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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 socio-economic 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).

temp, precip, vegetation
as proxy for mosquitos

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

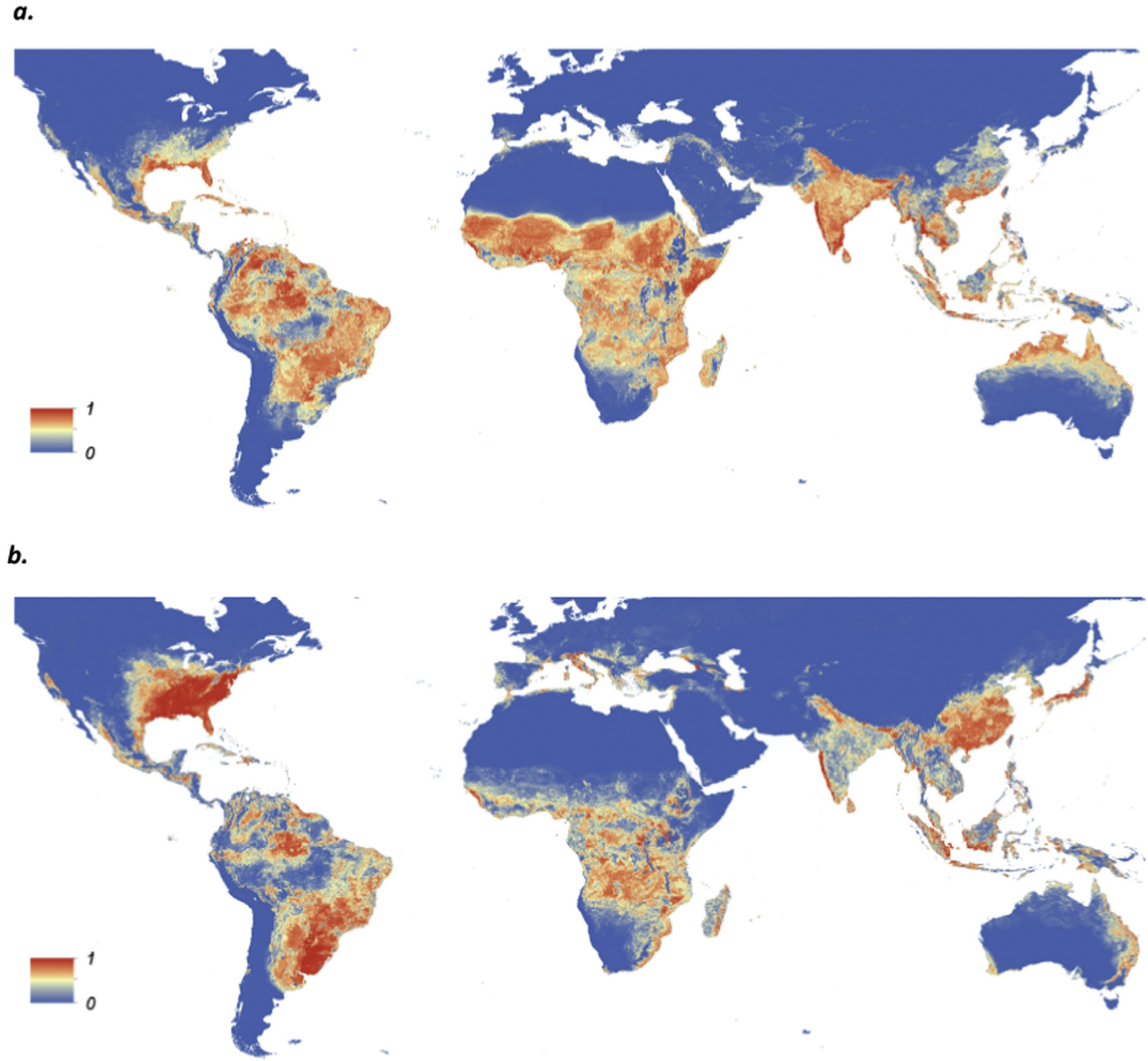

Fig. 1. Global maps of the probability of occurrence of a. Ae. aegypti and b. Ae. albopictus from 0 (blue) to 1 (red) at a spatial resolution of 5 km by 5 km. Source: Kraemer et al. (2015). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

capacity for DENV transmission than *Ae. aegypti*, and that the wider predicted distribution of this species could allow transmission during optimal seasons at higher latitudes than currently observed. *Ae. albopictus* eggs are especially hardy, facilitating survival over winter and on slow-moving transport, with subsequent colonization and survival in new geographies. The more limited evidence of this species transmitting DENV may be due to reasons including its ecology, and because most *Aedes* survey methods focus on household container types in which *Ae. aegypti* are more likely to be found. In addition to humans, *Ae albopictus* has catholic feeding habits, frequently targeting birds and other animals. This characteristic likely reduces the frequency of DENV transmission to humans and may explain why this species is considered less likely to cause dengue epidemics.

4. Control of *Aedes* mosquitoes

It is very difficult to control or eliminate *Aedes* mosquitoes, and after their introduction, they can become established if climatic and ecological conditions are suitable. They adapt to human environments and their populations often recover from natural disturbances, such as drought, or human control measures. Indeed, *Aedes* eggs can withstand drying and survive without water for several months on the inner walls of containers on which they were laid, hatching immediately after being submerged following rainfall. This speed of development means a population could recover within weeks after a vector control campaign successfully eliminates all larvae, pupae, and adult *Ae. aegypti* from a site (Dengue – entomology and ecology, 2015).

Given these challenges and the need for sustained, community-based vector control approaches, there has been a recent focus on implementing an integrated approach, incorporating locally appropriate packages of vector control interventions alongside improved dengue surveillance and outbreak response. A number of novel and promising vector control tools are under development that show some evidence of epidemiological impact; these remain a topic of ongoing research (Achee et al., 2015; Andersson et al., 2015).

There is increasing interest in developing early warning systems to predict dengue outbreaks with sufficient lead time for implementation of public health interventions. Numerous parameters have been used to attempt to forecast outbreaks of dengue (Racloz et al., 2012). Comparative assessment of the effectiveness of such models is difficult because of differences between approaches in terms of objectives, biological factors, spatio-temporal parameters, geographical scales, and mathematical equations (Supplementary Table S2). One review highlighted the benefits of combining climatic, environmental, epidemiologic, and socio-economic factors to forecast outbreaks and thus provide lead time for prevention and control activities (Racloz et al., 2012). However, Bowman et al. found little evidence of a quantifiable association between indices of mosquito populations and dengue transmission that could be reliably used for forecasting outbreaks (Bowman et al., 2014). This is reflective of a historical lack of association between dengue entomologic and epidemiologic parameters, and challenges the operational utility of predictive models in many settings (Bowman et al., 2014).

5. Factors affecting the magnitude and patterns of risks from dengue

The magnitude and pattern of dengue risk depends on inter-related human, vector, environment, and virus-related factors.

5.1. Weather and climate variability

Variations in weather and climate can affect the *Aedes* mosquitoes and DENV through multiple mechanisms (Fig. 2) (Morin et al., 2013). Temperature is an important determinant of biting rate, egg and immature mosquito development, development time of virus in the mosquito (extrinsic incubation period), and survival at all stages of the mosquito life cycle (Christophers, 1960). Laboratory studies assessing these factors indicated that the ideal temperature range for survival through all life phases of *Ae. aegypti* is between 20 and 30 °C (Tun-Lin et al., 2000). In some environments, elevated temperatures can thus increase the rate of mosquito mortality and decrease dengue risk. However, *Aedes* has adapted to human landscapes by overwintering in sewers and seeking shaded areas during daylight hours in hot environments. The time between feeding and virus detection in the salivary glands of *Ae. aegypti* decreased from 9 days at 26 °C and 28 °C to 5 days at 30 °C for DENV-1 and DENV-4 (Rohani et al., 2009). Feeding behavior is also more frequent at higher temperatures, further affecting transmission risk. Assuming mosquitoes are infected with DENV when they take their first blood meal, 10–39% should survive long enough to become infectious to humans, a proportion that is temperature dependent (Christophers, 1960).

Diurnal temperature range is also important for dengue transmission by *Ae. aegypti* (Lambrechts et al., 2011). Thermodynamic modeling predicts that at low mean temperatures (< 18 °C), increases in diurnal temperature ranges led to increased DENV transmission, whereas at mean temperatures > 18 °C, the effect was reversed. Indeed, at 26 °C, mosquitoes were susceptible to infection and survived for a shorter period under larger diurnal temperature ranges (Lambrechts et al., 2011). Carrington et al. found that a small diurnal temperature range had no effect on vector competence at a high mean temperature (30 °C), but a large diurnal temperature range at a low temperature (20 °C) increased the proportion of infected mosquitoes that could disseminate infection by 60% (Carrington et al., 2013). In line with these findings, Liu-Helmersson et al. showed that a higher diurnal temperature range was associated with increased dengue epidemic potential in both cold-to-temperate and extremely hot climates (Liu-Helmersson et al., 2014). The model suggested that small increases in dengue epidemic potential occurred over the past 100 years. Since 1950, diurnal temperature range increased and magnitudes of annual temperature cycles increased by 0.4 °C in temperate regions (Vasseur et al., 2014), which means possible impacts on dengue outbreak risk if this trend continues.

These temperature-dependent relationships differ depending on the *Aedes* species. Brady et al. created survival models for *Ae. aegypti* and *Ae. albopictus* across their range of viable temperatures, showing that *Ae. albopictus* has higher survival rates and thus may become a more important vector in some regions (Brady et al., 2014). *Ae. aegypti* can tolerate a wider range of temperatures, presumably by exploiting habitats in urban areas with favorable temperatures.

Precipitation provides habitats for the aquatic stages of the mosquito life cycle and strongly influences vector distribution

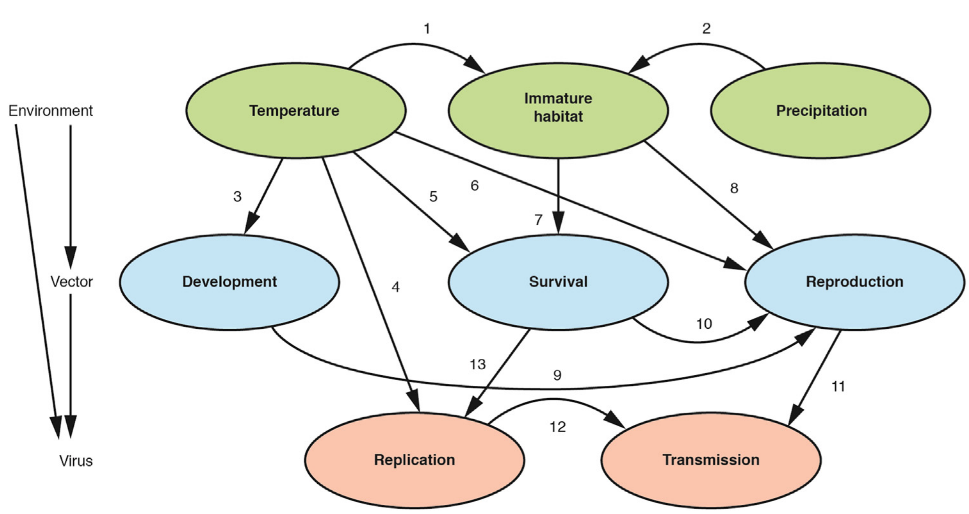

Fig. 2. Biophysical influences on dengue ecology showing the interactions between climate variables, vectors, and the virus. The numbers in the figure identify relationships between variables supported by research in the field and under controlled laboratory conditions: Habitat availability for mosquito larvae is influenced by (1) temperature through evaporation and transpiration, (2) incoming precipitation, Temperature is a major regulator of (3) mosquito development, (4) viral replication within infected mosquitoes, (5) mosquito survival, (6) the reproductive behavior of mosquitoes, Habitat availability is required for (7) survival, (8) egg-laying, Mosquito reproduction is accelerated by (9) faster mosquito development, (10) increased survival, Increased mosquito reproduction (11) enhances the likelihood of transmission by increasing the number of blood feedings, Faster viral replication (12) increases transmission by shortening the time for the virus to develop in the mosquito, Increased survival of the adult mosquito (13) increases the amount of viral replication. Source: Morin et al. (2013).

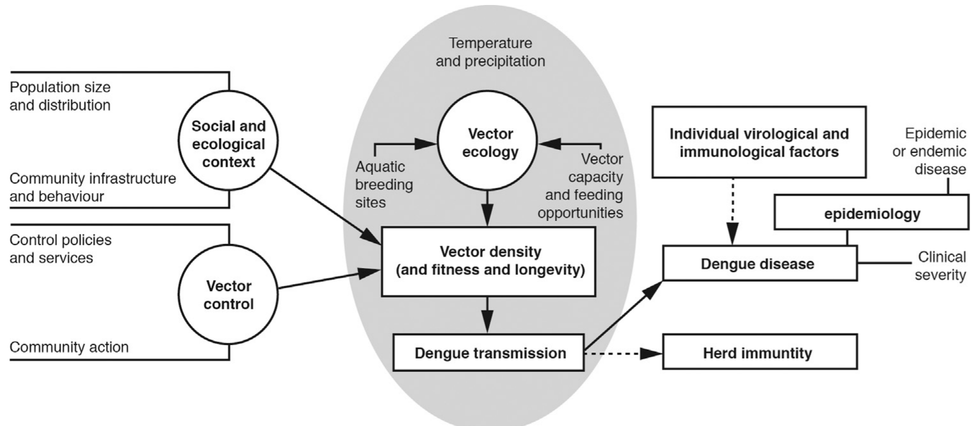

Fig. 3. Interaction of meteorological and other determinants of dengue transmission cycles and clinical disease. Source: World Health Organization and World Meteorological Organization (2012).

(Morin et al., 2013). The effects of precipitation and evaporation on available water sources can regulate the size, population, and behavior of *Aedes*. For example, in Taiwan, the risk of dengue increased over a period of up to 15 weeks, once the daily maximum 24-h rainfall reached >50 mm but there was a temporary one-month decrease in dengue risk following extreme rainfall (Chien and Yu, 2014). In some regions, precipitation changes with La Niña and El Niño conditions, which affects mosquito distributions (Kolivras, 2010).

Several studies identified climate-dengue relationships that could be used successfully for predictive modeling (Morin et al., 2013). Weather variables that predicted the intensity and timing of outbreaks included minimum, maximum, and mean temperature; relative humidity; and wind velocity. The seasonal timing of outbreaks was predicted by precipitation. The sign and strength of the relationships depended on the local weather context (Morin et al., 2013).

In their review of the associations between weather and climate variability and dengue incidence, Morin et al. (2013) concluded that changes in climate could alter the spatial and temporal dynamics of dengue ecology, potentially increasing vector ranges, lengthening the duration of vector activity, and increasing the mosquito's infectious period. At the same time, increasing temperatures in currently warm locations may reduce transmission. Weather and climate influence disease ecology at many levels, with feedback and non-linear relationships creating complex dynamics that are not easily modeled. Human factors, such as behavior, immunity, and socioeconomic factors, contribute to the complexity.

Other weather variables, such as humidity and evaporation rate, influence vector competence, biting behavior, and adult mosquito survival, but have received less attention. For example, in Thailand, ambient temperature appears to define a viable range for transmission, and humidity amplifies the potential within that range (Campbell et al., 2013). Eighty percent of severe dengue cases over the period 1983–2001 occurred when the temperature was 27–29.5 °C and mean humidity was >75%. Given that warmer temperatures can bring higher humidity, understanding these interactions is important for early warning systems and for projecting how a changing climate could alter the future burden of dengue.

A changing climate may also affect the geographic range and incidence of dengue through effects on human and natural systems, such as water storage, land use, and irrigation. Population movement can affect vector ecology and human exposure to infection. Further, natural climate variability and longer-term climate change can interact to affect dengue transmission. For example, temperature increases associated with El Niño events superimposed on long-term increases in ambient temperature may alter dengue transmission when heavy precipitation events wash away breeding sites. Relationships between dengue incidence and El Niño episodes were recently demonstrated in a multi-country southeast Asian study examining monthly data on a regional level (van Panhuis et al., 2015). Dengue epidemic patterns were associated with periods of high temperature, peaking in 1997–1998, a time coinciding with the strongest El Niño episode of the century. Cyclical, multi-annual epidemic cycles were also dependent on temperature.

5.2. Other drivers of dengue transmission

In addition to weather and climate conditions, socioeconomic factors and public health determinants are important drivers of the spatial patterns of *Aedes* and dengue transmission. Changes in natural environments, such as from intensive farming, dams, irrigation, unplanned urbanization, and increases in migration, travel, and trade can affect the distribution of vectors and the virus, for example by increasing the availability of breeding sites, or density of susceptible individuals. These interactions between climatic, socioeconomic, and other factors are complex, vary spatially and temporally, and can result in non-linear feedback. Many non-climatic factors, such as poor quality housing in urban areas, limited provision of safe water and improved sanitation, and limited access to waste management, would be expected to increase rather than reduce the effects of climate change, depending on the specific socioeconomic context (Campbell-Lendrum et al., 2015) (Fig. 3).

Important factors for the spread of *Aedes* and dengue are global trade and travel. Concern over the introduction of *Ae. albopictus* and the subsequent outbreak of chikungunya in Italy led the European Center for Disease Prevention and Control to quantify the relationship between the number of reported dengue cases imported into Europe and the volume of airline travelers arriving from dengue-affected areas internationally (Semenza et al., 2014). In 2010, over 5.8 million airline travelers entered Europe from areas affected by dengue, over 703,000 of whom arrived in 36 airports located in areas where *Ae. albopictus* was recorded. By 2013, 38% more travelers arrived into those areas of Europe where *Ae. albopictus* was recently introduced, highlighting the risk of local transmission (Semenza et al., 2014).

6. Projected climate change

The 5th Assessment Report of the Intergovernmental Panel on Climate Change summarized observations over the past 150 years of changes in temperature and other weather variables, and projected patterns of changes in weather over the course of this century based on modeling under different scenarios of greenhouse gas emissions (Intergovernmental Panel on Climate Change et al., 2013). Key findings were as follows:

- Since the 1950 s, many of the observed changes in temperature are unprecedented over decades to millennia. The globally averaged combined land and ocean surface temperature data show a warming of 0.85 °C (90% likelihood range: 0.65–1.06 °C) over the period 1880–2012. Each of the last three decades was successively warmer at the earth's surface than any preceding decade since 1850. In the Northern Hemisphere, 1983–2012 was likely the warmest 30-year period of the last 1400 years.
- It is highly probable that the number of cold days and nights decreased and the number of warm days and nights increased on the global scale. Human influence is considered likely to have contributed to observed global scale changes in the frequency and intensity of daily temperature extremes since the mid-20th century.
- Continued emissions of greenhouse gases will cause further warming and changes in all components of the climate system. Global surface temperature change for the end of the 21st century is likely to exceed 1.5 °C relative to the period 1850–1900, except under a very low emission scenario. It is virtually certain that there will be more frequent hot and fewer cold temperature extremes over most land areas on daily and seasonal timescales as global mean temperatures increase.

7. Dengue fever risk in a changing climate

Messina et al. reviewed modeling studies that projected the future global distribution of dengue (Messina et al., 2015). The projections were difficult to compare because of the differing modeling approaches, the variable quality of the data used, and the different variables used to drive disease distribution. The spread, establishment, and persistence of dengue depend not only on weather-related variables but also on characteristics of the natural and man-made environments, particularly urbanization, and on travel and trade. Socioeconomic status may also alter the establishment of dengue; for example, an increased use of air conditioning could decrease vector-human interactions (Khormi and Kumar, 2012).

Two basic modeling approaches are used to project the future geographic distribution and burden of dengue, often reaching different conclusions (Messina et al., 2015). Biologically based (mechanistic) approaches generally model the impact of weather variables on the survival and competence of *Aedes.* Projected changes in weather variables under different scenarios of climate change are then used to estimate the future distribution and burden of dengue. Empirically based (statistical) approaches generally model relationships between locations of known dengue occurrence and factors associated with current patterns. Projected changes in these factors are used to estimate the future distribution and burden of dengue. Challenges to statistical modeling include the lack of validated absence data for most locations (most vector surveys are conducted in known areas of transmission risk, not fringe areas of transmission) and the limited number of factors associated with dengue occurrence that have been projected more than a few years into the future. Further, because the risk of dengue is currently assessed based on past development patterns, such as water storage practices in low-income urban settings, the degree to which these relationships are predictive of future occurrence is unclear.

Liu-Helmersson et al. recently developed a biological model that projected dengue epidemic potential in 10 European cities based on historic and projected temperature between 1901 and 2099 (Liu-Helmersson et al., to be published). Over the past decade, relative vectorial capacity was not sufficiently high in Europe in the winter, spring, or autumn to allow dengue transmission, except for small areas in southern Europe during spring and autumn. During the summer, climatic conditions across Europe, not including the northern regions, are suitable for dengue epidemics. The intensity and duration of dengue transmission were predicted to rapidly increase over the course of the 21st century under a scenario of high greenhouse gas emissions and subsequent increases in temperature (Liu-Helmersson et al., to be published). Increasingly larger parts of Europe would have the potential for locally acquired dengue transmission, with a broader seasonal window, should *Ae. aegypti* be introduced. According to this model, by the end of this century, all studied cities could experience epidemics of dengue, including Amsterdam, Berlin, London, and Stockholm.

Campbell et al. used a statistical modeling approach (Campbell et al., 2015). They developed ecological niche models based on *Ae. aegypti* and *Ae. albopictus* occurrence data from 2013 and climatic variables, derived from monthly averages of maximum and minimum temperatures and precipitation for the period 1950–2000, to project the potential distributions of the vectors in 2050 under three scenarios of climate change. The models predicted the distributional potential of the two species to be relatively stable over coming decades, with geographic expansions in many regions and contractions in others. Geographic distributions could shift when a mosquito species overcomes dispersal barriers to colonize new areas, and could expand along the current edges of its distribution when conditions became suitable for reproduction and growth. The models also suggested that these distribution patterns may become reorganized in response to the ecological niche profiles of the mosquitoes, which may have consequences for dengue transmission. Under a moderate emissions scenario, geographic expansion was projected in eastern North America, farther south in South America, northward in southern Europe, more broadly in Central Africa, more broadly in East Asia, and across northern and eastern Australia (Fig. 4). Combining this information with projected population change would give an indication of the potential increase in at-risk populations.

Using another approach, Proestos et al. projected suitable global and regional *Ae. albopictus* habitats under a high emissions scenario and characterized uncertainty ranges using a fuzzy logic method to assess the influence of selected meteorological criteria (Proestos et al., 2015). Seven criteria were used to characterize a suitable habitat for *Ae. albopictus*: annual average precipitation of ≥ 200 mm; annual average temperature > 8.0 °C; minimum temperature > -4.0 °C in January (Northern hemisphere)/July (Southern Hemisphere); summer maximum temperature ≤ 40.0 °C; ≥ 60 days with > 1 mm rainfall; summer relative humidity of $\geq 30\%$; and winter relative humidity $\geq 50\%$. Habitat suitability index was calculated using an equal weight, geometric mean combination of the seven meteorological variables. The projections indicated that in 2050, approximately 2.4 billion people could live in an area of high *Ae. albopictus* habitat suitability; the land area was projected to be slightly smaller than the present day distribution, but projected population growth together with shifts in the geographic distribution would increase the risk of dengue.

Monaghan et al. projected that by 2061–2080, the global land area suitable for *Ae. aegypti* would increase 8% under moderate and 13% under high emissions pathways (Monaghan et al., 2016). The annual number of people exposed to the mosquito was projected to increase by 8–12% when only considering climate change; by 59–65% when considering climate change and a development pathway associated with population growth that peaks

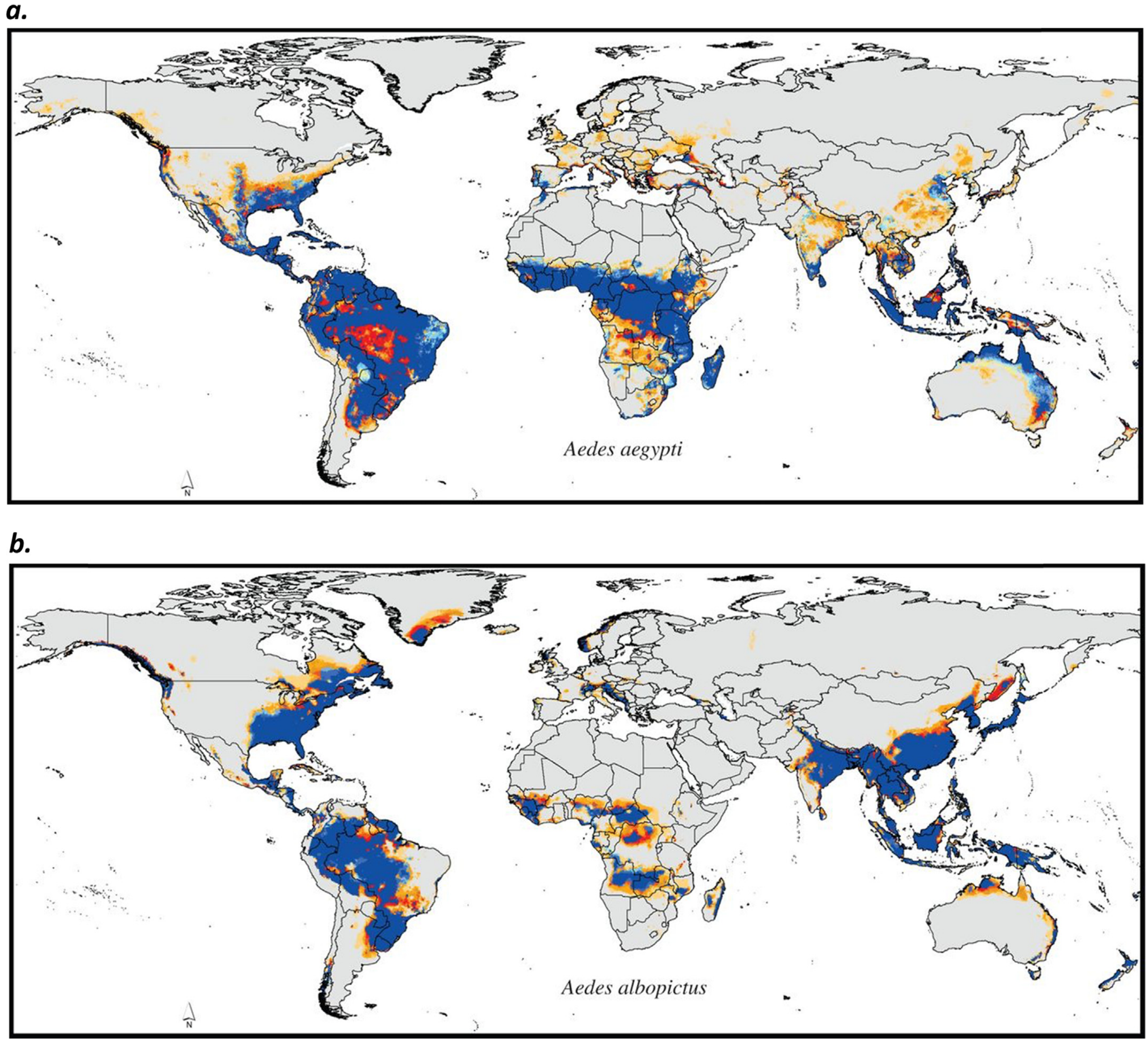

Fig. 4. Potential geographic distribution patterns of a. Ae. aegypti and b. Ae. albopictus in 2050 under a moderate emissions scenario. Present day only distributional areas are in blue, with model agreement regarding stability of present day distributional areas shown by the intensity of blue shading (light blue denotes low and dark blue denotes high model agreement). Future distributional potential is shown as shades of orange (light orange denotes low and dark orange denotes high model agreement in projecting future suitability). Source: Campbell et al. (2015). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mid-century and then declines; and by 127–134% when considering climate change and a development pathway associated with high population growth. Regionally, Australia, Europe, and North America were projected to have the largest percentage increases in human exposure when only considering climate change.

One of the few studies to explicitly consider the role of gross domestic product per capita (GDPpc), as a proxy for socioeconomic development, projected the future distribution of dengue in 2050 to be dependent on both climate and GDPpc under a moderate emissions scenario (Astrom et al., 2012). Based on an estimated 2.93 billion people currently at risk of dengue (48% of the world population), if GDPpc remains constant, climate change alone would increase the number of people at risk of dengue by 0.28 billion to 4.86 billion people or up to 56% of the world population projected in 2050. If climate and GDPpc change as projected, then the number of people at risk of dengue would decrease by 0.12 billion to 4.46 billion (52% of the world population), indicating that socioeconomic development could reduce some of the projected future risks of dengue with climate change.

All of the studies evaluated by Messina et al. projected an increase in the overall global extent of dengue transmission, but the results did not agree with regard to the specific geographies where expansion or intensification would likely occur (Messina et al., 2015). The authors recommended improving the quality and quantity of disease occurrence data, along with uncertainty estimates. A better understanding is needed of the relative importance of various drivers of the distribution and burden of dengue, including human movement and shipping practices, and economic and population factors: future environmental suitability does not guarantee future disease presence (Morin et al., 2013). Fischer et al., reviewing mechanistic and correlative niche modeling approaches of future climate suitability of *Ae. albopictus* in Europe, recommended that introduction gateways and dispersal pathways be considered in modeling future risks (Fischer et al., 2014).

New climate change and assessment scenarios provide standardized projections that could be used in future models of the risks of dengue transmission under different scenarios of climate and development (International committee, 2015). They also include quantifications of some key variables and narratives of other important drivers, such as investments in improving health systems in low- and middle-income countries (Ebi, 2014). These scenarios provide insights into global scale phenomena that will be key underlying drivers of the future distribution and burden of dengue, such as climate change, development, and demographic change, along with uncertainties in how these phenomena could evolve.

8. Conclusions

Research indicates that the daily mean temperature and the variation in temperature are two of the most important drivers of the current distribution and incidence of dengue. Precipitation and precipitation extremes, whether associated with drought or excess rainfall, also affect mosquito abundance and arbovirus incidence. Studies generally project that, as temperatures continue to rise and precipitation patterns change, opportunities are increasing for further geographical expansion of *Aedes* vectors and of dengue. Expansion is primarily expected along the current edges of dengue distribution, with contraction in some areas where conditions would no longer be suitable for *Aedes* reproduction and growth. Expansion could thus be expected to lead to a higher burden of dengue in low- and middle-income countries.

Effective policies and measures will be key to prepare for and manage changes in the geographic range and incidence of the disease. These include improved and harmonized surveillance systems; implementation of vaccination campaigns in target areas; improved and evidence-based vector control; increased awareness of the disease and its broader impacts among the public and decision-makers; development of accurate early warning systems based on environmental and other factors to allow timely preventive measures to be implemented; and increased support for research and development to better understand the current and likely future distributions of *Aedes* and DENV. Such initiatives require coordination and, importantly, improved access to adaptation funds to help low- and middle-income countries prepare for changing burdens of dengue as temperature and precipitation patterns continue to change. Achieving improved dengue control is limited by inadequate investment in the necessary human and financial resources, and in research, education, training, and capacity building. The current outbreak of Zika virus may lead to new and much needed resources, but only sustained and sustainable approaches will likely result in a future where dengue and other viruses carried by *Aedes* become occasional nuisances rather than significant and expensive sources of morbidity and societal damage.

Author contributions

KE and JN jointly planned the scope and methods of the review. KE reviewed the literature, selected citations to include, and wrote the original report and this manuscript. JN critically reviewed and provided suggestions to improve the scientific content and clarity of the report. Both KE and JN edited the final version, and reviewed and guarantee the content of the final manuscript.

Conflicts of interest

KE received consulting fees for conducting the literature review and authoring the report. JN is employed by Sanofi Pasteur. Sanofi Pasteur commissioned and funded this review, and through JN was involved the decision to submit and in all stages of the preparation of this report.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.07.026.

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