DENGUE: GLOBAL THREAT

Usa Thisyakorn and Chule Thisyakorn

Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Abstract. Dengue is a mosquito-borne viral disease, which is currently an expanding global problem. Four closely related dengue serotypes cause the disease, which ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever (DHF). DHF is characterized by fever, bleeding diathesis, and a tendency to develop a potentially fatal shock syndrome. Dengue infection with organ impairment mainly involves the central nervous system and the liver. Consistent hematological findings include vasculopathy, coagulopathy, and thrombocytopenia. Laboratory diagnosis includes virus isolation, serology, and detection of dengue ribonucleic acid. Successful treatment, which is mainly supportive, depends on early recognition of the disease and careful monitoring for shock. A severity-based revised dengue classification for medical interventions has been developed and validated in many countries. There is no specific dengue treatment, and prevention is currently limited to vector control measures. The world's first, large-scale dengue vaccine efficacy study demonstrated its efficacy and a reduction of dengue disease severity with a good safety profile in a study of more than 30,000 volunteers from Asia and Latin America.

Keywords: dengue, global threat

INTRODUCTION

Dengue is one of the most devastating mosquito-borne viral diseases in humans. The disease, caused by the four dengue virus serotypes, ranges from asymptomatic infection, undifferentiated fever, dengue fever (DF), to severe and fatal dengue hemorrhagic fever (DHF). The clinical spectrum of the infection undermines surveillance activities because the majority of cases are asymptomatic and go undetected. These cases can be an important source of infection for dengue virus transmission via the mosquito vector. DHF is characterized by fever, bleeding diathesis, and a tendency to develop a potentially fatal shock syndrome. The disease is a major public health concern in several countries, and the disease could potentially spread to non-endemic areas. It is one of the leading causes of hospitalization, placing tremendous pressure on strained medical resources with an associated major economic and social impact in countries where dengue disease is prevalent (Hemungkorn *et al*, 2007; Capeding *et al*, 2013).

Correspondence: Professor Usa Thisyakorn, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand.
Tel: +66 (0) 2354 7584
E-mail: fmeduty@mail.md.chula.ac.th

EPIDEMIOLOGY

Dengue is the most common arboviral infection of humans transmitted by *Aedes* mosquitoes, principally *Aedes aegypti*. These mosquitoes largely breed indoors in clean water, mainly in artificially water containers, and feed on humans during the daytime. There are four antigenically distinct serotypes of dengue virus (DEN 1, 2, 3 and 4), which belong to the genus *Flavivirus* of the family Flaviviridae. Primary infection with a particular dengue serotype confers long-lasting immunity for that serotype (homotypic immunity) while the immunity it confers to other dengue serotypes (heterotypic immunity) lasts for only a few months, after which patients are susceptible to heterotypic infection. Four viral serotypes cause disease in proportions that change over time and from place to place, even within the same country. A review of dengue virus incidence from 1973 to 1999 in Bangkok found that all four dengue serotypes could be found circulating in any one year, with one predominant serotype emerging and re-emerging as the cause of the epidemic. The authors concluded that the pathogenesis of DHF is complex, and that it is a product of host determinants, dengue serotype, and environmental factors (Nisalak *et al*, 2003).

Global phenomenon such as urbanization and international travel are key factors in facilitating the spread of dengue. Documenting the type-specific record of dengue virus spread has important implications for understanding patterns in dengue hyperendemicity and disease severity as well as vaccine design and deployment strategies. A series of global maps on the distribution of confirmed instances of each dengue virus serotype from 1943 to 2013 shows the worldwide expansion of the dengue virus, the hyperendemicity of the disease, and its establishment as an increasingly important infectious disease of global public health significance (Messina *et al*, 2014). Dengue, along with the mosquito vectors that transmit it, is now endemic in over 120 countries throughout the tropical and subtropical regions of the world (Bhatt *et al*, 2013; Thisyakorn and Thisyakorn, 2015). It is nearly ubiquitous in the tropics and has continued to emerge, or become hyperendemic, in new areas as the range of the *Aedes* mosquito vectors continues to expand.

Global dengue transmission has increased at least 30-fold in the past 50 years (WHO, 2009). The burden borne by the health and medical resources of affected countries is enormous, but nowhere is the burden greater than in the Southeast Asian and Western Pacific regions, where the incidence of dengue is already the highest in the world and continues to increase and cause epidemics. The estimated annual economic burden for Southeast Asia, excluding prevention and vector control, was nearly USD1 billion or USD1.65 per capita with two countries, Indonesia and Thailand, accounting for over 60% of this burden (Shepard *et al*, 2013). Currently, over 70% of the global population-at-risk for dengue lives in these regions (WHO, 2012).

The global increase in dengue cases and also the potential spread of the disease to non-endemic areas are due to factors such as atmospheric composition, climate change and human movement. Even with estimates of disease burden increasing, dengue is widely under-reported due to misdiagnosis and inconsistencies in diag-

nostics and surveillance systems. Dengue has spread into new geographical areas affecting both children and adults despite being significantly under-reported. Over half of the world's population lives in areas at risk of infection. About 70% of the overall disease burden, thought to have increased 30-fold in the last 50 years, is reported in the Asia-Pacific region. In recent years, there has been an increase in dengue cases in rural settings and also a shift towards increased incidence in older age groups in many countries where dengue is endemic. The trend has important implications for control and prevention (Thisyakorn and Thisyakorn, 2015). Vertical transmission of dengue virus from mother to child has also been reported for the first time in English literature (Thaithumyanon *et al*, 1994).

The severity of DF manifestations increases with age. DF causes fever, rash, muscle or joint pain, headache, eye pain but is rarely fatal. DHF is considered a distinct disease characterized by increased vascular permeability leading to leakage of plasma and dengue shock syndrome (DSS). Unusual manifestations of dengue patients with severe organ involvement such as liver, kidney, brain, or heart associated with dengue infection have been increasingly reported in patients with dengue infection. These manifestations may be associated with co-infections, co-morbidities, or complications of prolonged shock. Exhaustive investigations should be done in these cases (Innis *et al*, 1990; Thisyakorn and Thisyakorn, 1994a,b; Thisyakorn *et al*, 1999; Hemungkorn *et al*, 2007).

Research into the pathogenesis of dengue infection has exploded over the last half century. Issues that were considered simple have become more complex as additional data have been found. This has led to the development of a number of controversies that are being studied globally and debated in the literature as follows: the 1997 World Health Organization (WHO) case definition of DHF is not useful; DHF is not significantly associated with secondary dengue infection; DHF results from infection with a virulent dengue virus; DHF is caused by abnormal T-cell responses; DHF results from auto-immune responses; and DHF results from direct infection of endothelial cells. A clinically and physiologically applicable case classification that will allow robust pathological research into the different levels of disease severity is a major priority (Thisyakorn and Nimmannitya, 1993; Sosothikul *et al*, 2007; Halstead, 2012).

DIAGNOSIS

The incubation period of dengue infection is usually 4-7 days but can range from 3 to 14 days. Clinical and laboratory criteria for the diagnosis of DHF/DSS as established by the World Health Organization in 1997 (WHO, 1997) are as follows:

Clinical manifestations

- Fever: acute onset, high and continuous, lasting two to seven days in most cases.
- Any of the following hemorrhagic manifestations including a positive tourniquet test, petechiae, purpura, ecchymosis, epistaxis, gum bleeding, and hematemesis and/or melena.
- Enlargement of the liver is observed at some stage of the illness in 90%-98% of children. The frequency varies with time and/or the observer.
- Shock, manifested by tachycardia,

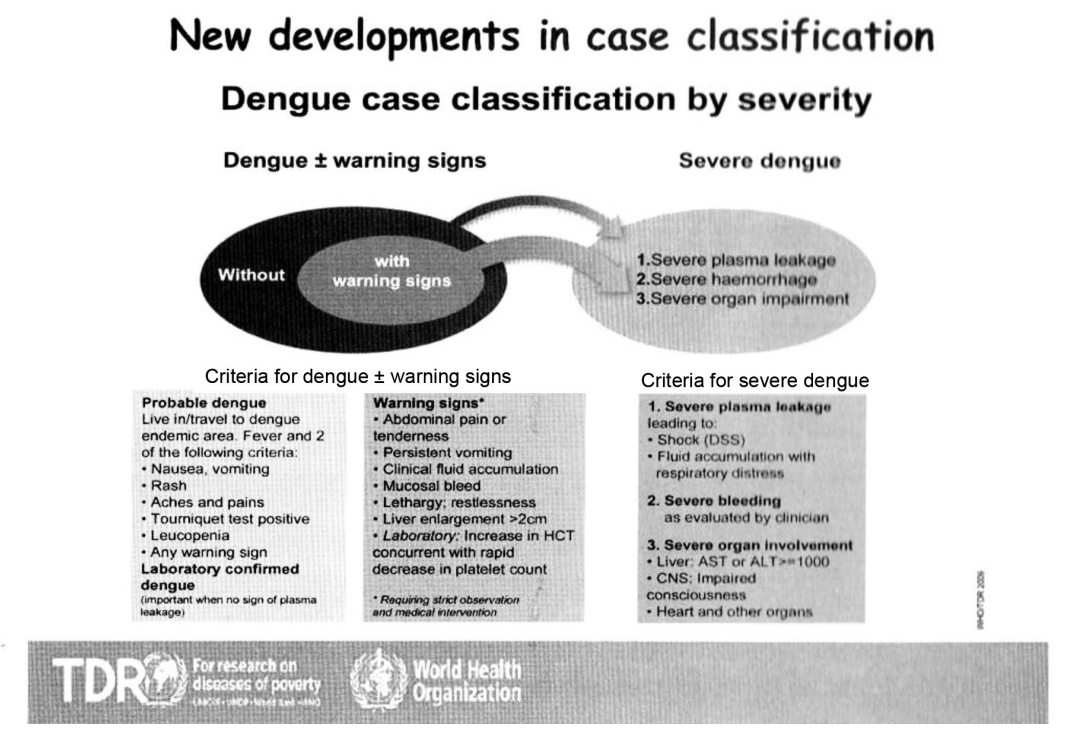

Fig 1–The 2009 WHO dengue case classification.

poor tissue perfusion with weak pulse and narrowed pulse pressure or hypotension with the presence of cold, clammy skin and/or restlessness.

Laboratory findings

- Thrombocytopenia (100,000 cells/mm^3 or less).
- Hemoconcentration; a hematocrit increase of more than 20% from the baseline of patient or population of the same age.

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 (Fig 1) has yet to be definitively proved to be effective. The question remains, therefore, whether this latest classification requires further modification (Hadinegoro, 2012).

Other common laboratory findings are hypoproteinemia, hyponatremia, and elevation of hepatic enzymes and blood urea nitrogen levels. Metabolic acidosis may be found in patients with prolonged shock. White blood cell count is variable, ranging from leukopenia to mild leukocytosis with an increase in the percentage of lymphocytes and the presence of atypical forms (Wells *et al*, 1980; Thisyakorn *et al*, 1984).

Hematological findings include vasculopathy, reduction of several coagulation factors, reduced platelet count, and platelet dysfunction. The tendency towards bleeding should be monitored in any dengue patient because it may cause severe and uncontrollable hemorrhage. The pathogenesis of bleeding in a dengue patient is not fully understood. The extent of endothelial

cells involvement, coagulation, and fibrinolysis activation in children with dengue infection seems to be correlated with dengue disease severity (Mitrakul and Thisyakorn, 1988; Setrkraising *et al*, 2007).

The laboratory diagnosis of dengue infection can be confirmed by serological tests, isolation of the virus, and detection of viral RNA by reverse transcriptase polymerase chain reaction. Commercial kits for dengue diagnosis are also available for routine use. A pilot evaluation of diagnostic values of ELISA and reverse transcription polymerase chain reaction from oral specimens yielded promising results. Collection of oral specimens is less invasive and may be more acceptable (Hemungkorn *et al*, 2007).

Clinical manifestations of dengue infection vary with age as DSS is more common in children than in adults. Infants with dengue infection present more frequently with convulsions, diarrhea, rash, cyanosis, and splenomegaly while co-morbidities in adults are associated with greater risk of mortality (Panpitpat *et al*, 2007; Tantawichien, 2012).

TREATMENT

Treatment of dengue infection is symptomatic and supportive. In most cases, early and effective replacement of lost plasma with fluid and electrolyte solutions, plasma, and/or plasma expanders results in a favorable outcome. The outcome depends on early recognition of infection and careful monitoring. Blood transfusion is indicated for patients with significant clinical bleeding mainly from the gastrointestinal tract. Blood components are required when disseminated intravascular coagulation (DIC) causes massive bleeding. Persistent shock despite adequate fluids and a decline in the hematocrit level suggest significant clinical bleeding requiring prompt treatment. DIC occurs in cases with severe shock and may play an important role in the development of massive bleeding and irreversible shock. Coagulation tests should be monitored in all cases of shock to document the onset and severity of DIC. Blood grouping and matching should be carried out as a routine precaution for every patient in shock.

The rate of fluid infusion needs to be carefully tailored according to the patient's vital signs, hematocrit, and urine output. In general, there is no need for fluid therapy beyond 48 hours after the cessation of shock. Reabsorption of extravasated plasma takes place, manifesting by a further drop in the hematocrit level. Excessive fluids during the recovery phase may cause hypervolemia, pulmonary edema, or heart failure. An extremely important point is that a drop in the hematocrit level at this stage not be taken as a sign of internal hemorrhage. A strong pulse and blood pressure with a wide pulse pressure and diuresis indicate good vital signs. They rule out the likelihood of gastrointestinal hemorrhage, which is mostly found during the shock stage (Thisyakorn and Thisyakorn, 1994c).

PREVENTION

Prevention of dengue depends on the control of the mosquito vector by limiting its breeding places and treatment of stored water with larvicide. These measures against dengue are effective only with a high level of government commitment, education, and community participation. Development of a dengue vaccine is seen as the best hope to fight this potentially fatal disease (Thisya-

korn and Thisyakorn, 2015).

A phase III efficacy trial of a recombinant, live, attenuated tetravalent dengue vaccine (CYD-TDV) in highly dengue-endemic areas in Asia and Latin America in more than 30,000 children demonstrated that this dengue vaccine is efficacious when given as a 0-6-12 month schedule to children. Severe dengue episodes were avoided with a reduction in hospitalization. Higher efficacy was observed in the immunogenicity subset seropositive at baseline. The safety profile was consistent with the good safety profile observed in previous studies over the 25-month follow-up period, showing no evidence of antibody dependent enhancement in partial or completely vaccinated individuals.

An interesting finding of this trial was that vaccine efficacy was higher for participants who were seropositive for dengue than for those who were seronegative. Furthermore, vaccine efficacy increased with age, which could be a marker of previous exposure to dengue. Results confirm the potential public health impact of the vaccine and support the vaccines potential at reducing the public health burden of dengue. It should be recognized as the dawn of a new era of dengue control because the potential use of this vaccine could be a major turning point for global dengue control. The interesting finding of this trial was that vaccine efficacy was higher for participants who were seropositive for dengue than for those who were seronegative (Capeding *et al*, 2014; Dengue Vaccine Initiative, 2014; Wilder-Smith, 2014). The results from Latin America complement those in Asia and provide a more global picture of the vaccine's potential to contribute to reaching the 2020 WHO target of reducing the global burden of dengue by decreasing morbidity by 25% and mortality by 50% (WHO, 2012).

A dengue vaccine could greatly alter the disease landscape, but this goal can only be realized if the many challenges to its implementation are addressed effectively. We have waited a long time for an effective intervention against dengue. Informed decisions must be made for each setting to determine how dengue vaccination should be implemented into existing national vaccinations programs: catch-up campaigns must be delivered; optimal vaccination strategies must be defined; and post-approval safety and efficacy must be monitored. Countries must plan for the vaccine's introduction. In particular, how the vaccine will complement existing vector management programs, and how dengue surveillance can be strengthened, which will be essential to assess the appropriate dengue vaccination strategy for each epidemiological setting. It is good news that a safe and effective dengue vaccine is on the horizon. While this stands to be a critically important achievement in the fight against dengue, we need to understand how to implement this new tool effectively, and this will require firm commitments from all affected countries if the WHO objectives are to be met (Thisyakorn *et al*, 2014b).

An independent scientific and educational Association of Southeast Asian Nations (ASEAN) Members States Dengue Vaccination Advocacy Steering Committee (ADVASC) was established in 2011 to address the practical challenges faced by ASEAN countries as they prepare for the eventual introduction of a dengue vaccine. The ADVASC convened workshops that drew together public health representatives

and dengue experts from ASEAN countries in order to make practical recommendations to improve current surveillance and diagnostics for dengue to enable countries to consistently assess and accurately communicate the impact of a dengue vaccine (Thisyakorn, 2012; Thisyakorn *et al*, 2014a).

A better understanding of new paradigms for a changing dengue epidemiology will not only feed into operational policy for dengue control but also provide fertile terrain for vaccine application strategies in the future. Epidemiological data of this kind will be both valuable for dengue vaccine efficacy trials and for consideration of age groups to be vaccinated, which will lead to universal dengue vaccine implementation in the future.

In summary, dengue poses a heavy economic cost to the health system and society. The potential economic benefits are associated with promising dengue prevention interventions such as a dengue vaccine and vector control innovations (Suaya *et al*, 2009).

REFERENCES

Bhatt S, Gething PW, Brady OJ, *et al*. The global distribution and burden of dengue. *Nature* 2013; 496: 504-7.

Capeding MA, Chua MN, Hadinegoro SR, *et al*. Dengue and other common causes of acute febrile illness in Asia: an active surveillance study in children. *PLoS Negl Trop Dis* 2013 Jul 25; 7: e2331.

Capeding MR, Tran NH, Hadinegoro SRS, *et al*. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children aged 2 to 14 years in Asia: a phase III randomized observer-masked, placebo-controlled trial. *Lancet* 2014; 384: 1358-65.

Dengue Vaccine Initiative. Statement by the Dengue Vaccine Initiative on the results of CYD-TVD Phase 3 trial in Latin America [webpage]. [Cited 2014 Sep 12] . Available from: http://www.denguevaccines.org/sites/default/files/DVI%20Statement%20-%20CYD15%20Sanofi%20Pasteur%20Results%20Prelease_0.pdf

Hadinegoro SR. The revised WHO dengue case classification: does the system need to be modified? *Paediatr Int Child Health* 2012; 32 (suppl 1): 33-8.

Halstead SB. Controversies in dengue pathogenesis. *Paediatr Int Child Health* 2012; 32 (suppl 1): 5-9.

Hemungkorn M, Thisyakorn U, Thisyakorn C. Dengue infection: A growing global health threat. *BioSci Trends* 2007; 1: 90-6.

Innis BL, Myint KSA, Nisalak A, *et al*. Acute liver failure is one important cause of fatal dengue infection. *Southeast Asian J Trop Med Public Health* 1990; 21: 695-6.

Messina JP, Brady OJ, Scott TW, *et al*. Global spread of dengue virus types: mapping the 70 year history. *Trends Microbiol* 2014; 22: 138-46.

Mitrakul C, Thisyakorn U. Hemostatic studies in dengue hemorrhagic fever. In: Suvatte V, Tuchinda M; Pediatric Association of Thailand, eds. Proceedings of the 1st International Congress of Tropical Pediatrics. Bangkok: International Society of Tropical Pediatrics, 1988: 215-7.

Nisalak A, Endy TP, Nimmannitya S, *et al*. Serotype-specific dengue virus circulation and dengue disease in Bangkok, Thailand from1973 to 1999. *Am J Trop Med Hyg* 2003; 68: 191-202.

Panpitpat C, Panpitpat A, Hemungkorn M, Thisyakorn U. Dengue patients in different age groups. *Asian-Oceanian J Pediatr Child Health* 2007; 6: 1-7.

Setrkraising K, Bongsebandhu-phubhakdi C, Voraphani N, Pancharoen C, Thisyakorn U, Thisyakorn C. D-dimer as an indicator of dengue severity. *Asian Biomed* 2007; 1: 53-7.

Shepard DS, Undurrga EA, Halasa YA. Eco-

nomic and disease burden of dengue in Southeast Asia. *PLoS Negl Trop Dis* 2013; 7: e2055.

Sosothikul D, Seksan P, Pongsewalak S, Thisyakorn U, Lusher J. Activation of endothelial cells, coagulation and fibrinolysis in children with dengue virus infection. *Thromb Haemost* 2007; 97: 627-34.

Suaya JA, Shepard DS, Siqueira JB, *et al*. Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. *Am J Trop Med Hyg* 2009; 80: 846-55.

Tantawichien T. Dengue fever and dengue haemorrhagic fever in adolescents and adults. *Paediatr Int Child Health* 2012; 32 (suppl 1): 22-7.

Thaithumyanon P, Thisyakorn U, Deerojanawong J, Innis BL. Dengue infection during parturition complicated by severe hemorrhage and vertical transmission. *Clin Infect Dis* 1994; 18: 248-9.

Thisyakorn U. ADVASC – New regional initiative supporting transition from dengue vaccine to vaccination in Southeast Asia. *Vaccine* 2012; 30: 5587-8.

Thisyakorn U, Capeding RM, Goh DY, *et al*. Preparing for dengue vaccine introduction in ASEAN countries: recommendations from the first ADVA regional workshop. *Expert Rev Vaccines* 2014a; 13: 581-7.

Thisyakorn U, Capeding RM, Hadinegoro SR. The first tetravalent dengue vaccine is poised to combat dengue. *WHO Dengue Bull* 2014b (in print).

Thisyakorn U, Nimmannitya S. Nutritional status of children with dengue hemorrhagic fever. *Clin Infect Dis* 1993; 16: 295-7.

Thisyakorn U, Thisyakorn C. Dengue hemorrhagic fever: unusual manifestation and problems in management. *JAMA SEA* 1994a; 10: 102-3.

Thisyakorn U, Thisyakorn C. Dengue infection with unusual manifestations. *J Med Assoc Thai* 1994b; 77: 410-3.

Thisyakorn U, Thisyakorn C. Diseases caused by arbovirus-dengue haemorrhagic fever and Japanese B encephalitis. *Med J Aust* 1994c; 160: 22-6.

Thisyakorn U, Thisyakorn C. Latest development and future directions in dengue vaccines. *Ther Adv Vaccines* 2014; 2: 3-9.

Thisyakorn U, Thisyakorn C. Dengue: a global threat. *J Med Assoc Thai* 2015; 98 (suppl 1): S1-5.

Thisyakorn U, Thisyakorn C, Limpitikul W, Nisalak A. Dengue infection with central nervous system manifestations. *Southeast Asian J Trop Med Public Health* 1999; 30: 504-6.

Thisyakorn U, Nimmannitya S, Ningsanond V, Soogarun S. Atypical lymphocyte in dengue hemorrhagic fever: its value in diagnosis. *Southeast Asian J Trop Med Public Health* 1984; 15: 32-6.

Wells RA, Scott RM, Pavanand K, Sathitsathein V, Chiamudom U, Macdermott RP. Kinetics of peripheral blood leukocyte alteration in Thai children with dengue hemorrhagic fever. *Infect Immun* 1980; 28: 428-33.

Wilder-Smith A. Dengue vaccine: dawning at last? *Lancet* 2014; 384: 1327-9.

World Health Organization (WHO). Dengue haemorrhagic fever: diagnosis, treatment and control. 2nd ed. Geneva: WHO, 1997.

World Health Organization (WHO). Dengue: guidelines for diagnosis, treatment, prevention and control. New edition. Geneva: WHO, 2009. [Cited 2014 Jun 14]. Available from: http://www.who.int/tdr/ publications/documents/dengue diagnosis.pdf

World Health Organization (WHO). Global strategy for dengue prevention and control 2012-2020. Geneva: WHO, 2012. [Cited 2014 Jun 7]. Available from: http://reliefweb.int/sites/reliefweb.int/files/resources/9789241504034_eng.pdf

SUGGESTED READING:

Villar L, Dayan GH, Arredondo-García JL, *et al*. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2015; 372: 113-23.