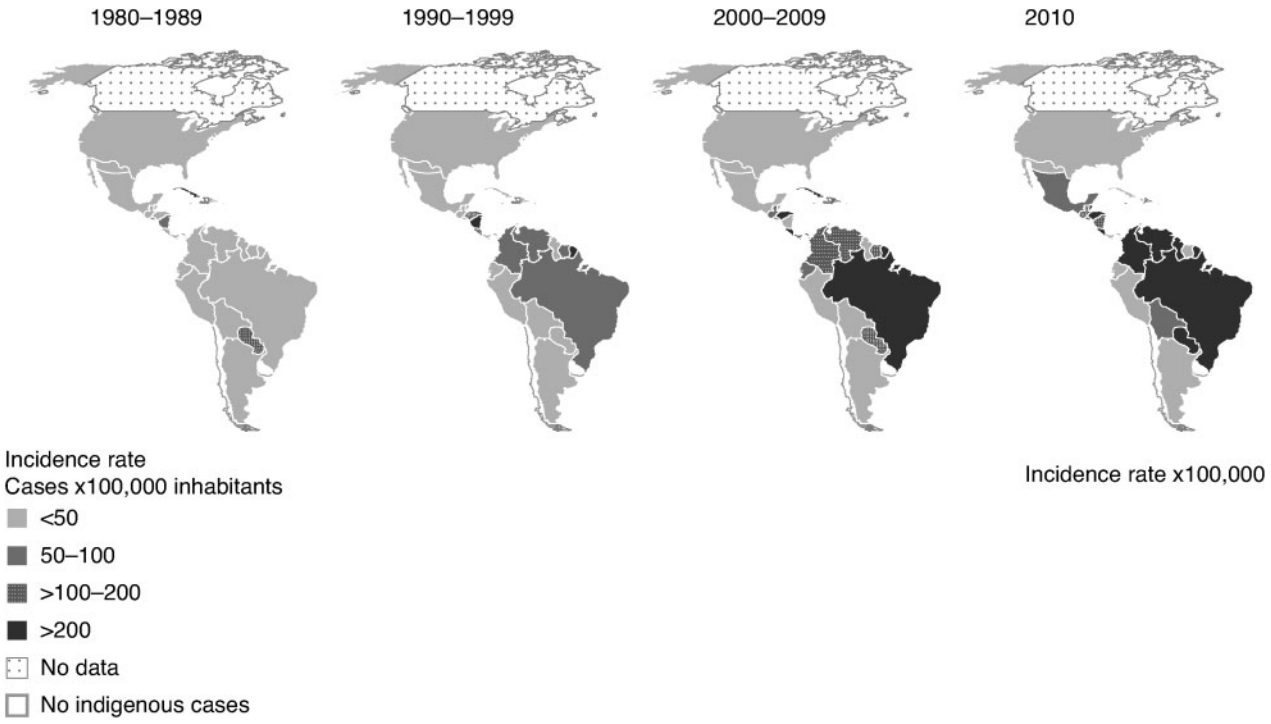

Figure 1 Average dengue incidence per 100,000 by country in the Americas, 1980–2010[4]

fever, the number of deaths and the case–fatality rate for 2010 (PAHO epidemiological week 52).[7]

By epidemiological week 50 in 2011, over 1 million cases of dengue fever had been reported throughout most Latin American countries, with over 18,000 cases of severe dengue and 716 deaths.[8] All four dengue serotypes are circulating in the region.[9]

Factors Influencing Re-infestation and the Challenges to Containment

Various political, environmental and social factors influenced re-emergence of the disease in the region in the late 1960s.[10] Following the passing of PAHO's resolution on vector control in 1947, only some Latin American countries had the political will to work on eradicating the vector.[10] Even in countries that successfully eliminated *A. aegypti*, interest in maintaining those efforts decreased over time. Furthermore, a slow response to re-infestation together with limited national budgets for vector control exacerbated the situation.[10]

Other determinants of the re-emergence of dengue have played a continuing role in its further dissemination. Dengue is largely an urban disease and, in the Americas, international travel and large-scale migration across the continent and changes from a rural to an urban environment have resulted in unprecedented urbanisation and the formation of mega-cities.[10,11] The accompanying overcrowding, poor sanitation and extreme poverty are optimal conditions for the establishment of vector breeding sites and dengue epidemics.[12] The impact of urbanisation is particularly significant in less developed countries such as those in Latin America where the local infrastructure is minimal and they are less able to cope with a swelling population.[11] Epidemics may become even more widespread in underdeveloped regions where the urban population is predicted to double by 2050 (Fig. 2).[11]

Although the link between climate change and dengue transmission is controversial, the intergovernmental panel on climate change and PAHO have concluded that climate change, leading to heavy rainfall, high temperatures and even drought, would cause a rise in infectious diseases such as dengue.[13] In fact, a 2008 study in Mexico found an association in many states between the incidence of dengue and increased temperatures and rainfall.[13]

Another consequence of uncontrolled urbanisation and climate change is an inadequate water supply,

Table 1 Cases of dengue and severe dengue in the Americas: incidence rate of dengue fever, number of deaths and case–fatality rate for 2010 (epidemiological week 52)[7]

Americas sub-region	Dengue fever	Incidence rate/100,000	Severe dengue	Deaths	Case–fatality rate
North & Central America & Mexico	205,756	140.0	10,411	152	1.46
Andean	305,744	294.1	19,744	224	1.13
Southern zone	1,019,130	418.9	16,570	688	4.15
Hispanic Caribbean	32,817	138.5	1,058	84	7.94
Caribbean	99,829	1258.1	1,171	46	3.93
Total	1,663,276	316.3	48,954	1194	2.44

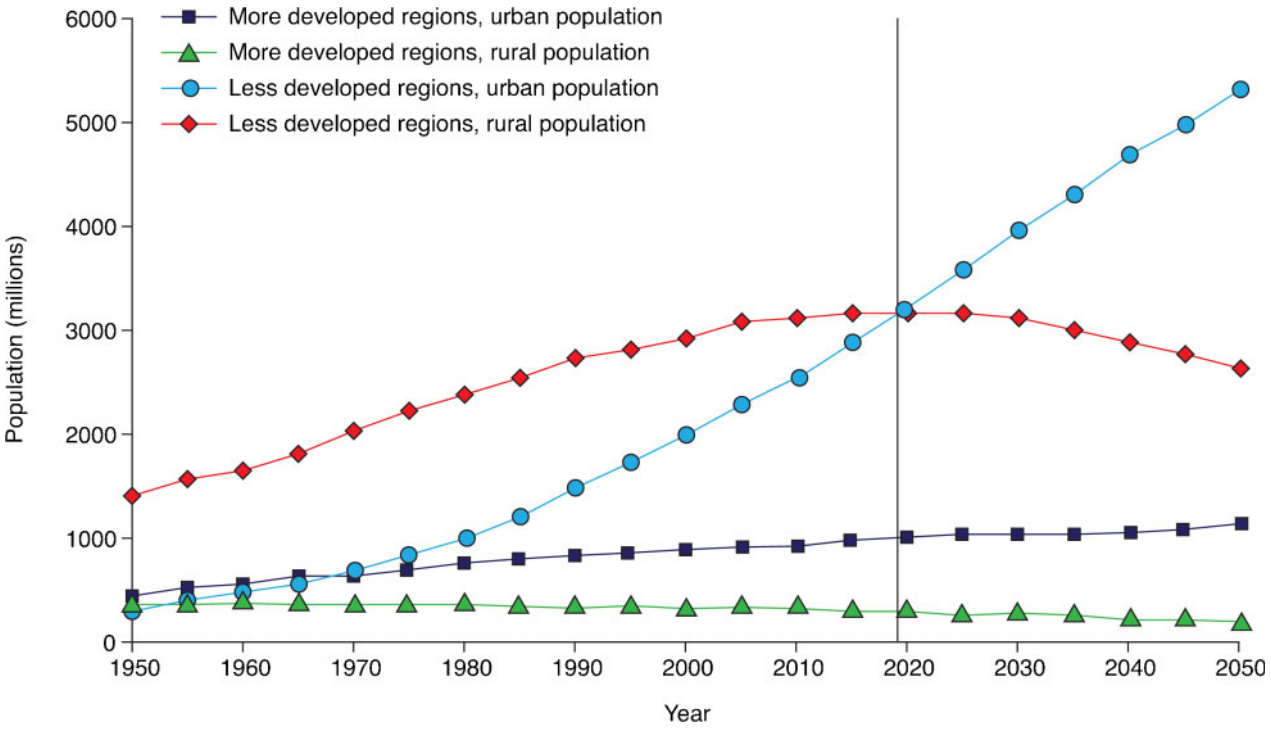

Figure 2 Global urban and rural population growth in developed and underdeveloped areas from 1950 to 2050.[11] Reprinted from Lancet Infect Dis, 11, Alirol E, Getaz L, Stoll B, Chappuis F, Loutan L, Urbanisation and infectious diseases in a globalised world, 131–241, Copyright 2012, with permission from Elsevier

leading to the domestic practice of storing water in containers, which serve as ideal vector breeding sites.[10,13] The abundance of these and other containers capable of holding water has led to increased vector densities and virus transmission.

Approaches to the Containment of Dengue

Control of dengue in the region will require an integrated approach to eradicate *A. aegypti* and improve living conditions and sanitation and, to be successful, national and community commitment will be needed.

PAHO has adopted a strategy to combat dengue through the destruction of *A. aegypti* using pesticides or disruption or removal of its habitat, known as the integrated management strategy for dengue prevention and control (IMS-Dengue).[14] The initiative aims to promote the integration of key components for dengue prevention and control, including integrated vector management (IVM). To sustain the benefits of vector control, the programmes emphasise collaboration between local communities and community leaders through social mobilisation and communication, as well as an interdisciplinary approach. IMS-Dengue and IVM will be discussed in further detail in this supplement in the article 'Community participation in the prevention and control of dengue: the *patio limpio* strategy in Mexico'.[15]

Government and community participation is particularly necessary following natural disasters such as floods. Strong and effective disease prevention and control measures are required before, during and, most importantly, after these events when public awareness of interventions is decreasing.

Reduction of vector breeding sites, such as used tyres, seems to be the most effective way to control the disease.[12] With increasing numbers of mosquito breeding sites, a basic cultural and societal shift in attitude to the storage of water and sanitation is required, which might be addressed by programmes such as IMS-Dengue.

Control of dengue in the region relies predominantly on funds being assigned for this purpose. Such funds, however, are rarely sufficient for the financial and health burden that dengue imposes. Recognition of the economic impact of dengue at both regional and national levels, coupled with scientific and social awareness, might facilitate appropriate apportioning of financial resources.[16]

In addition to a vaccine, the introduction of cost-effective technologies to impede vector breeding will be essential. To this end, effective leadership and commitment to act systematically using a multi-disciplinary and inter-sectoral approach, rather than discrete entities, are likely to have a significant impact on the disease.[12]

Preparation for Introduction of a Dengue Vaccine

With the lead candidate vaccine against dengue currently in the advanced stages of clinical development,[17] the availability of a licensed dengue vaccine is increasingly likely. If it is to be successfully introduced, however, several factors need to be considered.

These include the need for effective disease surveillance systems and laboratory networks that enable the determination of benchmark indicators for measuring the effects of the vaccine. The age-groups at risk of the disease, based on serological profiles, must be defined, as well as the vaccination strategies and target regions for use of the vaccine.[16]

In addition, local regulatory requirements must be anticipated by each country in the region to ensure that the vaccine is incorporated into national immunisation programmes as soon as it becomes available. Simultaneously, *ad hoc* decision-making bodies may be required as any delays in vaccination will inevitably lead to loss of life from the disease. Specially designed training programmes on the need for vaccination and its role in ongoing vector control strategies should therefore be made available to all those involved in its implementation.

Innovative mechanisms should be adopted to finance vaccination programmes, including cross-border schemes, to ensure that access to these programmes is not restricted for an individual nation because of inadequate resources.[16]

Finally, it is also essential to continue a vector control strategy, even with the availability of a dengue vaccine to limit the transmission of other infectious diseases for which *A. aegypti* is a vector.

Conclusion

The substantial burden imposed by dengue in Latin America encompasses all aspects of society and an effective prevention and control response must be widespread and inter-sectoral. Public policies that effectively influence the determinants of disease transmission, with the vector at the centre of the strategy, should be promoted and strengthened in order to have the greatest impact on eliminating the disease.

Although an effective dengue vaccination programme is vital, to be truly successful it must be accompanied by permanent changes in political and social attitudes to dengue. Therefore, effective leadership and commitment is paramount to contain and eventually eradicate dengue.

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The dengue situation in Africa

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Dengue outbreaks and epidemics have been reported in all regions of Africa, and it is believed that all four dengue virus serotypes are in circulation. Available data suggest that dengue is endemic to 34 African countries and that *Aedes aegypti* mosquitoes – the primary vector for dengue transmission – are known to be present in all but five countries. Whether populations in Africa are susceptible to dengue at the same rates as in Asia and Latin America is difficult to determine from the available data. Several factors may affect the transmission of dengue in Africa, including vector efficiency, viral infectivity, host vulnerability and environmental factors, such as increasing urbanisation. Current dengue prevention strategies in Africa focus on vector control, although the primary aim of such efforts is typically the prevention of malaria. Further research is needed to characterise the epidemiology of dengue in Africa and to better understand the factors involved in differences in vulnerability to dengue across Africa.

Keywords: Dengue, Africa, Epidemic, Epidemiology, Race

Dengue Risk Areas and Epidemic Activity in Africa

The World Health Organization (WHO) currently estimates that there are 50 million cases of dengue infection each year, with approximately 500,000 requiring hospitalisation. Of these severe dengue cases, approximately 5% will die.[1] *Aedes aegypti* mosquitoes – the primary vector for dengue transmission – are known to be present in all but five countries (Western Sahara, Morocco, Algeria, Tunisia and Libya), for which data are not available (Fig. 1).[2]

Dengue epidemics have been reported in Africa since the 19th century, in countries including Zanzibar (1823, 1870), Burkina Faso (1925), Egypt (1887, 1927), South Africa (1926–1927), and Senegal (1927–1928).[2] Between 1960 and 2010, 20 laboratory-confirmed outbreaks were reported in 15 African countries, with most occurring in Eastern Africa. All four dengue virus (DENV) serotypes have been isolated in Africa, with DENV2 reported to cause the most epidemics.[2]

Available data suggest that dengue is endemic to 34 countries across all regions of Africa (Table 1, Fig. 1).[2] Of these, 22 have reported local transmission, which is laboratory-confirmed in 20 countries, while two (Egypt and Zanzibar) do not have laboratory confirmation. The remaining 12 countries have only diagnosed dengue in travellers who had returned to non-endemic regions.

More detailed epidemiological data are required to assess the impact of dengue in Africa. Data on incidence and prevalence are not available for Africa, despite the fact that outbreaks have been recorded.[2] Under-reporting and under-recognition of dengue are key concerns, since the majority of febrile illnesses are treated as presumptive malaria.[2]

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Factors Influencing Transmission of Dengue Virus

Vector efficiency

The principal vector for dengue fever, *A. aegypti*, originated in Africa and has spread throughout the continent and to other tropical regions.[2] Other *Aedes* species present in Africa, which also act as potential vectors, include *A. albopictus*, *A. africanus* and *A. luteocephalus*.

Susceptibility of different mosquito strains to DENV has been shown to vary geographically. African strains of *A. aegypti* and *A. albopictus* have shown uniformly lower susceptibility to all four subtypes of DENV in laboratory settings.[3–5] This reduced vector efficiency for dengue transmission may explain the apparent lower than expected prevalence in Africa, though further study is urgently needed.[2]

Viral infectivity

Dengue is caused by four genetically related but antigenically different viruses (DENV1–4) and all four serotypes are present in Africa and maintained in enzootic cycles, most likely between non-human primates and arboreal mosquitoes.[6,7]

Although the enzootic forms of DENV may be becoming less infective in Africa, there is still a potential for endemic forms of the virus to emerge from sylvatic cycles between mosquitoes and non-human primates.[7] However, more infective varieties

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Figure 1 Dengue and *Aedes aegypti* in Africa.[2] The 34 countries in a dark colour indicate those in which dengue has been reported, including dengue reported only in travellers, and the presence of *Aedes aegypti* mosquitoes. Light-coloured areas indicate the 13 countries in which dengue has not been reported but where *Aedes aegypti* mosquitoes are present. White indicates five countries for which data are not available.

Table 1 Countries reporting transmission since 2000[2]

	Countries reporting overall transmission since 2000	Countries reporting transmission to travellers since 2000
West Africa	Burkina Faso Ghana Senegal Cameroon Côte d'Ivoire Cape Verde Equatorial Guinea Gabon Mali Togo	Equatorial Guinea Gabon Mali Togo
East Africa	Madagascar Zimbabwe Ethiopia Tanzania Uganda	Ethiopia Tanzania Uganda
Central Africa	Angola Democratic Republic of the Congo	Angola Democratic Republic of the Congo
Southern Africa	Namibia Zambia	Namibia Zambia

from Asia and the Western Pacific may be increasing in Africa due to travel, and it is thought that recent African outbreaks are due to spill-over from other regions rather than from sylvatic cycles.[2,8]

Host vulnerability

Race may be a factor in resistance to dengue infection, with some studies suggesting that black patients are more resistant. During a 1981 epidemic in Cuba, a country with a majority white but significant black population, white individuals were disproportionately susceptible to dengue infection, as well as to severe dengue and fatality.[9,10] Dengue cases were reported in Los Angeles in 1998, but only among Hispanic and white ethnic groups.[1] Genetic polymorphism in cytokines and coagulation proteins has been proposed as a potential mechanism conferring resistance to black individuals.[1]

Age is also a key factor in terms of vulnerability to dengue infection. While dengue fever is often thought

of as a childhood disease, it has been observed that the incidence of dengue haemorrhagic fever is increasing in older age groups.[1]

Travellers may be more susceptible to dengue infection than locals. This is particularly the case for travellers from non-endemic to endemic areas. It is not certain whether partial immunity among the locals may be responsible for this phenomenon.[11]

Environmental factors

Increasing urbanisation creates favourable conditions for increased transmission, increases in the vector population and perhaps changes in the ecological balance of different strains.[12] Since the 1950s, there has been a three-fold increase in urban population density across Africa.[13] Informal settlements can be associated with increased risk of dengue infection, since artificial water collection increases the available habitat for vectors.

Recent reports are however showing a global increase in rural epidemics, especially in Africa. This is one of the emerging paradigms of dengue fever. It is not certain whether this is related to modernisation of villages or deforestation shifting the vector nearer to settlements.[1]

Recent Epidemics and Dengue Prevention in Africa

Dengue epidemics have occurred in all regions of Africa in the 5 years between 2006 and 2011 (Table 2).[2] It is likely that all four subtypes of the dengue virus are present but the lack of formal laboratory testing or surveillance initiatives means that it is difficult to verify this.

Given the occurrence of dengue epidemics and the paucity of diagnostic infrastructure, preventative measures are required across Africa. Current dengue prevention strategies in Africa focus on vector control, although the primary aim of such efforts is typically the prevention of malaria.[14,15] Reduction of breeding sites and targeted destruction of vector populations with insecticides are used throughout all regions. Insecticide-impregnated bed nets are also provided in many regions, but inconsistent provision and low uptake may attenuate the benefits of this measure.[15] Personal protection is available for travellers, including insect repellants and information to raise dengue awareness.

Table 2 Overview of most recent epidemics in Africa[2]

Region	Year	Serotype	Reach
West Africa	2008–2009	3	Local and exported
East Africa	2009–2010	Unknown, 2	Local
Central Africa	2006–2007	Unknown	Local and exported
Southern Africa	2006	Unknown	Exported

Robust surveillance programmes must be established in Africa to accurately determine the true burden of dengue and – particularly in the dengue vaccine era – assess the effectiveness of prevention programmes.

Conclusions

Dengue fever outbreaks and epidemics are frequently reported in Africa, with recent outbreaks occurring predominantly in the Eastern region.[2,16] However, many outbreaks in Africa are not well characterised, due to the poor surveillance infrastructure and under-recognition of the disease. Whether populations in Africa are susceptible to dengue at the same rates as in Asia and Latin America is difficult to determine from the available data. The African population is thought to be less vulnerable to infection than other ethnic groups, and there may be differences in terms of vector efficiency and viral infectivity between Africa and other dengue-endemic regions. However, environmental factors, including rapidly rising urbanisation in Africa, are associated with increased transmission. Further research is needed to characterise the epidemiology of dengue in Africa and to understand in more detail the factors involved in differences in vulnerability to dengue across Africa.

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Dengue fever and dengue haemorrhagic fever in adolescents and adults

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Dengue fever (DF) is endemic in tropical and subtropical zones and the prevalence is increasing across South-east Asia, Africa, the Western Pacific and the Americas. In recent years, the spread of unplanned urbanisation, with associated substandard housing, overcrowding and deterioration in water, sewage and waste management systems, has created ideal conditions for increased transmission of the dengue virus in tropical urban centres. While dengue infection has traditionally been considered a paediatric disease, the age distribution of dengue has been rising and more cases have been observed in adolescents and adults. Furthermore, the development of tourism in the tropics has led to an increase in the number of tourists who become infected, most of whom are adults. Symptoms and risk factors for dengue haemorrhagic fever (DHF) and severe dengue differ between children and adults, with co-morbidities and incidence in more elderly patients associated with greater risk of mortality. Treatment options for DF and DHF in adults, as for children, centre round fluid replacement (either orally or intravenously, depending on severity) and antipyretics. Further data are needed on the optimal treatment of adult patients.

Keywords: Dengue, Adults, Adolescents, DHF, Dengue haemorrhagic fever, Age

Background

In hyperendemic areas in Asia, dengue fever (DF) and dengue haemorrhagic fever (DHF) affect mainly children under 15 years of age.[1] The age distribution is different in the Americas where these syndromes occur in all age groups, although the majority of fatalities during epidemics occur in children.[2] This article discusses the impact of dengue in adolescents and adults.

Dengue in Different Age Groups

Data from several South-east Asian countries have shown that the average/mean age of reported dengue cases has increased from 5–9 years to older children and adults.[3–7] In Thailand, affected adults over 15 years of age comprise 30–40% of dengue cases. At present, the morbidity rate of DHF is declining in Thailand, while the average age of patients with dengue infection is increasing.[8,9] Dengue infection in adolescents and adults is also a potential hazard in international travellers returning from endemic areas, especially South-east Asia,[10–13] a topic covered in more detail in the Wilder-Smith article 'Dengue infections in travellers' in this supplement.[14]

Dengue virus infection produces a spectrum of clinical illness ranging through undifferentiated fever, DF and self-limiting febrile illness associated with headache, myalgia and thrombocytopenia. DHF and dengue shock syndrome (DSS) are more serious and can be fatal.[15,16] The classification of dengue fever severity is explored in the Hadinegoro article 'The revised WHO dengue case classification: does the new system need to be modified?', also in this supplement.[17]

Several factors may influence disease severity, including host factors, virus serotype or genotype, sequence of virus infection, differences in dengue cross-reactive antibody, and T-cell responses.[18] DF is usually self-limiting, and death is uncommon. However, age-related differences in dengue severity are poorly understood and data on clinical features in adult patients are limited.[3–5] Older age has previously been reported to be a risk factor for mortality in patients with DF or DHF as the co-morbidities associated with ageing and waning immunity pose a substantial risk for fatality in elderly patients with active infection.[19,20] Although shock and plasma leakage seem to be more prevalent in younger patients, the frequency of internal haemorrhage augments as age increases.[21] Furthermore, complications of dengue infection observed in adults, including DF with unusual bleeding and DHF, have been increasing.[22–24]

Clinical Manifestations

The clinical characteristics in 140 adults infected with dengue virus during the Bangkok dengue epidemic in 1997–1998 are summarised in Table 1.

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Manifestations of dengue fever

During the acute febrile phase of DF, usually lasting 3–8 days, many of the clinical symptoms resemble those of DHF, including fever, nausea/vomiting, headache, rash and myalgia; abdominal pain and severe or widespread bleeding are less frequent in DF.[25] Minor haemorrhagic manifestations such as petechiae, epistaxis and gingival bleeding do sometimes occur in DF, although they are rarely associated with severe haemorrhage leading to shock.[26]

Manifestations of dengue haemorrhagic fever

Owing to differences in capillary permeability, adults may be at lower risk than children of developing DHF.[27] DHF can be distinguished from DF by the presence of increased vascular permeability (plasma leakage syndrome) and marked thrombocytopenia (<100,000/μl) associated with bleeding, hepatomegaly and/or abnormal liver function. Acute respiratory failure, although a rare complication in adults, has a high mortality rate.[28] Although children are more likely to develop hypovolaemic shock characterised by increased microvascular permeability in DHF, a high mortality rate has been observed in adult patients.[29] The outcome of DHF and DSS depends largely on early diagnosis and the immediate replacement of fluid.

Haemorrhage contributes to dengue morbidity and mortality, especially during the severe thrombocytopenia and toxic haemorrhagic stage (3–5 days after illness onset).[30] In Thailand, bleeding manifestations including petechiae, epistaxis and menorrhagia have been observed frequently in adults with DF or DHF (own data, Table 1), although upper gastro-intestinal (GI) bleeding is the most common type of severe haemorrhage.[30] In reports of endoscopic examination of dengue patients with upper GI tract bleeding, haemorrhagic gastritis was the most common finding (40.9–58.5%).[31–33] However, massive haematemesis may occur in adults with DF or DHF owing to peptic ulcers, which is not associated with profound shock, as in previous reports in children.[33] In patients with pre-existing peptic ulcers, severe or even fatal bleeding can be precipitated by dengue infection, though in most cases supportive therapy and blood transfusions are adequate to manage this complication.[33] Subcapsular splenic bleeding and rupture have also been reported in adults with dengue infection.[34,35] However, splenic rupture in patients with haemorrhagic dengue is uncommon and can happen spontaneously or as a result of trauma, which may be minor or unnoticed.[34,35]

Menorrhagia is common in female adults with DF/DHF (up to 25%).[7] Uterine haemorrhage resulting in spontaneous abortion, premature labour and severe postpartum bleeding has been observed in women with DF/DHF.[36–38] In patients with dengue during onset of labour, blood or platelet transfusion may be required in cases with severe bleeding or where caesarean section is required.[38,39]

Increased liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] have been found in children and adults during dengue infection, indicating liver involvement.[40–42] Unlike conventional viral hepatitis, AST level is higher than ALT in dengue infection,[41] with levels increasing to a maximum 7–9 days after onset of symptoms, decreasing to normal within 2 weeks.[41] Pre-existing liver disease such as chronic hepatitis and haemoglobinopathies are

Table 1 The clinical manifestations of DF in 140 adults during the Bangkok epidemic in 1997–1998

	DF/DHF *n*=140	DF *n*=89	DHF *n*=51
Age, y, mean, [range]	26.9 [15–67]	28.6 [15–67]	23.4 [15–44]
Total duration of fever, d, mean, [range]	5.2 [2–8]	5.2 [2–8]	5.2 [3–8]
Fever, %	100	100	100
Nausea/vomiting, %	47.1	40.4	58.8
Headache, %	37.8	38.2	37.3
Diarrhoea, %	25.0	33.3	21.2
Myalgia, %	25.7	25.8	25.6
Abdominal pain, %	23.6	12.3	43.1
Haemorrhagic manifestations, %	35.7	24.7	54.9
Petechiae	22.1	14.6	35.2
Epistaxis	7.8	4.4	14.3
Gum bleeding	7.1	5.5	10.2
Haematemesis	2.1	0	5.9
Vaginal bleeding	24.6	21	31.6
Bleeding >2 sites	27	6.7	19.6
Rash (occurring in convalescence), %	27.8 (5)	31.5	21.6
Hypotension/pulse pressure <20 mmHg, %	2.1	0	5.8
Jaundice, %	0.7	0	1.9
Epigastric or RUQ tenderness, %	18.6	10.1	29.4
Hepatomegaly, %	21.4	11.2	39.2
Splenomegaly (by ultrasonography), %	2.1	0	5.9
Ascites (by ultrasonography), %	3.6	0	9.8
Pleural effusion (by chest radiograph), %	10.7	0	29.4

RUQ, right upper quadrant

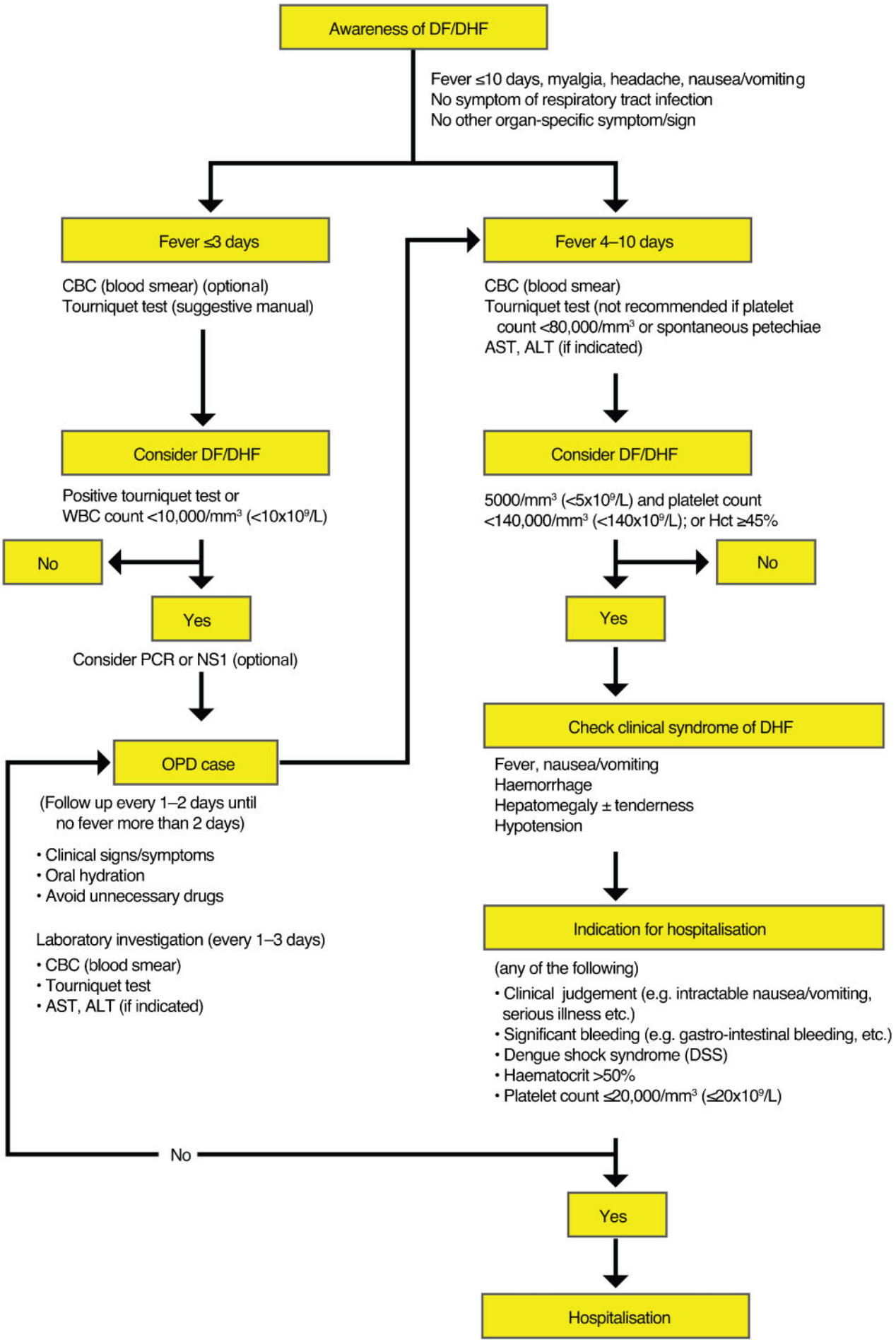

Figure 1 Management of adult dengue in Thailand (clinical practice guidelines by the Infectious Diseases Society of Thailand, 2006)

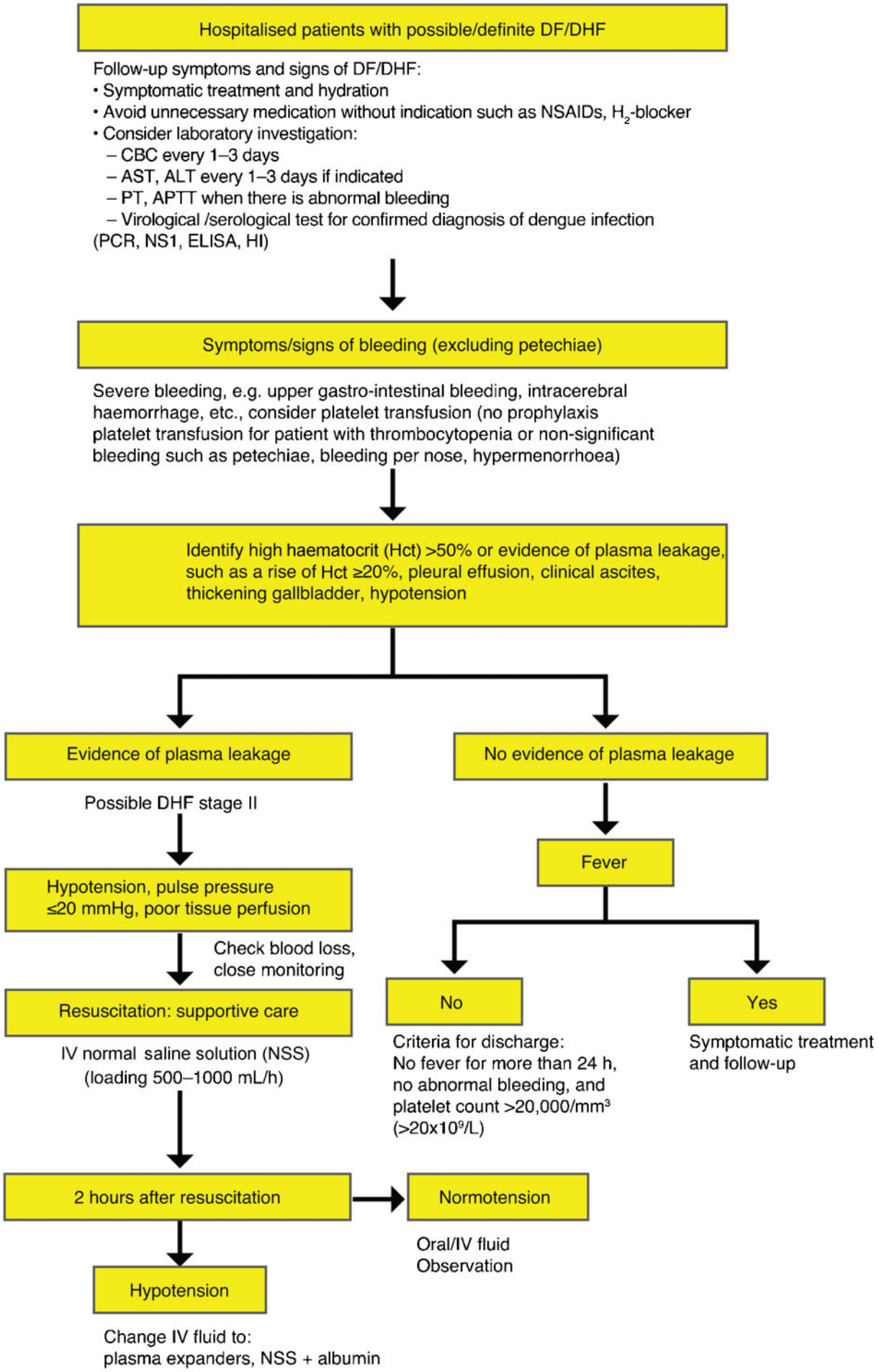

Figure 2 Management of adult dengue in Thailand, continued (clinical practice guidelines by the Infectious Diseases Society of Thailand, 2006)

more likely to be present in adults than in children with dengue and may aggravate the liver impairment.[19,43] Liver injury is often self-limiting, but fulminant hepatitis and death have been reported.[42,44] The association between severe liver disease and encephalopathy is well described in children and adults with DF/DHF, and high mortality has been reported in dengue patients with hepatitis and encephalopathy.[45]

More unusual manifestations of dengue infection in adults include severe internal haemorrhage, cardiomyopathy, cardiac arrhythmias, adult respiratory distress syndrome (ARDS), rhabdomyolysis, pancreatitis, appendicitis, co-infection with other tropical diseases, and neurological phenomena such as altered consciousness, seizures and coma owing to encephalitis and encephalopathy.[46–53] Neurological manifestations secondary to dengue infection were ascribed to non-specific complications such as myelitis, optic neuritis, polyradiculopathy or neuropathy.[54,55] Possible causes of dengue encephalopathy include hypotension, cerebral oedema, focal haemorrhage, hyponatraemia and fulminant hepatic failure.[51,55,56] However, a recently documented possibility is dengue invasion of the nervous system.[57,58] Furthermore, some studies have indicated that 5.5% of patients with DHF have dual infections such as urinary tract infection, diarrhoea or bacteraemia.[19] Failure to correctly diagnose any concurrent infection in patients with DHF may lead to greater morbidity or mortality, which would otherwise be preventable. Prolonged fever and acute renal failure are independent predictive factors for dual infection.[19]

Treatment of Dengue Infection in Adults

Currently, there are no specific therapeutic agents for dengue. In adults, early recognition of dengue infection, bleeding and signs of circulatory collapse reduces mortality with dengue (Figs 1 and 2).

Mild dengue infection may be treated with oral hydration and antipyretics.[59] Agents such as salicylates, non-steroidal anti-inflammatory drugs and traditional medicines that may have hepatotoxic effects must be avoided.[16] Attentive clinical monitoring of patients with suspected DHF, along with anticipatory and supportive care, are life-saving and reduce fatality rates. To identify the need for intravenous fluid therapy, circulation and vascular leakage must be monitored by serial clinical assessments of pulse, blood pressure, skin perfusion, urine output and haematocrit.[16] Patients with DHF need to be monitored closely for signs of shock for at least 24 hours after defervescence.[29] Prompt fluid resuscitation remains the mainstay of treatment to counteract massive plasma leakage. In most adult cases, timely and effective intravenous crystalloid replacement of plasma losses results in a favourable outcome. If shock persists, immediate volume replacement with Ringer's lactate, Ringer's acetate or physiological saline should be followed by plasma or colloid solutions.[60] Recently, three randomised controlled trials evaluated therapeutic responses to colloid and crystalloid solutions.[61–63] Results indicate that Ringer's lactate performed least well.[61–63] Patients with a narrow pulse pressure ($\leqslant$10 mmHg), indicating more severe DSS, should benefit from initial resuscitation with colloid solution rather than crystalloid solution.[61–63] Preventive transfusions may be harmful and should be avoided, and invasive procedures should be minimised to avoid haemorrhagic complications.

Conclusion

Dengue infection is generally considered to be a paediatric disease but is currently a growing problem in adults throughout the tropics. Furthermore, dengue infection can be more severe in adults in whom early recognition of dengue infection, bleeding tendencies and signs of circulatory collapse would reduce mortality. Fluid replacement is the gold-standard therapeutic option for adults with dengue fever, as it is for children. However, further studies in adults are required to establish the best therapeutic approaches and determine whether any specific factors should be considered in terms of warning signs and risk factors.

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Dengue infections in travellers

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Dengue has been designated a major international public health problem by the World Health Organization (WHO). It is endemic in most tropical and sub-tropical countries, which are also popular tourist destinations. Travellers are not only at significant risk of acquiring dengue but they also contribute to its spread to non-endemic regions. Furthermore, they may serve as sentinels to alert the international community to epidemics in dengue-endemic regions. GeoSentinel, a global surveillance network, monitors all travel-related illnesses and estimates that dengue accounts for 2% of all illness in travellers returning from dengue-endemic regions. In fact, in travellers returning from South-east Asia, dengue is now a more frequent cause of febrile illness than malaria. Dengue-infected travellers returning home to countries where the vector exists can place the local population at risk of further spread of the disease with subsequent autochthonous cycles of infection. The true incidence of dengue amongst travellers may be underestimated because of variability in reporting requirements in different countries and under-diagnosis owing to the non-specific clinical presentation of the disease. Risk factors for acquiring dengue include duration of stay, season of travel and epidemic activity at the destination. Any pre-travel advice on the risks of developing dengue infections should consider these factors.

Keywords: Dengue, Travellers, GeoSentinel, Autochthonous spread, Sentinel surveillance

Introduction

Dengue is endemic in most tropical and sub-tropical countries, and has been designated a major international public health concern by the World Health Organization (WHO) (Fig. 1).[1,2] Many countries in dengue-endemic regions are also popular tourist destinations, and the rise in international travel to these regions has played a significant role in the global spread of the disease.[3] With forecasts of international tourist arrivals predicted to reach 1.8 billion by 2030, increasingly involving emerging growth markets in Asia and Latin America,[4] the potential for dengue to expand to areas currently free of the disease is significant.

Travellers are at significant risk of acquiring the disease and also contribute to its spread to non-endemic regions.[5] They may further serve as sentinels to alert the international community to epidemics in dengue-endemic regions and to the spread of dengue virus serotypes and genotypes.[6] This article discusses the impact of travel in the epidemiology of dengue infections.

Epidemiology and Risk of Travel-Related Dengue

An estimated 50 million dengue infections occur every year, with approximately 2.5 billion people living at risk of infection in endemic regions.[6] There has been a 30-fold increase in the incidence of dengue over the past 50 years, with spread to new regions; and international travel is increasingly a contributory factor.[6]

GeoSentinel, a data-collection network that monitors all travel-related illnesses across 54 clinics globally, has estimated that dengue accounts for 2% of all illness in travellers returning from dengue-endemic regions.[7] A study found that, between 1997 and 2006, dengue was imported most commonly from South-east Asia (51%), followed by South Central Asia (17%), Latin America (15%), the Caribbean (9%), parts of Africa (5%) and Oceania (2%).[7]

The proportion of febrile travellers returning from tropical and sub-tropical countries being diagnosed with dengue has increased from 2% in the early 1990s to 16% by 2005.[3] Dengue is now a more frequent cause of febrile illness than malaria in travellers returning from South-east Asia.[8]

Prospective seroconversion studies of travellers to endemic countries estimated an incidence of 2.9% in Dutch travellers who spent approximately 1 month in Asia[9] and 6.7% in Israelis who travelled to tropical countries for approximately 6 months.[10] However, the true incidence of dengue in travellers may be underestimated because of variability in reporting requirements in different countries and under-diagnosis owing to the non-specific clinical presentation of the disease.[11]

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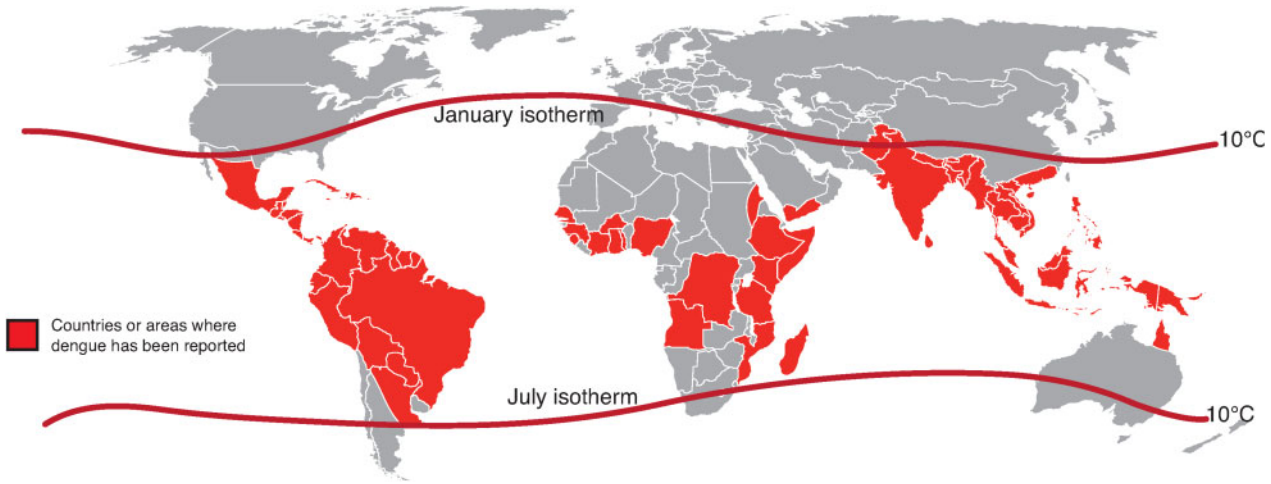

Figure 1 Regions at risk of dengue transmission in 2010, as indicated by the contour lines of the January and July isotherms, which define the geographical limits between which *Aedes aegypti* survives year-round[2]

Spread of Dengue to New Regions

Dengue-infected travellers returning home can place the local population at risk of further spread of the disease wherever the mosquito vectors, *Aedes aegypti* and/or *A. albopictus*, the primary and secondary vectors, respectively, are present.[6] The increasing global spread of the vectors means that many non-endemic countries harbour populations of mosquitoes capable of spreading the dengue virus introduced by infected returning travellers.[3]

In Europe, for example, imported cases of dengue have been reported to have risen from 64 in 1999 to 224 in 2002, although the number of reported cases has subsequently stabilised.[12] Dengue infections occur commonly in US citizens returning from endemic areas and are more prevalent than malaria among those returning from the Caribbean, South America, South Central Asia and South-east Asia.[13] Australia has also seen a dramatic rise in the number of dengue cases in returned travellers, particularly those who have visited South-east Asia, with an increase of approximately 350% in the number of reported dengue cases between 2004 and 2007 and 2008 and 2011.[14,15]

Following the return from dengue-endemic countries of infected travellers, autochthonous cycles of infection can subsequently be established.[3] Locally acquired dengue infections have been reported in Europe,[16,17] the United States (US)[18] and Australia.[19]

Populations in non-endemic countries may also be at risk of acquiring dengue by other means. Although representing only a small proportion of dengue cases, the disease can also be spread by mechanisms not involving mosquitoes as vectors, such as hospital-acquired transmission mainly through blood transfusion. Dengue transmission via needle-stick injury[20] or mucocutaneous exposure to blood[21] has been reported in healthcare workers in non-endemic countries. However, blood products are not screened for dengue, and further studies are needed to assess the risk of infected blood for transmission.[22]

Travellers as Sentinels

Travellers may also play an important role as sentinels in alerting the international community to the onset of epidemics in endemic regions where surveillance is often poor.[6,23]

During a 2002 epidemic in South-east Asia, for example, GeoSentinel provided an international alert by publicising an increase in travel-related dengue originating from Thailand,[24] before official Thai surveillance data became available. Furthermore, analysis of the 1998 travel-related disease pattern of infection from the GeoSentinel database predicted the 2002 epidemic.[7]

Seasonality and Trends in Dengue Infections

Risk factors for acquiring dengue include duration of stay, season of travel and epidemic activity at the destination.[7–9] Although reports of dengue cases increase in the rainy season, this varies according to country and even between regions within countries. It is therefore difficult to definitively correlate rainfall with the incidence of dengue.[7]

The GeoSentinel study of cases between 1997 and 2006 examined the seasonality of dengue (Fig. 2).[7] Seasonal patterns were observed during the study period in Asia, the Caribbean and South America, but were not as strong in Central America and Africa. However, the study demonstrated a difference in seasonality between outbreak and non-outbreak years. For South-east Asia, for example, there were peaks in dengue cases in June and September in non-epidemic years, while during epidemics excess cases were recorded for almost every month, particularly during April to August. Results of the study therefore suggest that any pre-travel advice on the risks of

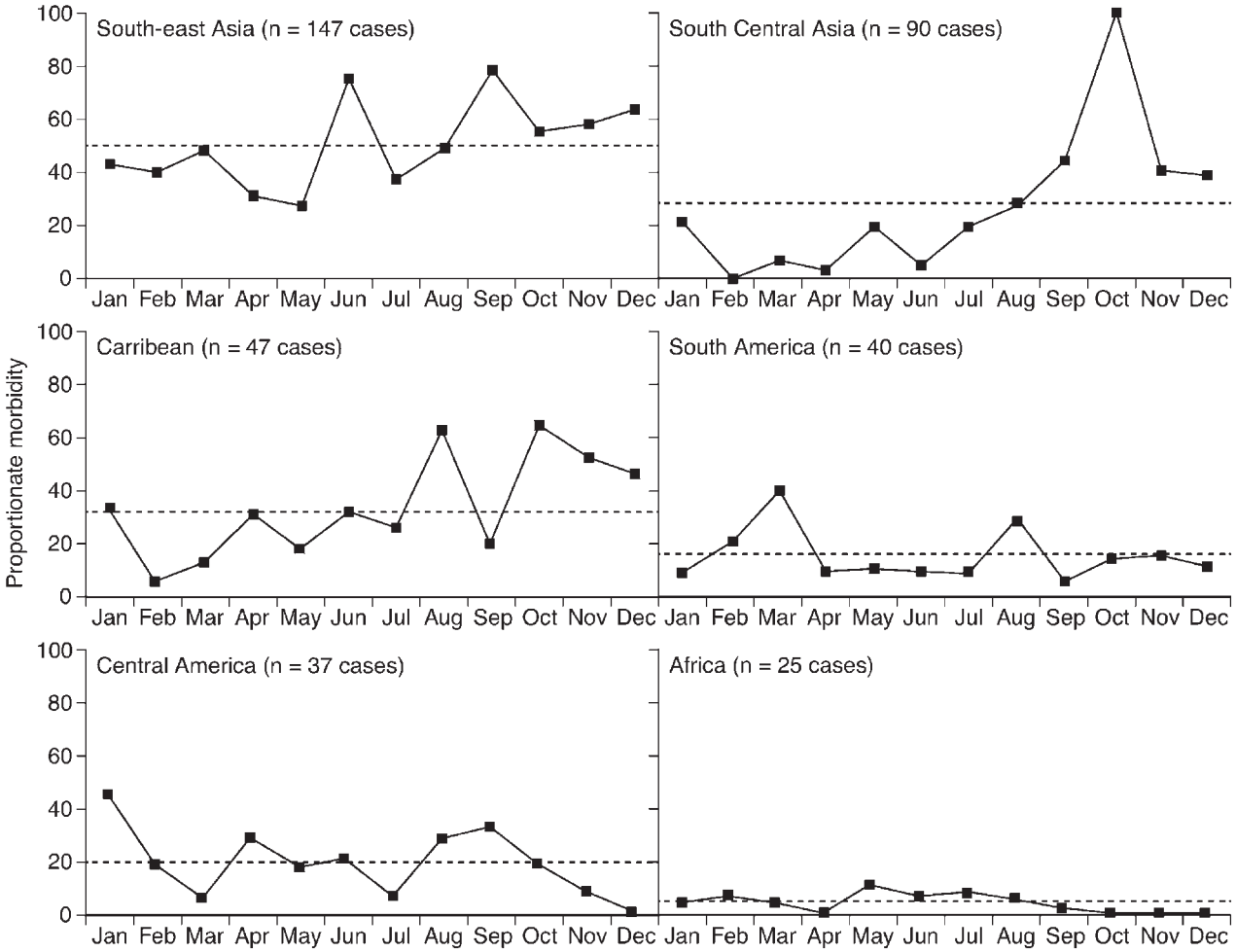

Figure 2 Seasonality of dengue in returned travellers according to region. The dashed lines represent the mean proportionate morbidity (the number of dengue cases per 1000 ill returned travellers) in travellers for all months for the specified region during 1997–2006[7]

developing dengue infections should consider epidemic activity and seasonal patterns.

Mathematical models take these risk factors into account and may be useful tools in providing evidence-based estimates of the risk of dengue transmission in travellers to dengue-endemic regions. For example, such models estimated that a non-immune traveller staying in Singapore for 1 week during the high season in 2005 had a 0.17% risk of acquiring dengue.[25]

Characteristics of Travel-Related Dengue

A large proportion of cases of travel-related dengue, as in endemic populations, are asymptomatic or minimally symptomatic.[9,26] However, when symptoms do develop, because of their non-specific nature, they are often misdiagnosed as some other febrile illness such as chikungunya, malaria, typhoid fever and rickettsial infection.[23] Furthermore, as laboratory-based diagnosis is often unavailable at the time of care, diagnosis frequently has to be made solely on the clinical presentation.[3] However, in patients with febrile illness, life-threatening but potentially treatable diseases such as typhoid fever and malaria should always be excluded first. Also, given the short incubation period, a diagnosis of dengue is unlikely if the initial presentation is more than 2 weeks after return from an endemic country.[3]

Dengue disease is considered to occur as a continuous spectrum of severity.[27] The current WHO case definition for diagnosis of dengue is separated into patients with severe and non-severe dengue, with the large group of those with non-severe dengue being sub-divided into patients with and without warning signs.[6] Surveillance reports from the European Network on Imported Infectious Disease Surveillance (TropNetEurop) showed that European travellers present with a wide variety of symptoms, but the majority with a confirmed or probable diagnosis of dengue presented with uncomplicated dengue with the typical symptoms of fever, headache, fatigue and musculoskeletal pain.[22]

However, certain combinations of clinical features and laboratory abnormalities may be better able to predict dengue in travellers. In a study of ill returned Australian travellers, a diagnosis of dengue was 18-, 71-, and 230-times more likely if the combinations of fever and leucopenia, fever and rash, and fever, rash

and leucopenia, respectively, were present.[14] Owing to the increasing prevalence and non-specific symptoms of dengue, it is important that healthcare professionals across the world be familiar with its clinical features.

Dengue *vs* Malaria

The GeoSentinel study described above compared traveller characteristics in patients with dengue and malaria.[7] Dengue affected both sexes equally, unlike malaria, which affected male travellers more frequently than female travellers. Duration of travel was slightly shorter for travellers with dengue who visited as tourists than for those with malaria who predominantly visited friends or relatives.

Severe Dengue

According to the WHO case definition, severe dengue, encompassing the symptoms of dengue haemorrhagic fever (DHF), is characterised by severe plasma leakage, haemorrhage and organ impairment.[6] Severe dengue appears to be less common in travellers than in populations in endemic countries.[12] In endemic areas, approximately 6% of symptomatic dengue cases progress to DHF.[28] In comparison, intensified surveillance in travellers performed within TropNetEurop revealed that, of 219 dengue-infected travellers, 0.9% fulfilled the 1997 WHO criteria for DHF,[29] although 11% of patients experienced severe clinical manifestations.[30]

Secondary dengue infection is considered to be a significant risk factor for DHF[31] as it is thought that non-neutralising cross-reacting antibodies from the primary infection enhance the infecting ability of virus particles.[32] Given their lack of previous exposure, travellers are unlikely to have pre-existing antibodies to dengue.

Another contributory factor to the lower incidence of DHF in travellers is that the large majority are adults[33] who are reported to have a lower risk of DHF than children.[34]

Dengue in Children

Children represent a significant proportion of the travelling public, accounting for 7% (1.9 million) of travellers living in the US.[33] Classic and severe dengue in children pose a significant burden on endemic countries such as Thailand, which has a mean annual burden attributable to dengue of 465.3 disability-adjusted life-years over 5 years.[35]

A study of over 1500 ill paediatric travellers reporting to GeoSentinel clinics in 19 countries identified dengue and typhoid fever as the most frequent causes of systemic febrile illness in children returning from tropical regions other than sub-Saharan Africa.[33]

Children have a higher risk than adults of developing severe dengue,[34,36] a leading cause of morbidity and death in this age-group (Fig. 3).[34] The risk of mortality from a secondary infection is nearly 15-fold higher than in adults.[36] It is believed that 10% of children with secondary infection go on to develop DHF.[31]

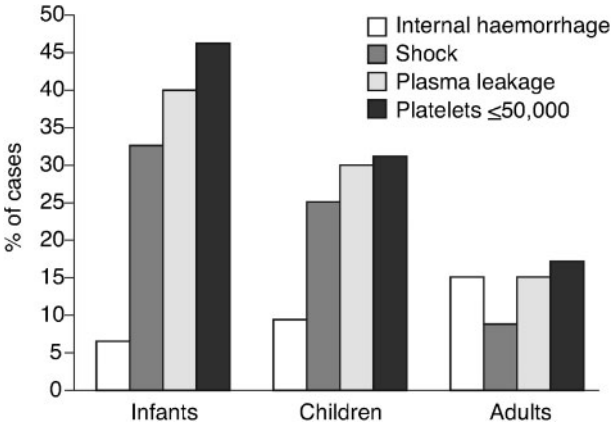

Figure 3 Prevalence of severe dengue symptoms (internal haemorrhage, shock, signs of plasma leakage and/or marked thrombocytopenia) in infants, children and adults[34]

Protection for Travellers Against Dengue

There is currently no licensed dengue vaccine, and measures such as vector control are proving inadequate in reducing the incidence of the disease.[37,38] Therefore, with only supportive treatment of dengue available, protection against dengue is limited to avoidance of mosquito bites with the use of insect repellents, protective clothing and insecticides.[39] Avoidance of litter and containers with stagnant water is also advised.[39] Protective measures need to be taken during the day as this is when mosquitoes bite, with only limited effectiveness of night-time measures such as insecticide-treated bed-nets.[3] An effective and cost-effective vaccine against dengue would therefore be a major advance in controlling the disease.[28,38] Given the high incidence of the disease in travellers, a vaccine for them may also be indicated, provided that it is safe, convenient to administer and affordable.[40] The vaccine candidate furthest in development is a chimeric vaccine by Sanofi Pasteur. With the lead candidate vaccine showing encouraging results in late-stage clinical trials, the outlook for introduction of a vaccine against all four dengue serotypes into national immunisation programmes of endemic countries is promising.[41]

Conclusion

The incidence of dengue in international travellers, including children, is rising. Furthermore, travellers contribute to the geographic spread of dengue and its introduction to previously uninfected areas. The rising numbers of dengue cases reported worldwide, and identification of locally acquired dengue infections in non-endemic regions, emphasise the need for surveillance of travellers returning from endemic

areas. Since the incidence of dengue demonstrates seasonality and variation according to destination of travel, pre-travel advice should take into account epidemic activity, seasonal patterns and travel destination.

Acknowledgments

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The revised WHO dengue case classification: does the system need to be modified?

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There has been considerable debate regarding the value of both the 1997 and 2009 World Health Organization (WHO) dengue case classification criteria for its diagnosis and management. Differentiation between classic dengue fever (DF) and dengue haemorrhagic fever (DHF) or severe dengue is a key aspect of dengue case classification. The geographic expansion of dengue and its increased incidence in older age groups have contributed to the limited applicability of the 1997 case definitions. Clinical experience of dengue suggests that the illness presents as a spectrum of disease instead of distinct phases. However, despite the rigid grouping of dengue into DF, DHF and dengue shock syndrome (DSS), overlap between the different manifestations has often been observed, which has affected clinical management and triage of patients. The findings of the DENCO study evaluating the 1997 case definitions formed the basis of the revised 2009 WHO case definitions, which classified the illness into dengue with and without warning signs and severe dengue. Although the revised scheme is more sensitive to the diagnosis of severe dengue, and beneficial to triage and case management, there remain issues with its applicability. It is considered by many to be too broad, requiring more specific definition of warning signs. Quantitative research into the predictive value of these warning signs on patient outcomes and the cost-effectiveness of the new classification system is required to ascertain whether the new classification system requires further modification, or whether elements of both classification systems can be combined.

Keywords: Dengue, Classification, Diagnosis, World Health Organization

Introduction

Approximately 1 million cases of dengue, a major cause of morbidity in tropical and sub-tropical regions, are reported annually to the World Health Organization (WHO).[1] The 2009 revised WHO dengue case classification for the diagnosis and management of the illness follows previous guidelines published by WHO between 1974 and 1997.[1,2] This article investigates the clinical application of the 1997 and 2009 criteria to the reporting and management of dengue and the difficulties of using the classification schemes. The article also explores whether the changes to the 1997 guidelines have been beneficial and discusses whether the revised 2009 guidelines may benefit from further modification.

Clinical Presentation of Dengue

Expert consensus groups have suggested that dengue is a single entity with different clinical presentations and infected patients present with a range of clinical symptoms that vary according to severity and age.[3] Infection by any of the four dengue serotypes may be asymptomatic or lead to classic dengue fever (DF) or more severe forms of the disease, haemorrhagic fever (DHF) and dengue shock syndrome (DSS).[4] Confirmation of dengue infection may be possible during the acute phase by testing the serum for presence of the non-structural protein (NS1) antigen.[5] Following an incubation period, the illness begins abruptly, going through three phases: febrile, critical and recovery.[6] DF is observed more frequently in adults and adolescents, and can present with either mild fever only or a more incapacitating disease. This latter presentation is characterised by the sudden onset of high fever, severe headache, retro-orbital pain, myalgia, arthralgia and rash,[3,7] symptoms occurring predominantly in the early febrile stage.[8] In the critical phase, the skin is flushed with the appearance of a petechial rash. This usually occurs around the time of defervescence, typically on days 3–7, and is associated with capillary leakage and haemorrhage.[4]

DHF or severe dengue usually affects children younger than 15 years, although it can occur in adults.[7] DHF is characterised by a transient increase in vascular permeability resulting in plasma leakage,

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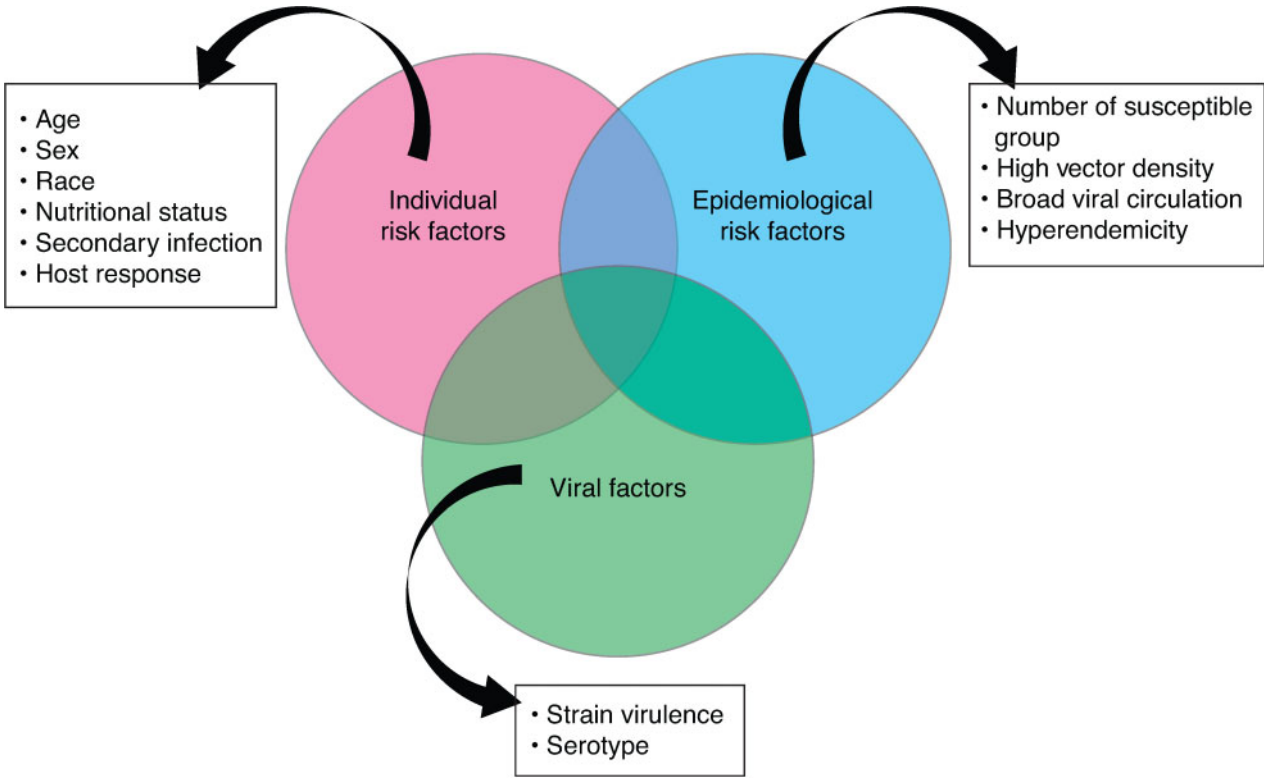

Figure 1 Risk factors for dengue haemorrhagic fever[8]

with high fever, bleeding, thrombocytopenia and haemoconcentration, which can lead to shock (termed dengue shock syndrome (DSS).[8] However, it can be difficult to differentiate DHF from DF and other viral diseases, e.g. typhoid fever, particularly during the acute phase of the illness.[7]

Secondary dengue infection is considered to be the principal risk factor for DHF, but the interaction of virus, host and epidemiological risk factors are determinants of the occurrence of DHF epidemics (Fig. 1).[8]

WHO Dengue Case Classification

Central to dengue case classification is the differentiation between classic DF and DHF or severe dengue. For greater clarity on these distinctions, a WHO committee developed case classification guidelines in 1974, based on studies of disease patterns in children in Thailand in the 1960s, which were subsequently modified and published a number of times.[9] However, it became apparent that this classification system is not universally applicable for appropriate clinical management, and in 2006 the WHO Dengue Scientific Working Group recommended additional research into dengue diagnostics and triaging of patients for optimised clinical management.[10]

Further studies on the use of clinical guidelines for dengue diagnosis, including the Dengue Control (DENCO) study, led to the re-classification of dengue into non-severe and severe cases.[10] This was subsequently revised into dengue with and without warning signs and severe dengue, and was published in 2009.[6]

The 1997 Dengue Case Classification

The 1997 guidelines (Fig. 2) classified dengue into DF, DHF (Grades 1 and 2) and DSS (DHF Grades 3 and 4).[9,11] The case diagnosis for DF emphasised the need for laboratory confirmation and the suggested DF classifications are shown in Box 1, together with those for DHF and DSS.

Experience with this classification system has exposed a number of limitations. It is based on clinical data in Thai children, which may not be universally representative of dengue, following its expansion to additional tropical regions and older age groups.[12] A range of clinical tests requiring repetition is also needed, which can be difficult for countries with limited resources to perform regularly.[13] Integral to the 1997 case definitions is the tourniquet test, a measure of capillary fragility and thrombocytopenia, for the diagnosis of DHF. However, the test does not differentiate effectively between DF and DHF[11,13,14] and dengue and other febrile illnesses.[11]

Studies have demonstrated overlap between case definitions of DF, DHF and DSS, supporting the concept of dengue as a continuous spectrum of disease rather than distinct entities.[11,14] Another study found that strict application of the criteria did not detect severe dengue manifestations in many patients, particularly adults.[15] Indeed, the term DHF is considered to place undue emphasis on haemorrhage when plasma leakage leading to shock is a more significant warning sign.[11] Manifestations of severe dengue include organ failure, but this was not included in the 1997 case

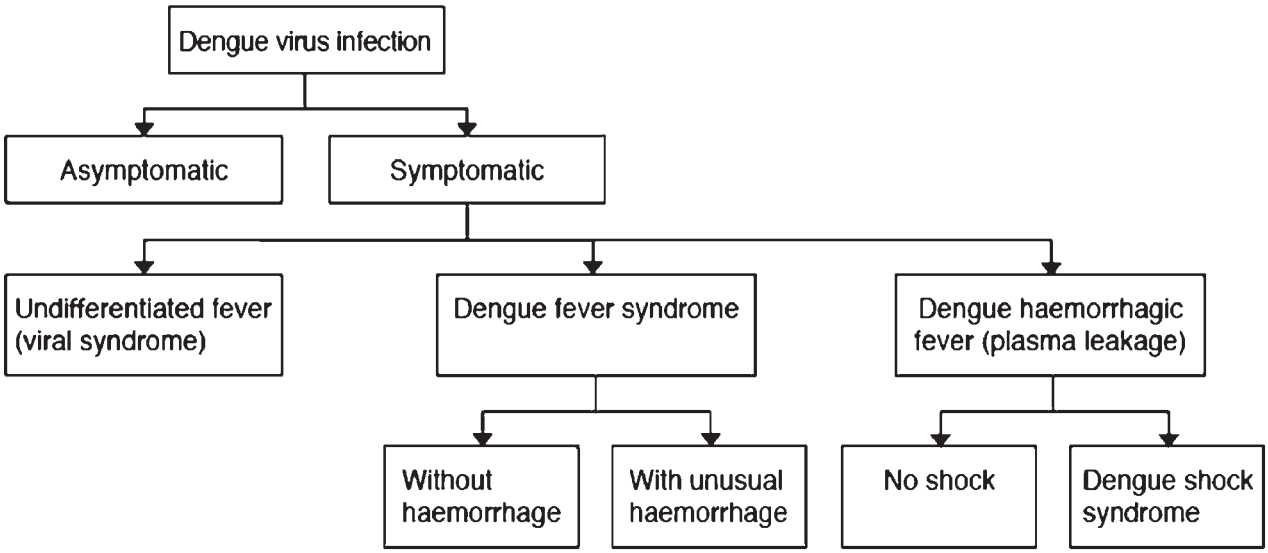

Figure 2 The 1997 WHO classification of dengue virus infection.[11] Reprinted from Lancet, Deen JL, Harris E, Wills B, Balmaseda A, Hammond SN, Rocha C, *et al*, The WHO dengue classification and case definitions: time for a reassessment, 170–3, Copyright 2012, with permission from Elsevier

definitions.[2] New classifications were developed to account for observed disease patterns.[2,11,16]

The DENCO Study: Evaluating the 1997 Classification

The international DENCO study was designed to evaluate the perceived limitations of the 1997 criteria in all age groups in South-east Asia and Latin America to develop an evidence-based classification that would better reflect clinical severity.[17,18]

Over 1700 confirmed cases of dengue were categorised into one of three intervention groups according to disease severity. Potential warning signs were identified by comparing data of patients who did and did not progress to severe disease. The study found

Box 1 WHO 1997 case definitions for DF, DHF and DSS[10]

DF

Probable
- An acute febrile illness with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations and leucopenia

and
- Supportive serology (a reciprocal haemagglutination-inhibition antibody titre ⩾1280, a comparable IgG enzyme-linked immunosorbent assay (ELISA, see chapter 4[9,10]) titre or a positive IgM antibody test on a late acute or convalescent-phase serum specimen)

or
- Occurrence at the same location and time as other DF cases

Confirmed
- A case confirmed by one of the following laboratory criteria:
  - Isolation of the dengue virus from serum/autopsy samples
  - An at least four-fold change in reciprocal IgG/IgM titres to one or more dengue virus antigens in paired samples
  - Demonstration of dengue virus antigen in autopsy tissue, serum or cerebrospinal fluid samples by immunohistochemistry, immunofluorescence or ELISA
  - Detection of dengue virus genomic sequences in autopsy tissue serum or cerebrospinal fluid samples by polymerase chain reaction (PCR)

Reportable
- Any probable or confirmed case should be reported

DHF

For a diagnosis of DHF, a case must meet all four of the following criteria:
- Fever or history of fever lasting 2–7 days, occasionally biphasic
- A haemorrhagic tendency shown by at least one of the following: a positive tourniquet test; petechiae, ecchymoses or purpura; bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations; or haematemesis or melaena
- Thrombocytopenia [⩽100,000 cells/mm^3 (100×10^9/L)]
- Evidence of plasma leakage owing to increased vascular permeability shown by: an increase in haematocrit ⩾20% above average for age, sex and population; a decrease in the haematocrit after intervention ⩾20% of baseline; signs of plasma leakage such as pleural effusion, ascites or hypoproteinaemia

DSS

For a case of DSS, all four criteria for DHF must be met, in addition to evidence of circulatory failure manifested by:
- Rapid and weak pulse

and
- Narrow pulse pressure (<20 mmHg or 2.7 kPa)

or manifested by
- Hypotension for age

and
- Cold, clammy skin and restlessness

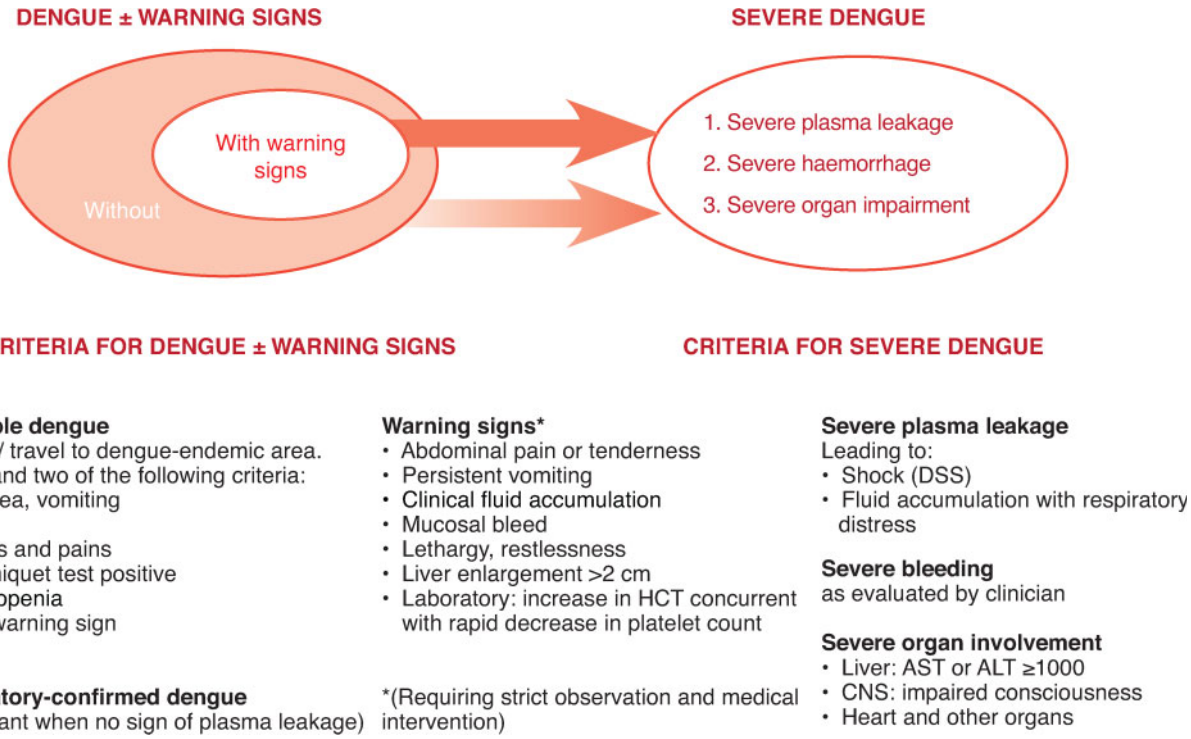

Figure 3 The 2009 revised dengue case classification[6]

that 22% of patients with shock did not fulfil all the criteria for DHF.[17] These results formed the basis of the revised 2009 WHO classification system.

The 2009 Dengue Case Classification

The 2009 WHO criteria (Fig. 3) classify dengue according to levels of severity: dengue without warning signs; dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure).[6] Patients who recover following defervescence are considered to have non-severe dengue, but those who deteriorate tend to manifest warning signs.[6] These individuals are likely to recover with intravenous rehydration. However, further deterioration is classified as severe dengue, though recovery is possible if appropriate and timely treatment is given.[6]

Applicability and Perceptions of the 2009 Classification System

The 2009 classification into severity levels is considered to be more sensitive in capturing severe disease than the 1997 guidelines, with observed sensitivities of up to 92% and 39%, respectively.[18,19] A multi-centre study across 18 countries demonstrated that approximately 14% of cases could not be classified using the DF/DHF/DSS classification, even when strict DHF criteria were not applied, compared with only 1.6% with the revised system (Table 1).[10] The study also examined acceptance by and user-friendliness to healthcare professionals.[10] The new classification was particularly useful with respect to triage and management of dengue, reporting during surveillance and for endpoint measurements in dengue clinical trials.[6,10]

However, problems with the use of the revised classification have also been noted. Additional training for healthcare workers and dissemination of information may be required to remedy any confusion over the changes to the system.[10]

Other Considerations for the 1997 and 2009 Classification Systems

Geographical considerations

Local guidance for the diagnosis and classification of dengue, based on the WHO DF/DHF/DSS criteria,

Table 1 Comparison of the 1997 and revised classifications[10]

DF/DHF/DSS classification by expert reviewer	Revised classification by expert reviewer				
	Not classifiable*	Dengue WS negative	WS positive	Severe dengue	Total
Not classifiable	23 (8.6%)	57 (21.3%)	159 (59.3%)	29 (10.8%)	268 (100%) (13.7% of all)
DF	7 (0.5%)	551 (41.8%)	684 (51.9%)	75 (5.7%)	1317 (100%) (67.1% of all)
DHF (grades 1 & 2)	2 (0.7%)	8 (2.8%)	240 (83.0%)	39 (13.5%)	289 (100%) (14.7% of all)
DSS (DHF grades 3 & 4)	0	0	12 (13.6%)	76 (86.4%)	88 (100%) (4.5% of all)
Total	32 (1.6%)	616 (31.4%)	1095 (55.8%)	219 (11.2%)	1962 (100%)

* Not classifiable, classification was not possible; WS, warning signs

varies between countries and regions.[20] In addition, the incidence by patient age varies according to region.[4] The resulting inconsistent application of the guidelines highlights the importance of standardising case classification and management. Furthermore, variations in the warning signs defined by the revised classification can be observed in different regions, thus requiring local adaptation of the guidelines in the future.[10] In fact, although considered particularly valuable for dengue case management and triage, there is concern that the use of warning signs in highly dengue-endemic countries such as Indonesia, can contribute to unnecessary hospital admissions.

Classification of dengue during an outbreak

Between 1966 and 1997, the application of the original WHO case definition guidelines, dengue morbidity and mortality decreased, with mortality in Indonesia reduced from 45% in 1969 to 1.2% in 2009.[2] However, during dengue outbreaks in Jakarta, mortality from severe, hospitalised cases increased from 25% of cases with shock in 1988 to approximately 47% of those with severe complications during the 2004 outbreak.[21] This supports the need to include complications of dengue such as haemorrhage, fluid overload, organ involvement and encephalopathy in the case definition of severe dengue.

Potential modifications to the 2009 classification system

Some of the concepts, including triage, warning signs and dengue severity, are discussed in the 1997 guidelines[9] and components of the previous classification may be suitable for clinical practice. Furthermore, research on the revised 2009 classification system is necessary in order to optimise dengue case definitions. There is a need for more precise definition of warning signs to enable optimal triaging for more accurate identification of patients who require hospitalisation as opposed to those who can be treated as outpatients.[10] Quantitative research into the predictive value of these warning signs on patient outcomes across all affected geographical areas and age groups is also crucial.[10] There is an additional need to explore the potential barriers to and cost-effectiveness implications of implementing the new classification system.

Conclusions

The 1997 WHO case classification system for dengue was revised because of differences across the broad geographical areas and the age groups affected by dengue. However, the current 2009 WHO classification has yet to be definitively proved to be effective. The question remains, therefore, whether this latest classification requires further modification. A solution may be to incorporate elements from the 2009 classification of severe dengue into the 1997 guidelines, much of which remains relevant for use. This may be resolved by conducting multi-centre, prospective studies using standardised protocols in Asia and Latin America in a full range of patient age groups.

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Fluid management for dengue in children

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Dengue is a serious public health problem worldwide. Dengue shock syndrome (DSS), the severe form of dengue fever, can cause death within 12–24 hours if appropriate treatment is not promptly administered. For patients with DSS and the 30% of non-shocked dengue patients who require intravenous fluid therapy, a range of solutions is available for plasma volume support. Crystalloid solutions, such as normal 0.9% saline or Ringer's lactate, are the ones most commonly used. In severe cases, colloid solutions may be administered for their greater osmotic effect, although they carry a greater risk of adverse events. This paper summarises the key clinical data, comparing fluid regimens in children with severe dengue, and concludes that the majority of patients with DSS can be treated successfully with isotonic crystalloid solutions. If a colloid is thought necessary, a medium-molecular-weight preparation that combines good initial plasma volume support with good intravascular persistence and an acceptable side-effect profile is optimal. Further research should aim to determine whether there are benefits to early treatment with colloids, and which colloid solution is most effective for resuscitation of DSS patients.

Keywords: Dengue, Dengue haemorrhagic fever, Fluid, Management, Clinical

Principles of Fluid Management for Dengue in Children

Dengue infection causes a broad spectrum of clinical disease, which can range in severity from febrile illness to serious bleeding and shock. Two major pathophysiological responses are associated with severe dengue infection – plasma leakage leading to hypovolaemic shock and/or abnormal haemostasis leading to haemorrhage.[1,2]

The clinical course of dengue includes febrile, critical and recovery phases (Fig. 1), and there are different challenges for fluid management at each stage.[1] In the initial febrile stage, the aim is to treat dehydration. The majority (70%) of non-shocked dengue patients can be treated as outpatients with oral rehydration regimens; however, the remaining 30% of these patients and all DSS patients require intravenous (IV) fluid therapy.[3]

During the critical stage, there is an increase in capillary permeability and shock can result if a large volume of plasma is lost through leakage. The recommended regimen for the treatment of DSS is: immediate and rapid replacement of the plasma loss with isotonic crystalloid solutions or, in the case of profound shock, colloid solutions; continued replacement of further plasma losses to maintain effective circulation for 24–48 hours; correction of metabolic and electrolyte disturbances; and blood transfusion in cases with severe bleeding. If large amounts of fluid are required, these should be reduced gradually as plasma leakage decreases in order to prevent hypervolaemia, an excess in plasma volume which can cause oedema, respiratory distress or congestive heart failure, during the recovery stage.[1,2]

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Choice of Intravenous Fluid

Replacement of plasma lost because of increased vascular permeability is a mainstay of severe dengue management, particularly during the critical stage.[3] Two main types of volume expander are used to replace lost fluid in the management of dengue fever: crystalloids and colloids.[1] Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules, whereas colloids contain larger insoluble molecules such as gelatin, dextrans or starches.

The most commonly used crystalloid is 0.9%, or 'normal' saline, a hypertonic solution with an osmolality of 308 mOsm/L that has higher sodium and chloride levels than normal plasma. Normal saline is a suitable option for initial fluid resuscitation but repeated large volumes of 0.9% saline may lead to hyperchloraemic acidosis and decreased blood pH owing to excessive chloride levels. Therefore, if serum chloride begins to exceed the normal range, other alternatives such as Ringer's lactate may be preferable.[1]

Ringer's lactate has lower sodium and chloride contents than 0.9% saline, and an osmolality of 273 mOsm/L. It should be avoided, however, in individuals with liver failure as they have a reduced ability to metabolise lactate.

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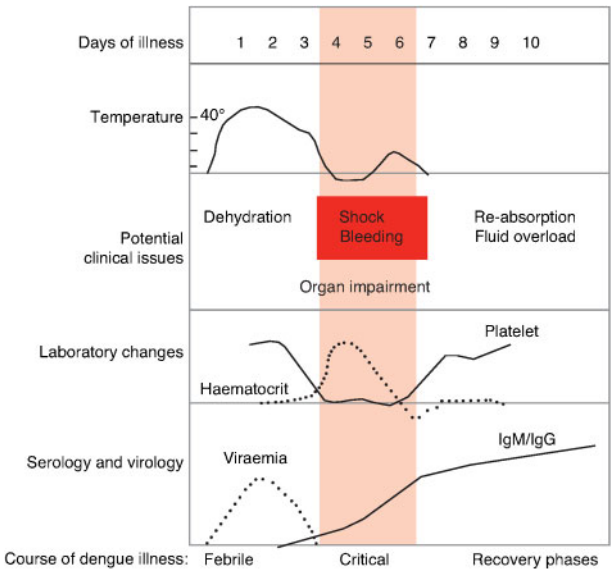

Figure 1 Clinical course of dengue[1]

The most common types of colloid used for plasma volume support are gelatin-, dextran- and starch-based solutions (summarised in Table 1).[4] In contrast with crystalloid solutions, colloid infusion can expand volume in excess of the actual volume administered and so may be beneficial for rapid fluid delivery for emergency resuscitation of hypovolaemic shock. Furthermore, colloid molecules may show increased efficacy since they increase plasma oncotic pressure, thereby altering the flux of fluid across the capillary membrane and drawing fluid back into the capillary from the interstitial space.

One of the greatest concerns regarding colloid use is the impact on coagulation. Dextrans theoretically bind to von Willebrand factor/Factor VIII complex and impair coagulation; however, this has not been observed to be of clinical significance in fluid resuscitation of dengue shock patients.[1] Gelatin has a lesser effect on coagulation but the highest risk of allergic reaction. Allergic reactions have also been observed in patients treated with dextran 70 and dextran 40, and can potentially cause osmotic renal injury in hypovolaemic patients.[6,7]

Care should be exercised in storing colloid solutions, particularly in warmer climates, since dextrans and gelatins are very sensitive to temperatures exceeding 20–30°C which can cause degradation into smaller molecules.[8] In clinical terms, this would decrease the solutions' intravascular volume effect and increase their renal elimination.

Randomised Controlled Trials of Fluid Management in Dengue Fever

A number of randomised controlled trials have been undertaken to compare the efficacy of different fluid regimens in managing DSS in children. A pilot study involving 50 children with DSS showed minor differences in the immediate clinical responses to different fluids.[9] Children were randomised to receive either normal saline ($n=12$), Ringer's lactate ($n=13$), dextran 70 ($n=12$) or 3% gelatin ($n=13$). In a pooled comparison of crystalloids and colloids, patients who had received colloid infusions had significantly greater increases in mean haematocrit ($P=0.01$), blood pressure ($P=0.005$), pulse pressure ($P=0.02$) and cardiac index ($P=0.02$). In individual comparisons, dextran 70 was found to be the most effective solution for improving cardiac index and haematocrit.

A larger study of 230 children with DSS that compared the same four fluids initially suggested improved pulse pressure recovery time following early treatment with colloids.[10] However, pulse pressure at presentation was identified as a potential confounder, and, when only the most severe cases (presenting pulse pressure $\leqslant 10$ mmHg, $n=51$) were compared, fewer differences were found. Of children who received gelatin, significantly fewer had a recovery time of more than 1 hour compared to those who received Ringer's lactate ($P=0.017$). Comparisons between all other solutions were not significant. This study suggests that the majority of patients with DSS have mild-to-moderate shock and will respond well to conventional treatment with crystalloids. A small minority with more serious disease may require more aggressive management

Table 1 Characteristics of colloids used for plasma volume support[4]

	Initial volume expansion (%)*	Duration of volume effect (hrs)	Adverse effect on coagulation	Allergic potential	Other significant side-effects
3% Gelatine (MW=35,000)	60–80	3–4	+/−	++	
10% Dextran 40 (MW=40,000)	170–180	4–6	++	+	Renal failure in hypovolaemic patients
6% Dextran 70 (MW=70,000)	100–140	6–8	++	+	
6% Hydroxyethyl starch (MW=200,000/0.5)	100–140	6–8	+	+/−	
6% Hydroxyethyl starch (MW=400,000)	80–100	12–24	++	+	

Management of dengue; Wills B. Halstead SB (Ed.) Copyright 2008 Imperial College Press
*Infused volume
MW, molecular weight

with colloids from the outset. However, this study was statistically underpowered and the differences in presenting pulse pressure may have obscured some of the results; for example, any benefit associated with 3% gelatin would be expected to be more pronounced with dextran 70, but there were very few severe patients to compare in the dextran 70 group. Further large-scale studies, stratified for admission pulse pressure, were recommended.

The largest randomised study to date included two arms, with patients stratified for presenting pulse pressure.[11] Children with moderately severe shock (pulse pressure >10 to $\leqslant 20$ mmHg, $n=383$) were randomised to receive Ringer's lactate ($n=128$), 6% dextran 70 ($n=126$) or 6% hydroxyethyl starch (HES) 200/0.5 ($n=129$). Ringer's lactate was found to be as effective as colloid therapy on the primary outcome measure of requirement for colloid rescue or fluid resuscitation. However, patients treated with Ringer's lactate took longer to achieve cardiovascular stability than patients receiving either colloid ($P=0.02$).

A further 129 children with severe shock (pulse pressure $\leqslant 10$ mmHg) were randomised to receive one of the colloids – dextran 70 ($n=67$) or HES ($n=62$) – and both colloid preparations performed equally well with regard to cardiovascular stability and the number of patients who required resuscitation. However, the dextran preparation was associated with more adverse events than HES, with 8.0 *vs* 0.5%, respectively, reporting allergic-type reactions including transient high fever and rigors. These adverse events responded to symptomatic treatment alone and there were no differences in severe adverse events such as significant new bleeding or clinical fluid overload.

This study indicated that Ringer's lactate, the cheapest and safest preparation available, was the best treatment for moderate shock in children with DSS and early intervention with colloids was not necessary. A clinical trial that compared normal saline and lactate solutions in a large, heterogeneous population in intensive care suggested that these fluids are equally effective.[12] For children with severe shock, there were no clear advantages of dextran over starch solutions, but starch may be preferred for its lower adverse event profile.

A study of 104 DHF patients with severe plasma leakage who had failed to respond to crystalloids and required fluid resuscitation compared bolus doses of two colloids, 10% dextran 40 ($n=57$) and 10% HAES-steril ($n=47$), for their effectiveness, impact on renal function and haemostasis and any complications.[13] HAES-steril was found to be as effective as dextran 40 on measures of haematocrit change and in terms of the number of doses and volume of fluid required. Both colloidal solutions were deemed safe in these patients; there were no allergic reactions or interference with renal function or haemostasis.

Conclusions

Taken together, these studies show that the majority of children with DSS can be treated successfully with isotonic crystalloid solutions. If a colloid is considered necessary, clinicians must continue to rely on personal experience, familiarity with particular products, local availability and cost. A medium-molecular-weight preparation that combines good initial plasma volume support with good intravascular persistence and an acceptable tolerability profile is probably the optimal choice.

It should be noted that the positive overall outcomes described in these studies probably reflect the quality of care as much as the interventions themselves. Hourly observations and immediate access to haematocrit testing coupled with a conservative intervention policy allow fluid requirements to be met as early as possible and carefully titrated. In more poorly resourced settings, intensive care provision is more challenging and complications such as fluid overload are more likely to occur.

Further research using higher patient numbers, stratified for severity, will be needed to determine whether early treatment with a colloid confers a true advantage in those with severe shock, and which colloid solution is most effective for resuscitation of DSS patients.

Acknowledgments

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