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Dengue: what it is and why there is more

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Abstract

In 2014, China experienced the worst outbreak of dengue fever in the last decade with over 40,000 dengue cases including six deaths by the end of October. As one of the “neglected” tropical diseases, dengue is affecting substantially increasing number of people and proportion of global population due to factors including globalization, human settlement, and possibly climate change. Here, the authors summarized the most recent data about dengue outbreaks in China and reviewed the global trend of dengue epidemiology. Future directions for dengue surveillance, control and prevention are also introduced.

Keywords

Dengue; Vector control; One Health; China

In 2014, China experienced the worst outbreak of dengue fever (DF) in the last decade (Fig. 1a, b). A total of 44,591 dengue cases were reported to the national notifiable infectious diseases reporting system by the end of October including six deaths, and 99 % of cases were reported in south China provinces, such as Guangdong, Fujian, Yunnan and Zhuang Autonomous Region [1]. On November 3, the U.S. Centers for Disease Control and Prevention (CDC) issued a travel notice for Guangdong province, China because of the dengue outbreak [2].

1 The global threat of dengue

Dengue fever (DF), caused by any one of the four closely related dengue viruses (DENV 1–4), is a viral illness transmitted by *Aedes* mosquitoes. Originating in monkeys, dengue viruses were transmitted to humans between 100–800 years ago, and dengue remained a relatively minor and geographically restricted disease until the 1950s when epidemics occurred in the Philippines and Thailand [3, 4]. Dengue has emerged as a worldwide problem, with a 30-fold increase in incidence globally in the past 50 years (Fig. 2) [4]. Today, dengue is regarded as the most prevalent and rapidly spreading mosquito-borne viral disease of humans [4]. It is found in at least 100 tropical and subtropical countries, including

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countries in Africa, Southeast Asia, the western Pacific, the Americas, the Caribbean, and the eastern Mediterranean regions [3, 5]. More than one-third of the world's population lives in areas at risk of infection with dengue virus [3], and a recent estimate using cartographic approaches in 2013 showed that 390 million people have dengue virus infections per year, of which 96 million cases manifest symptoms worldwide [6].

Dengue is a complex disease with a wide spectrum of clinical presentation. Classic DF is characterized by acute onset of high fever 3–14 days after the bite of an infected mosquito, and the high fever can persist for 2–7 days accompanied by frontal headache, retro-orbital pain, myalgias, arthralgias, rash, and low white blood cell count [7, 8]. Due to the severe muscle, joint and bone pains, dengue is also known as “break bone fever”. Most dengue patients recover after a few days, but some DF patients develop dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), which are severe and sometimes fatal forms of the disease [7]. About three quarters of dengue infections can be asymptomatic, especially in children and those with previous dengue infection, but they can still infect mosquitoes [3, 7]. However, secondary dengue infection is one of the two factors thought to be associated with increased risk of disease severity; the other factor is infection by particularly virulent strains of dengue viruses [8].

At present, no vaccine exists to prevent dengue infection, nor are there specific medications to treat the disease. The most effective protective measures are those that prevent mosquito bites, namely vector control [3]. The main arthropod vector for dengue virus transmission is *Aedes aegypti*, and a second, less effective vector is *Aedes albopictus* [8]. Control of dengue vectors has mainly been addressed by community-based source reduction: The elimination of containers that are favorable sites for oviposition and development of the aquatic stages [4]. For individuals, preventive measures include sleeping under a mosquito bed net, eliminating mosquito indoors and wearing repellent [3].

The World Health Organization (WHO) described dengue as a “neglected” tropical disease (NTD) in its Dengue Prevention and Control Strategy 2012–2020, due to the lack of global coordination efforts, research, and political will [4]. The contemporary worldwide distribution of the risk of dengue virus infection and its public health burden is poorly known, and the greatest uncertainties in national burden estimates are in India, Indonesia, Brazil, and China [6]. The economic burden of dengue on both governments and individuals is high. Based on a systematic review analysis, the estimated cost of dengue disease in the Americas including North America, Central America and Mexico, the Andean region, Brazil, the Southern cone, and the Caribbean region is 2.1 billion USD per year on average, excluding cost on vector control [9]. Another 12-country economic analysis also showed high dengue burden in Southeast Asia, with an annual average of 950 million USD resulted from 2.9 million dengue episodes and 5,906 deaths [10]. Information on economic burden of dengue in China, however, is not available.

2 Dengue in China

NTDs including dengue are still widespread and create a substantial burden in China [11]. Infectious diseases in China are divided into three categories (A, B, and C) according to

their transmission modes, speed, and hazard to humans; DF, together with Severe Acute Respiratory Syndrome (SARS), H1N1 influenza, rabies, tuberculosis etc., belong to infectious diseases category B. In 2005, China established a national monitoring program for DF in humans and vector monitoring in *Aedes* mosquitoes, focusing on five provinces (Guangdong, Fujian, Yunnan, Guangxi Autonomous Region, and Hainan) with 16 national monitoring sites. Other efforts that China has made to prevent and control dengue include control of mosquito vector density, enhanced surveillance for imported cases, improvement of diagnosis and treatment, enhancing the cooperation among the related different public health departments and neighboring countries, and engaging communities to combat the epidemic [11, 12]. In response to the dengue outbreak in 2014, four technical guidelines [13], including surveillance of DF cases, laboratory tests and diagnosis, surveillance of dengue vectors, and control of dengue vectors, were developed and issued by China CDC, together with the previous two dengue guidelines (Diagnosis and Treatment of Dengue Fever in 2014 and Dengue Outbreak Investigation and Management in 2006) issued by the National Commission for Health and Family Planning, formed a complete national technical framework for dengue control and prevention [13].

DF in China's mainland was characterized as an imported epidemic disease and was not confirmed as an endemic in the past [4], but after the 2014 large dengue outbreak, it is possible that DENV will be endemic in southern China, especially in Guangdong [14]. All four dengue viruses are detected in China [11]. Upon review of the surveillance data collected by the monitoring program started in 2005 with a focus on southern provinces as described above for the past years, a changing circulation pattern of DF has been observed in Guangdong, from non-endemicity (no virus sustained), to hypo-endemicity (one serotype present), and even hyper-endemicity (multiple serotypes present) of dengue infections [15]. In the last two decades, the biological behavior and vectorial capacity of *Aedes* mosquitoes have changed significantly in China, possibly due to urbanization and global climate changes [12]. Therefore, dengue illnesses have spread from southern coastal regions to the relatively northern and western areas of the country, and the interval between epidemics has become shorter since the 1990s compared to those that occurred before the 1990s, beginning with the first reported outbreak of DF in Guangdong in 1978 [11, 12]. In 2013, a severe dengue outbreak of 1,245 cases happened in Yunnan Province, with a significant proportion of severe dengue cases; DENV-3 was identified to be the cause of the outbreak using real-time RT-PCR assays [16]. In the same year, the first dengue outbreak in central China was reported in Henan Province, a northern temperate province of China; 73 of 106 suspected DF cases of this outbreak were confirmed DENV-3 infections [17].

The recent data from Guangdong, the most affected province of the 2014 dengue outbreak, showed that as of December 15, 20 prefectures reported a total of 45,171 clinical or laboratory confirmed dengue cases according to the case definition in China's dengue surveillance guideline 2005, with the highest number (37,354) reported in the capital city of Guangzhou, followed by Foshan City with 3,542 cases [18]. According to the Guangdong Provincial CDC, the peak of the dengue outbreak was reached on October 1, and case numbers started to decline after October 11 [19]. Guangdong is located in a subtropical zone in China, and it has a high relative humidity, which may have created climatic and

environmental conditions conducive to the proliferation of *Aedes* species. The DF epidemic area in Guangdong was mainly located in the old town which is under construction, and the poor sanitary infrastructure may contribute to this DF epidemic. A previous study from Guangdong showed that urbanization substantially increased the density, larval development rate, and adult survival time of *Aedes* species, which in turn potentially increases the vector capacity, and therefore, disease transmissibility [20].

3 Future directions for dengue control

Experts predict geographic expansion and increased incidence of dengue in the future [8]. The expansion of dengue is multifactorial, and the main “drivers” of increase in dengue incidence include globalization, travel, trade, socioeconomic factors, human settlement, viral evolution, and possibly also climate change [8].

With the substantial increase in the number of people and the proportion of the global population at risk of DF, a safe and effective dengue vaccine is greatly needed. Very recently, a tetravalent dengue vaccine has been reported showing efficacy against DF and severe DF, leading to fewer hospitalizations in a randomized, blinded, placebo- controlled trial in Latin America [21]. The observed reduction in the severity of clinical disease and the prevention of hospitalization are encouraging, and the progress is considered a milestone in dengue prevention and control [22].

Accurate disease burden estimates and sensitive out- break monitoring for dengue through improved epidemiological and entomological surveillance are another key for dengue control. Dengue is an acute febrile illness, and only diagnostic testing can accurately determine the etiology of the syndrome and differentiate dengue from acute febrile illness caused by other pathogens. However, the current dengue surveillance programs in China and internationally are all syndrome based (that is, entail clinical case-definitions without laboratory confirmation) and almost all are passive [23]. With the development of sensitive and specific diagnostic algorithms and increased awareness of dengue expansion, robust, laboratory-based dengue surveillance is needed to document and monitor the regional and global dengue incidence, and to evaluate the effectiveness of dengue control interventions. More accurate epidemiological and surveillance data will support greater political prioritization for this currently “neglected” disease. It would also allow improved decision making and rational allocation of financial, research, and other resources to the areas of greatest need [24].

Although the current control approach has shown some effectiveness, innovative vector control tools are still needed to control mosquito more effectively [25]. Recent systematic review and meta-analysis showed low relative effectiveness (25 %) with high heterogeneity of community-based interventions with educational message for dengue control [26]. Vector-borne diseases such as dengue have raised public health concern worldwide due to climate change, global trade, worldwide travel, and urban crowding. “One Health” is a relatively new term, but the concept that the health of humans is connected to the health of animals and the environment has long been recognized [27]. It has become more important in recent years because many factors have changed the interactions among humans, animals,

and the environment, which have caused the emergence and reemergence of many diseases, including dengue. Successful public health interventions for disease control require the cooperation of the human health, veterinary health, and environmental health communities [27].

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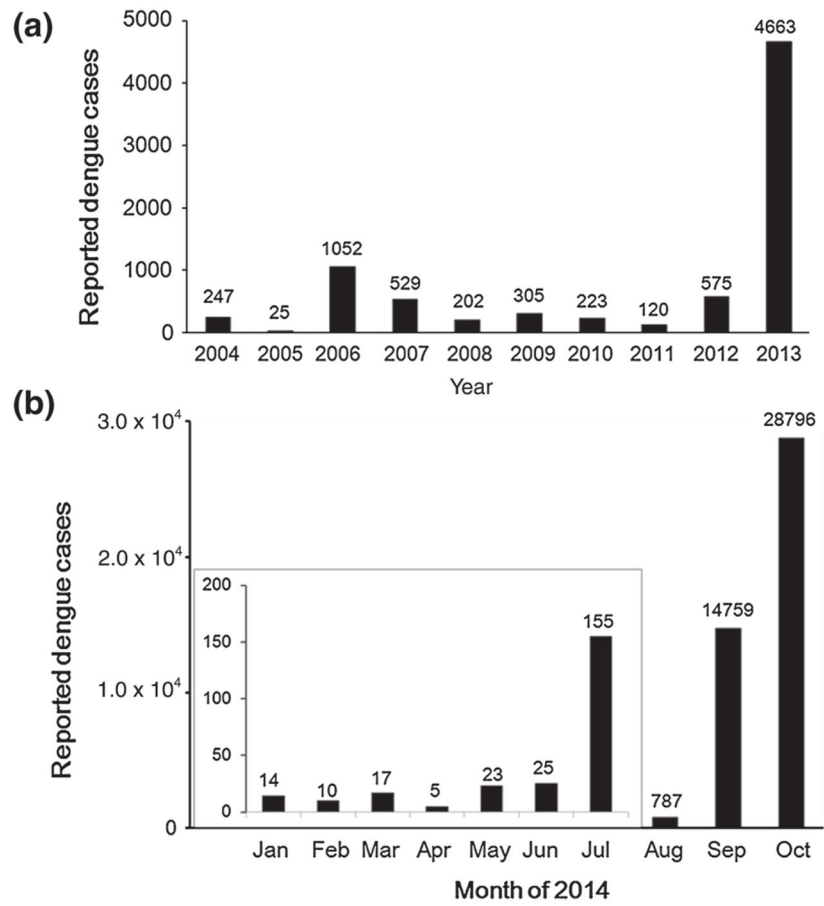


Fig. 1. Number of reported dengue fever (DF) cases in China’s mainland from 2004 to 2013 **(a)** and from January to October 2014 **(b)**. Data source: Notifiable infectious disease reporting summary, China CDC [1]

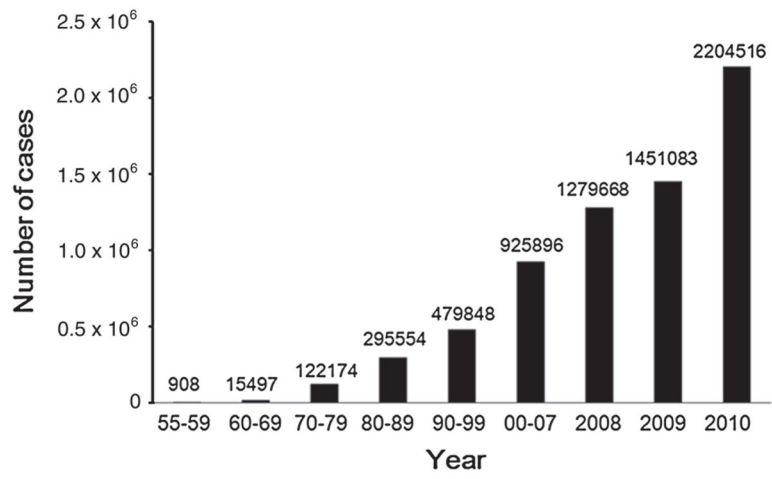


Fig. 2. Average number of dengue and severe dengue (DHF) cases reported to WHO from 1955 to 2007 [4]