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Dengue in a changing climate

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ABSTRACT

Dengue is the world's most important arboviral disease in terms of number of people affected. Over the past 50 years, incidence increased 30-fold: there were approximately 390 million infections in 2010. Globalization, trade, travel, demographic trends, and warming temperatures are associated with the recent spread of the primary vectors *Aedes aegypti* and *Aedes albopictus* and of dengue. Overall, models project that new geographic areas along the fringe of current geographic ranges for *Aedes* will become environmentally suitable for the mosquito's lifecycle, and for dengue transmission. Many endemic countries where dengue is likely to spread further have underdeveloped health systems, increasing the substantial challenges of disease prevention and control. Control focuses on management of *Aedes*, although these efforts have typically had limited effectiveness in preventing outbreaks. New prevention and control efforts are needed to counter the potential consequences of climate change on the geographic range and incidence of dengue, including novel methods of vector control and dengue vaccines.

1. Introduction

Worldwide, dengue is the most important vector-borne viral disease that is transmitted to humans by mosquitoes. The burden of disease has increased an estimated 30-fold over the past 50 years (Global alert and response, 2015). Globalization, trade, urbanization, travel, demographic change, inadequate domestic water supplies and warming temperatures are associated with the spread of the main vectors *Aedes aegypti and Aedes albopictus* (Murray et al., 2013). *Ae. aegypti*, originally from Africa, and *Ae. albopictus*, from Asia, rapidly expanded their range over the past 50 years, transported among continents and spread overland by the global shipping industry, in rubber tires or other containers in which eggs had been laid. Dengue virus (DENV) also spreads rapidly via infected travelers (Wilder-Smith, 2012), whose numbers have increased over recent decades (Semenza et al., 2014). Climate change may lead to changes in these determinants of dengue transmission by multiple, inter-related mechanisms.

The identification of factors, particularly environmental variables, that can be used to forecast epidemics is important to allow sufficient time for health systems to be prepared, and will improve our understanding of how a changing climate may contribute to the geographic expansion of mosquitoes and disease into new areas. Here, we synthesize recent literature, offering insights into the projected future distributions of *Aedes* vectors and dengue transmission under climate change.

2. Worldwide burden and distribution of dengue fever

Dengue disease (varying in clinical manifestations from acute febrile illness, self-limiting episodes [dengue fever, DF] to severe hemorrhagic manifestations [dengue hemorrhagic fever, DHF] and death) is caused by any one of four closely related dengue viral serotypes (DENV- 1, DENV-2, DENV-3, and DENV-4) of the genus *Flavivirus*, belonging to the family *Flaviviridae*. The worldwide distribution and incidence of dengue infections and cases are difficult to accurately establish because only approximately 20% of those infected with dengue virus exhibit apparent clinical symptoms. Disease occurs across a spectrum, and many patients with milder manifestations never seek health care. Additionally, of those patients who enter healthcare facilities, non-specific symptoms may be confused with other diseases or fail to satisfy reporting criteria: national passive surveillance systems are not designed to capture all symptomatic cases. Consistent burden estimates are elusive; from 2010 to 2013, the World Health Organization (WHO) reported an increase from 2.4 million to over 3 million reported cases from the three affected regions (Americas, South-East Asia, and Western Pacific). Accordingly, their 2012 Global Strategy estimated a total of 50–100 million infections per

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year (Global alert and response, 2015; World Health Organization, 2012).

These estimates were updated following a study in which the global distribution of dengue was modeled to map the risk of disease based on an exhaustive assembly of records of dengue occurrence. These data included environmental and socioeconomic covariates known or hypothesized to affect transmission (Bhatt et al., 2013). The authors estimated that worldwide in 2010, there were approximately 390 million (range 284–528 million) dengue infections, 96 million (range 67–136 million) of which were clinically apparent. These infection rates were more than three times higher than those previously estimated by the WHO (Global alert and response, 2015), and included cases from 36 countries previously considered dengue-free (Brady et al., 2012). People in more than 125 countries, or over 50% of the world's population, were identified as being at risk of infection, including 824 million individuals in urban and 763 million in peri-urban areas (Brady et al., 2012). Dengue was predicted to be ubiquitous year-round in the tropics, with the highest risk zones in the Americas and Asia. Asia bore 70% of the global burden of apparent infections, with India contributing 34% of the total. The Americas accounted for 14%, with more than half occurring in Brazil and Mexico. Africa contributed 16%, with the predicted risk unevenly distributed and more widespread than previously suggested; however, documentation of data was poorest in Africa suggesting this could be an underestimate. Overall, this analysis may overestimate the number of dengue infections in some countries, such as in Hong Kong where, in contrast to a study estimate of $>300{,}000$ episodes annually, very few cases occur, and underestimate it in others; in the USA, the study predicted zero dengue transmission whereas local transmission occurs along the US-Mexico border and in Florida (Radke et al., 2012; Ramos et al., 2008).

Suitable local temperature and high levels of precipitation were the variables most strongly associated with elevated dengue risk; in some locations, dengue is associated with humidity and vapor pressure (Bhatt et al., 2013; Estallo et al., 2015). Proximity to low-income urban and peri-urban centers was also associated with greater risk, particularly for those with good transport connections (Bhatt et al., 2013). Climatic changes resulting in increased temperature and rainfall, together with urbanization, may therefore be associated with increased dengue incidence and outbreak risk.

In addition to the public health impacts, the economic burden of dengue can be substantial. Shepard et al. suggest that the economic costs of endemic dengue for individual professional healthcare systems can exceed hundreds of millions of US$ annually (Shepard et al., 2014). A review of 17 publications conducted in different geographic and health system settings reported that estimated costs for outbreaks in 2011 (in 2012 US$) ranged from US$2.8 million in the Dominican Republic to US$12 million in Vietnam (Stahl et al., 2013). Overall, the global aggregate direct (medical care and travel) and indirect (lost time and productivity) cost of dengue has been estimated as US$8.9 billion (Shepard et al., 2015).

3. *Aedes* mosquitoes

Historically, the prevention and control of dengue depended on controlling the *Aedes* vector mosquitoes. The primary vector, *Ae. aegypti*, is closely associated with humans and their dwellings. Water-holding containers in and around homes are used by the mosquitoes to complete their development, while people provide the blood meals required by female mosquitoes for egg development. *Ae. aegypti* preferentially rests in dark, cool areas, such as closets, and generally bites indoors (See Supplementary Table S1 for a comparison of *Ae. aegypti* and *Ae. albopictus*).

Eggs are laid on the side of water-holding containers and hatch into larvae after rain or flooding. The larvae transform into pupae, and then adult mosquitoes, in little over a week under favorable environmental conditions. Females are predominantly infected with dengue viruses after biting a viremic human. Vertical transmission between generations also may occur to an extent, although its significance is debated (Grunnill and Boots, 2016). It takes between 5 and 33 days at 25 °C, with a mean of 15 days, for viruses to multiply, mature, and migrate to the salivary glands before the mosquito can transmit the virus to another person (Chan and Johansson, 2012).

The geographic range of *Aedes* has varied over time. In the first half of the 20th century, *Ae. aegypti* was reported sporadically in Europe from the Atlantic coast (Britain, France, and Portugal) to the Black Sea, with a wider distribution than today (Aedes aegypti, 2015). The same is true for North America and Australia. The reductions observed since in these regions were possibly due to eradication programs, but were more likely caused by developmental changes including improvements in piped water, sanitation, and housing conditions. *Ae. aegypti* subsequently re-colonized Madeira, Portugal (leading to a dengue outbreak in 2012 with more than 2000 cases), parts of southern Russia and Georgia, and was imported to the Netherlands (Almeida et al., 2007; Scholte et al., 2010). In the United States, dengue reappeared in the early 2000s following 75 years of absence, leading to locally acquired disease (Anez and Rios, 2013). This re-emergence was due to the widespread distribution of *Aedes*, insufficient mosquito control measures, availability of mosquito habitats in urban landscapes, and increased frequency of DENV-infected visitors. In 2014, Japan recorded its first cases of locally acquired dengue fever after 70 years of absence; 160 cases were confirmed in a Tokyo outbreak between August and October (Kutsuna et al., 2015). *Ae. albopictus* was the likely vector. Overall, there has been a small pole-ward shift of the mean absolute latitude of *Ae. albopictus* distribution since 1960 and small equator-ward shifts of the mean absolute latitude of *Ae. aegypti* and of dengue (Rogers, 2015).

Kraemer et al. mapped the global distribution of *Ae. aegypti* and *Ae. albopictus* and the geographical determinants of their ranges based on occurrence data from published literature and entomological surveys between 1960 and 2014 (Kraemer et al., 2015). The authors paired the database with environmental variables, including species-specific temperature suitability and land-cover variables, to predict the global distribution of each mosquito species. The model predicted *Ae. aegypti* to exist primarily in the tropics and sub-tropics, with concentrations in northern Brazil and southeast Asia (including all of India) and low occurrence in Europe and North America (Fig. 1a). It predicts that in Australia, *Ae. aegypti* is largely confined to the east coast, while the distribution of *Ae. albopictus* extends into southern Europe, northern China, southern Brazil, northern United States, and Japan (Fig. 1b). For both species, temperature was the most important predictor of distribution, with precipitation and vegetation also providing valuable information. Urbanization was poorly correlated (Kraemer et al., 2015).

The predicted distributions of *Ae. aegypti* and *Ae. albopictus* contained most but not all of the locations where dengue disease occurs, indicating areas of further opportunity for dengue to spread. Brady et al. determined the global temperature constraints on the persistence of these two species and on their competence for DENV transmission (Brady et al., 2014). Temperature was important not only in limiting the absolute geographic limits of DENV transmission, but also in supporting different levels of endemicity. The authors concluded that when considering the full range of transmission determinants, and in contrast to its perceived status as a “secondary” vector, *Ae. albopictus* has a greater