CHAPTER 7

ASK THE EXPERTS

Surveillance of global dengue distribution

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1. What is the present global dengue distribution & burden & how is it changing?

Dengue is found in 128 countries and is ubiquitous throughout the tropics, with regional and local spatial variations in risk [1]. There is a disproportionate burden of infection borne by Asian countries, which account for 70% of the world's total burden, recently estimated at 96 million apparent infections [2]. Half of this is attributable to India. The Americas account for approximately half of the remaining burden (14%); this is primarily attributable to cases from Brazil and Mexico. While Africa was previously considered at low risk from dengue, more recent estimates suggest its burden is comparable with that of the Americas, with significant underreporting and misdiagnosis as other symptomatically similar illnesses. While Oceania is also at high risk from dengue, its relative contribution to the global burden is low (<2%). Dengue also appears to be spreading on multiple frontiers, with recent incursions into the southern states of the USA, continental Europe and southern Argentina. Many of the socioeconomic and environmental changes that accompany global development are favorable to the transmission of dengue and thus augur for its continued expansion [3].

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2. What are the main factors that determine the global dengue pattern at present?

Dengue is transmitted by *Aedes aegypti* and *Aedes albopictus,* so the absolute distribution of these vectors defines its global limits. The spread of *A. albopictus* in particular is facilitating the global spread of dengue into new areas. Meteorological factors affect the lifecycle and survival of *Aedes* populations, therefore determining their abundance within the limits of their distribution. Specifically, precipitation is important because *Aedes* requires water-filled containers for laying eggs, while temperature affects vector growth and behavior as well as dengue virus (DENV) incubation within the vector [4–6]. When combined with the population dynamics of the DENV in human populations and a myriad of human–environment interactions, these factors affect the duration of dengue establishment and viral diversity (often correlated), therefore resulting in spatially heterogeneous patterns of local risk. At the global scale, patterns in climatic variables such as precipitation and temperature have thus been resolved as important predictors of risk for dengue [2]. Socioeconomic and demographic factors (e.g., urban extents) are also very important when assessing global patterns of dengue risk, since *A. aegypti* and *A. albopictus* are adapted to human-modified environments [2]. Large cities in tropical zones therefore suffer a disproportionately high share of the total global dengue burden. Increasing global connectivity also has probable implications for rises in the global cocirculation of DENV types, the epidemiological consequences of which are poorly understood.

3. What is the current status of dengue surveillance systems in endemic areas?

In most dengue-endemic areas, disease reporting is mandatory, but the level of severity at which the disease gets reported varies regionally. In South and Central America, most endemic countries report an inclusive range of dengue classifications (clinical/laboratory-diagnosed dengue fever, dengue hemorrhagic fever, dengue deaths) weekly by province. These data may be supplemented by vector surveillance in urban areas, such as the Brazilian Levantamento Rapido de Indice para *Aedes aegypti* (LIRAa) system, which monitors *A. aegypti* abundance at the pupal and larval stages during household surveys. Many countries in south and southeast Asia

currently only report the more severe forms of the disease.

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The majority of reporting is government hospital inpatient based, although patients' addresses may be recorded in some instances for surveillance purposes (e.g., Singapore). In countries such as India, where many patients seek private healthcare or are treated mostly as outpatients, there may be significant gaps in dengue surveillance [1]. Furthermore, no dengue-endemic country conducts regular surveillance of inapparent infections. The accuracy of the case numbers that then get reported to the WHO is also considerably variable across space and time.

4. What should be the priorities for improving dengue surveillance?

Routine surveillance

Routine dengue surveillance should ideally be composed of human cases of the disease, laboratory-based surveillance and vector surveillance in an integrated system [7]. Reporting of human cases should have both consistent passive and enhanced sentinel components. In sentinel sites, all febrile illness cases should be tested for the presence of anti-DENV IgM antibodies and clinical capacities should be augmented. Any detection of positive dengue cases should trigger site-specific entomological surveillance and control responses.

Outbreak detection

Peaks in dengue mortality often occur during outbreaks that cause healthcare infrastructures to be overwhelmed. Major problems still need to be solved in the definition of an outbreak, its early detection and, most importantly, the set of resulting administrative responses at the vector control and healthcare levels. Much of the highly variable practice in this area is founded upon a poor evidence base that must also be rapidly improved [8].

Endemicity

In any location, it is important to understand the age-structured ratio of all dengue infections, as this provides for a richer understanding of the local epidemiology of

the disease. This will be required if we are to estimate and measure the impact of control and ultimately vaccination. Ideally, this would involve national programs of annual age-stratified seroprevalence surveys; however, these are likely to be financially prohibitive [3]. More feasible would be sentinel surveillance of cohorts in a representative sample of environments. These would also help to greatly improve national and global burden estimates.

5. What are the reasons for the disappointing results of the Sanofi Pasteur dengue candidate? What is the probable timeframe for the incorporation of an efficacious vaccine into immunization programs?

The Sanofi Pasteur (Lyon, France) candidate is a live attenuated tetravalent dengue–yellow fever 17D virus vaccine. The Phase IIB efficacy study conducted in Thai schoolchildren showed a surprisingly low overall efficacy of 30.2% [9]. Given the enormous burden of dengue and the fact this was the leading dengue vaccine candidate, these were very disappointing results for global public health.

The reasons for these results are not completely clear. One of the major difficulties with dengue vaccine development is our incomplete understanding of dengue pathogenesis and, in particular, our lack of knowledge of what the correlates of dengue immunity are and how best to measure them [10]. However, we do know that infection with one DENV serotype induces lifelong immunity against that serotype and short-lasting crossreactive immunity against the other serotypes. The investigators propose that the DENV2 incorporated into the yellow fever chimera may not have been able to induce protective antibodies against the DENV2 circulating in Thailand at the time of the study [9]. Others have suggested that a failure to induce balanced viremias or immune responses across the four serotypes of DENV may have been partially responsible for the low efficacy observed [11]. In addition, the results of this trial have pointed towards the potential limitations of using primate dengue vaccine challenge models to inform us of efficacy in humans [12]. It is possible a dengue human challenge model may play an important role in vaccine development [13].

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It remains to be seen whether the Sanofi vaccine candidate offers protection against

severe disease, and ongoing Phase III trials may demonstrate this. There are other vaccine candidates in earlier stages of development [14]. Most of the candidates in early stages of clinical development are also tetravalent live attenuated vaccines, although some others in preclinical development have adopted different designs. While it is exciting that there are numerous potential vaccine candidates at various stages of development, it is important to remember that the vaccine development process is lengthy [15]. Should the Phase III trials of the Sanofi candidate prove disappointing, we are many years away from a commercially available vaccine. The challenge of funding vaccine development remains – traditionally this has been the remit of commercial entities but the global importance of dengue may justify increased noncommercial funding. Once an efficacious dengue vaccine has been developed, individual countries must make economic justifications for its introduction and incorporation into immunization programs. It is likely that countries with a high burden of dengue cases will be the first to introduce a dengue vaccine into their immunization programmes. In addition, there is likely to be a market for a dengue vaccine for travelers and the military.

While a dengue vaccine is highly desirable for global health, it is essential that other components of dengue control are not neglected, for example individual clinical management and vector control.

6. What are the major factors contributing to the continued spread & intensification of dengue?

The global burden of dengue is large, with recent work suggesting there are an estimated 390 million infections each year [2]. This figure is three-times higher than the WHO's previous estimates of the global dengue burden. One of the key factors in both the spread and intensification of dengue is the spread of efficient disease vectors, in particular the highly domesticated and urbanized mosquito *A. aegypti* [16,17]. This spread has been augmented by the current lack of effective vector control measures. *A. aegypti* is thought to have emerged from Africa during the slave trade and spread into Asia as a result of trade expansion. Dengue outbreaks in Africa, such as that seen in Cape Verde in 2009, may well reflect increased trade between Asia and Africa [18]. In the

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last 50 years, *A. aegypti* has spread throughout the tropical world, reflecting increased globalization with increased international trade and huge population movements [19]. Another potential dengue vector, *A. albopictus*, has extended its global range dramatically in recent years, including spread into Europe and North America [20]. However, as *A. albopictus* is not the primary dengue vector, it is not clear how much its expansion has contributed to the global spread of the disease. In addition, the rapid and, at times, uncontrolled expansion of urban centers in Asia, Latin America and increasingly in Africa has supported the proliferation of vector breeding sites [19]. The proliferation of domesticated disease vectors combined with large nonimmune populations have led to explosive disease outbreaks and the establishment of dengue endemicity. The intensification of dengue is dependent on transmission intensity and time since disease establishment. It is inferred by increasing diversity and stability of DENV serotypes in a given geographic location.

7. What are the goals of the WHO 2012–2020 global strategy for dengue prevention & control?

Dengue is an increasing global public health concern. Dengue causes individual patient suffering, places immense strain on struggling health systems and results in a significant economic burden. The WHO global strategy seeks to address these problems by reducing the burden of dengue [21]. Specifically, the strategy aims to reduce the mortality and morbidity from dengue by 50 and 25%, respectively, using 2010 WHO estimates as a baseline by using and building on existing knowledge.

Earlier and better case detection and improved individual case management will hopefully result in the desired mortality reduction. To reduce morbidity, the strategy suggests developing outbreak detection tools and supporting improved integrated vector control measures. The achievement of these aims will require appropriate research and implementation of relevant evidence-based activities.

While we fully support the aims of the WHO global strategy, one concern is that the 2010 WHO dengue estimates are thought to be significant underestimates of the global disease burden [2]. Improved case detection will result in more realistic disease estimates but will make achieving the specific objectives of the global strategy impossible.

8. How can dengue morbidity & mortality be reduced?

> “Early case detection and improved individual patient management will result in reductions of both mortality and morbidity.”

Early case detection and improved individual patient management will result in reductions of both mortality and morbidity. The dengue field could build on the platform of enhanced surveillance adopted for influenza after the 2009 pandemic resulting in earlier outbreak detection and improved patient management [8,22]. Reassuringly, in experienced settings, the mortality from dengue is very low. Treatment is supportive and in severe cases requires careful fluid resuscitation and, in cases of hemorrhage, administration of blood products [16]. As the period of significant plasma leak is transient, it is common in inexperienced settings to give too much fluid, with the danger of overloading the patient. The 2009 WHO dengue guidelines classify dengue into ‘dengue’ and ‘severe dengue’, and place emphasis on various warning signs that may indicate a patient progressing to more severe disease [7]. While there has been significant debate about the merits of the new disease classification, the guidelines are designed to make management of patients with dengue easier and recognition of patients with potentially more severe disease more efficient [23]. Thus the implementation of the new guidelines has the potential to reduce dengue mortality and morbidity. At the moment, there are no specific therapeutics that can be used in dengue, although both antiviral and immunomodulatory drugs have been trialled [24–26]. The development of a safe therapeutic agent that can reduce the duration of illness and the risk of progressing to severe disease would be a major advance in our efforts to control dengue.

Successful prevention strategies have enormous potential to result in significant reductions in dengue mortality and morbidity. An efficacious vaccine is of course highly desirable but, as discussed above, is still years away. Vector control strategies have previously had limited success in controlling dengue, but exciting new advances may change this. For example, infection of mosquitoes with fruit fly strains of symbiont *Wolbachia* bacteria appears to reduce mosquito lifespan and interfere with pathogen replication [27,28]. Releases of *Wolbachia*-infected *A. aegypti* have been commenced in Australia and parts of southeast Asia. The impact of this imaginative approach to dengue control remains to be seen.

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