

DENGUE: GLOBAL HEALTH THREAT

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The cases of dengue, both globally and the severe type, are climbing up at a staggering pace since WHO first documented records in 1955, with the most recent in 2010. The figures rose from a modest 1,000 cases per year to over 2.2 millions. The distribution is mainly in Asia, particularly in ASEAN countries. It is likely this endemic will reach Europe due to climate change.

Yip (1980) described a pattern of dengue infection. The organ impairment stage occurs between Days 2 to 8. However, unusual manifestations were reported by a number of countries, such as Myanmar, Indonesia, Malaysia, and Thailand. This was reported in Thailand following the largest outbreak ever recorded in Thailand in 1988, which included encephalopathy, encephalitis and fulminant hepatitis (Thisyakorn and Thisyakorn, 1994). In 2011 WHO SEARO recognized this entity and termed it as 'Expanded dengue syndrome' or 'Isolated Organopathy' (WHO SEARO, 2011).

Dengue with organopathy (WHO, 2009) involves several systems, for example, neurological, gastrointestinal/hepatic, renal, cardiac, respiratory, musculoskeletal, lymphoreticular/bone marrow, eye, and others. Dengue infection with central nervous system (CNS) manifestations is probably more common than once thought. Neurological manifestations of dengue include alteration of consciousness, sei-

zures, pyramidal tract signs, meningeal signs, and headache. Cerebrospinal fluid (CSF) examination may show lymphocytic pleocytosis in 20% of patients, while IgM is present in a few (Thisyakorn *et al*, 1999).

A similar work in Vietnam concluded that in dengue endemic areas patients with encephalitis and encephalopathy should be investigated for this infection, whether or not they have other features of the disease (Solomon *et al*, 2000). Liver function is also known to be affected, with the impairment of hepatic functions in dengue patients takes place through hepatocellular injury as manifested by hepatomegaly, elevation of ALT and coagulopathy (Pancharoen *et al*, 2002). All of which are common in dengue hemorrhagic fever (DHF) and in dengue fever (DF), though hepatomegaly is absent. Acute liver failure is one important cause of fatal dengue infection where liver injury is either a direct effect of viral replication in the liver itself or a consequence of host responses to infection (Innis *et al* 1990). Co-infection can modify clinical presentations of dengue disease and result in missed or delayed diagnosis and treatment, and possible misinterpretation as unusual manifestations (Pancharoen and Thisyakorn, 1997). This is demonstrated in co-morbid state of dengue and Kawasaki reported by three separated authors in three children (Sophontammarak and Pruekprasert, 2000; Tourneux *et al*, 2002; Mekmullica *et al*, 2005).

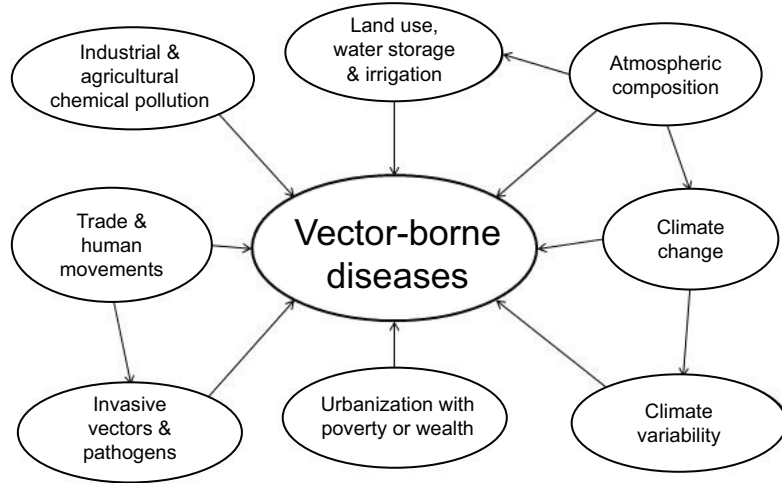


Fig 1–Vector-borne diseases are interconnected with the climate and human activity.

World distribution of dengue

Dengue disease is present in over 112 countries. The four virus serotypes have been isolated in all tropical regions of the globe where related health problems are mounting. The four related but antigenically distinct serotypes viruses are transmitted via mosquito-borne flavivirus infection (*Aedes aegypti* and *Aedes albopictus*). A predicted potential distribution by the year 2030 will see dengue spreading across Europe as the Continent warms up (ECDC, 2009). Vector-borne diseases are interconnected with the climate and human activity (Fig 1).

Dengue infection in adult population

The greatest dengue burden is in the Asia-Pacific region where three-quarters of the infection occurs. Indonesia, Thailand, and Vietnam have the largest number of reported cases (Shepard *et al*, 2013). Age shifting to adults is being detected and on the rise. Fluid leakage happens in all age groups. A study in Bangkok Metropolitan

appears to confirm these findings (Liulak, 2013). Another work in Thailand's Ratchaburi Province on dengue vaccine also discovered an increasing trend of patients outside the pediatric population being affected (Tanayapong *et al*, 2013).

For visitors to dengue endemic areas an extra caution should be adopted. They are advised to seek medical attention if fever and/or rash develop. Severe dengue virus infection in travelers as related to risk factors and laboratory indicators have been proposed in 2007 (Wichmann *et al*, 2007). A serological analysis found a secondary immune response in 17% of the 219 patients with imported dengue diseases (Wichmann *et al*, 2007). Spontaneous bleeding was observed in 8% and was associated with increased serum alanine and aspartate aminotransferase levels, and lower median platelet counts. Eleven percent had severe clinical manifestations such as internal hemorrhage, plasma leakage, shock, or marked thrombocytopenia. A secondary immune

response was significantly associated with both spontaneous bleeding and other severe clinical manifestations. A recommendation is that severe dengue should be considered if the patient has been to the area of dengue risk when presenting with fever of 2-7 days plus any of the following (Wichmann *et al*, 2007):

1) There is evidence of plasma leakage, such as: High or progressively rising hematocrit; Pleural effusions or ascites; Circulatory compromise or shock (tachycardia, cold and clammy extremities, capillary refill time greater than three seconds, weak or undetectable pulse, narrow pulse pressure or, in late shock, unrecordable blood pressure).

2) There is significant bleeding.

3) There is an altered level of consciousness, such as lethargy or restlessness, coma, convulsions.

4) There is severe gastrointestinal involvement, such as persistent vomiting, increasing or intense abdominal pain, or jaundice; or

5) There is severe organ impairment, such as acute liver failure, acute renal failure, encephalopathy or encephalitis, cardiomyopathy or other unusual manifestations.

Dengue incidence is underreported for the following reasons: non-universal case definition, limited diagnostic means or misdiagnosis, surveillance and reporting system development, inadequate information from major at-risk regions, such as China, sub-Saharan Africa, and India.

The economic burden of dengue infection is significant and likely to be greater than estimated due to direct and indirect

factors, such as medical care, surveillance and reporting, and preventive strategy for the former; and premature death, lost productivity of the patient and caretaker for the latter.

Prevention of dengue infection

Dengue is the most important arthropod-borne viral disease of humans. As widely accepted, prevention is the key to success. Herein, there are two elements: the control of mosquito and a vaccine. Integrated vector management should take into account of advocacy, social mobilization, and legislation. Collaboration, through integrated approach and capacity building, within the health sector and with other sectors is crucial (WHO, 2012).

Dengue vaccine road map

The past success of immunization has paved the way for better things to come. Dengue is no exception, but many challenges lie ahead. At present there is no vaccine available despite over sixty years of work in this field. Some explanations for the difficulty are that there is no animal model for the disease. Not only one, but four different viral serotypes need to be looked at. The theoretical risk of immunopotential after sequential infections means that a combined tetravalent vaccine is the best option (Thisyakorn and Thisyakorn, 2014). A live-attenuated vaccine technology provides the optimal protection; the need for efficacy study and industrialization of the production process of vaccine and consistent large-scale manufacturing are ideally required. Although no licensed dengue vaccine is yet available, several vaccine candidates are under development, including live-attenuated virus vaccines; live chimeric virus vaccines; inactivated virus

vaccines; and live recombinant, DNA and subunit vaccines.

Only one product, the live chimeric virus vaccine—where dengue structural genes are inserted into the infectious cDNA backbone of the well-established yellow fever vaccine virus strain 17D—has entered a Phase III clinical trial (Thisyakorn and Thisyakorn, 2014). The protective efficacy of the recombinant, live-attenuated CYD (combined yellow fever and dengue) tetravalent dengue vaccine in the Thai school children undergoing a randomized, controlled phase 2b trial showed for the first time that a safe vaccine against dengue is possible (Sabcharoen *et al*, 2012). Ongoing large-scale Phase III studies in various epidemiological settings will provide pivotal data for the CYD dengue vaccine candidate.

The CYD dengue vaccine was given to an additional 30,000 adults and children, mostly in dengue-endemic countries (Halstead, 2012b). Results from these ongoing vaccine trials should amalgamate DENV-specific disease efficacy rates and provide direct evidence of vaccine efficacy in severe disease. Future dengue vaccine trials should provide robust evidence of efficacy against severe disease by selecting populations weighted to assure inclusion of sufficient numbers of at risk children (Halstead, 2012a). It is speculated that the Phase III will be announced one year from now. Individuals stand to reap the benefits while public health spending reduces.

An ASEAN team on dengue vaccine known as ASEAN Member States Dengue Vaccination Advocacy Steering Committee (ADVASC) has for their objectives as following (Thisyakorn, 2012):

- 1) Identify and making practical recommendations on: Improved surveillance and case diagnostics; Select initial groups for vaccination; Address program feasibility; Prepare and implement risk management plan.

- 2) Communicating recommendations to all stakeholders.

- 3) Collaborating with other relevant dengue initiatives.

The recommendations of the recent ASEAN Dengue Vaccination Advocacy (ADVA) workshop are to standardize the monitoring and reporting of dengue in the ASEAN region (Thisyakorn *et al*, 2014). For case definition and classification, the report suggests a reconciled and harmonized WHO 1997, WHO 2009, and WHO 2011-SEARO guidelines for simplified surveillance and meeting key diagnostic criteria. In addition, the information on DHF, DSS is preserved in order to compare with historical data.

The second recommendation focuses on data collection and analysis. It suggests that all data should be collected at all levels and reported. Vaccination status should be linked to existing surveillance systems. Promoting regional networks is to be supported.

The third recommendation aims at laboratory testing. A choice of diagnostic tests is to be made available. The results of all tests should be linked to surveillance systems. If testing of all cases is not possible, sentinel sites and representative sampling of cases are acceptable. Quality control is to be conducted by a central reference laboratory. Viral detection is used in the early stage and antibody for the latter. Based the research, ADVA suggests

continuing the strength through evidence and evaluating the current surveillance. The work must be transparent, information shared, awareness campaign organized, and exploration initiatives continued and build partnerships to ensure sustainable, long-term financing for dengue prevention and control.

WHO global strategy for dengue prevention and control 2012-2020 (WHO, 2012) has its goal to reduce the burden of dengue, with the objectives of reduction of dengue mortality by at least 50% together with reduction of dengue morbidity by at least 25% by 2020 and to estimate the true burden of the disease by 2015. The year 2010 is used as the baseline.

The technical elements include diagnosis and case management, integrated surveillance and outbreak preparedness, sustainable vector control, future vaccine implementation, and basic operational and implementation research. The enabling factors for effective implementation of the global strategy are advocacy and resource mobilization, partnership, coordination and collaboration, communication to achieve behavioral outcomes, capacity building, monitoring, and evaluation (ECDC, 2009).

When looking into the treatment, success depends largely on early recognition and careful monitoring of DHF developing into DSS. Controversies in dengue remain in a number of areas, as stated as follows (Halstead, 2012b): Inadequacy of the 1997 WHO case definition; DHF is not significantly associated with second dengue infections; DHF is caused by virulent viruses; DHF results from an abnormal T cell response; DHF results from dengue infection-induced autoimmunity; and DHF results from DENV-infected endothelial

cells.

The conclusion is that the human and economic costs of dengue are significant and likely to be even higher than estimated. Disease prevention is a key to public health dimension.

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