Factors of Concern Regarding Zika and Other *Aedes aegypti*-Transmitted Viruses in the United States

Short title: **Zika and Other *Aedes aegypti*-Transmitted Viruses in the United States**

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Abstract

The recent explosive outbreaks of Zika and chikungunya throughout the Americas has raised concerns about the threats that these and similar diseases may pose to the United States (U.S.). The commonly accepted association between tropical climates and the endemicity of these diseases has led to concerns about the possibility of their redistribution due to climate change and transmission arising from cases imported from endemic regions initiating outbreaks in the United States. While such possibilities are indeed well founded, the analysis of historical records not just confirms the potential critical role of traveling and globalization but also reveals that the climate in the United States currently is suitable for local transmission of these viruses. Thus the main factors keeping these diseases from occurring in the United States today are more likely socioeconomic such as lifestyle, housing infrastructure, and good sanitation. As long as such conditions are maintained, it seems unlikely that local transmission will occur to any great degree, especially in the northern states. Indeed, a contributing factor to explain the

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current endemicity of these diseases in less developed American countries may well be explained by socioeconomic and some lifestyle characteristics in such countries.

Introduction

The recent rapid spread of chikungunya and Zika viruses throughout the tropical areas of the Americas has given the reasonable impression that a tropical climate is required for their efficient transmission. Although this assumption appears plausible, it may, in part, also be due to the association with certain low socioeconomic conditions, which are more common in the tropical countries where the outbreaks have occurred. Indeed, as indicated in the literature for malaria and yellow fever, large outbreaks previously occurred in North America during the 17-19th centuries (Patterson 1992); the latter is a virus also transmitted by the same mosquito vector of Zika, chikungunya, and dengue viruses [*Aedes aegypti* (L.)] (Wong et al. 2013, CDC 2016a). These outbreaks occurred in states with some common characteristics. They were located on the East and Gulf coasts or in contact with the Mississippi River and were actively engaged in trade with the Caribbean Islands (Fig. 1.). The latitude at which these states are located and the large numbers of fatalities, >100,000 deaths during the 1693–1905 time period from yellow fever alone (Patterson 1992), indicates that at least during the summer season the climate of the United States is suitable for the transmission of these pathogens and the establishment of *Ae. aegypti* when cultural conditions allow it. Such climatic suitability in most of the contiguous United States has also been confirmed by modeling studies (Kraemer et al. 2015a,b; Messina et al. 2016; Monaghan et al. 2016). Yellow fever and malaria (with the latter transmitted by *Anopheles* sp.) are no longer prevalent in the United States. Because the socioeconomic conditions in this country are clearly different today, as compared with when yellow fever and malaria were endemic, we believe that the critical factors determining the absence of these diseases in the United States today are socioeconomic rather than climatic.

This perception has been supported by contemporary cross-sectional comparisons regarding dengue transmission in contiguous cities near the United States-Mexico border. In studies addressing the latter case, the lower dengue prevalence on the U.S. side was explained by the higher socioeconomic conditions and not by climatic differences (Reiter et al. 2003, Ramos et al. 2008). Yet, both climate and socioeconomic conditions, are in one way or another related to the various factors influencing the transmission of these viruses and, as such, need to be considered when analyzing the potential threat of transmission in the United States.

Climate and Socioeconomic Factors

As it is the case with other vectors of infectious diseases, the survival of *Ae. aegypti* and its potential to transmit viruses largely depends on both climatic (Morin et al. 2013) and socioeconomic conditions (Reiter et al. 2003, Ramos et al. 2005). Here we present a brief description of the climatic and sociocultural conditions that may be critical determinants of outbreaks due to *Ae. aegypti*-transmitted viruses.

El Niño and Meteorological Factors

The fact that the Zika outbreak that recently occurred from Brazil to Mexico coincided with the occurrence of a strong El Niño event (elevated sea surface temperatures over the tropical eastern Pacific Ocean) may not be a random coincidence. Indeed, the literature has suggested a direct relationship between El Niño and increases in vector-borne diseases such as dengue (Poveda et al. 2000, Kovats 2000, Gagnon et al. 2001, Kovats et al. 2003, Hurtado-Díaz et al. 2007, Fuller et al. 2009), which, as mentioned above, is transmitted by the same vector as yellow fever, chikungunya, and Zika viruses (Wong et al. 2013, CDC 2016a). It is worrisome that, apparently due to climatic changes since 1950, El Niño oscillations seem to be increasing in intensity according to the time series data from the National Oceanic Atmospheric

Administration (NOAA) (Cai et al. 2014, CPC 2015). Conversely, the spread of chikungunya virus across the Americas, which started 2 yr earlier, was not during the El Niño event. This suggests that the outbreaks of chikungunya and Zika may have been due to the introduction of new pathogens into an immunologically naive population with a well-established virus transmission system and that, in the case of Zika, the outbreak simply coincided with an El Niño event.

However, if El Niño conditions actually favor these outbreaks, then the mechanism through which this influence is exerted requires further investigation, as it is not yet well understood. It has been proposed that the higher temperatures associated with El Niño events may enhance virus transmission (Patz et al. 2005). Depending on the ranges of local temperatures relative to those of optimal temperature for *Ae. aegypti* mosquitoes and virus replication (Brady et al. 2013), increased environmental temperature may affect vector survival, extrinsic incubation period, and the duration of the gonotrophic cycle differently (Morin et al. 2013). Numerous studies have shown that environmental temperature affects *Ae. aegypti* larval development, with maximal survival between 20 and 27°C, and more rapid development in warmer temperatures (Rueda et al. 1990, Tun-Lin et al. 2000, Richardson et al. 2011, Brady et al. 2013). Similarly, the extrinsic incubation period and the duration of the gonotrophic cycle may be shortened with an increase in temperature, therefore increasing vectorial capacity and thus the epidemic potential (Watts et al. 1987, Rueda et al. 1990, Rohani et al. 2009). Even if their life span may be shorter, mosquitoes could transmit the virus much sooner when held at warmer temperatures, making them more efficient vectors. In addition, there is a growing concern that the increase in temperature associated with global climate change may allow *Ae. aegypti* (and other vectors) to increase their range to higher latitude and altitude. This latter case is illustrated by the recent finding of *Ae aegypti* at elevations not reported previously, i.e., at 2,130 m above sea level

(ASL) in Mexico (Lozano-Fuentes et al. 2012) and at 2,300m ASL in Colombia (Ruiz-López et al. 2016).

With regard to rainfall, the possible relationship between El Niño and *Aedes*-transmitted viruses is even less clear. El Niño was associated with different rainfall patterns in the areas affected by the recent Zika outbreak in Latin America. Above-average rainfall occurred in some areas such as Ecuador, but below-average rainfall occurred in others, such as in the Central and Caribbean parts of Colombia (Kovats 2000). In Ecuador, it would seem logical to associate higher rainfall with more rainwater-filled containers and thus more mosquito larval rearing sites. Such explanation, however, would not apply in Colombia, where lower rainfall during El Niño coincided with a higher incidence of several vector-borne diseases, including dengue (Kovats et al. 2003), which is transmitted by the same vector as Zika virus. One reason that could explain this apparent contradiction of positive and negative associations of rainfall with the incidence of *Ae. aegypti*-transmitted viruses could be based on the peridomestic environments that this mosquito prefers. Such environments are characterized by the presence of larval habitats such as flower pots, tires and water storage tanks (Lounibos 2002) that may be filled with water by humans rather than because of rainfall.

The dependence of *Ae. aegypti* on larval sites provided by humans may make its reproduction independent of rainfall fluctuations in certain areas (Chareonviriyaphap et al. 2003). Indeed, Stanforth et al. (2016) using a principal component analysis and remote sensing technology, detected a low influence of rainfall on dengue incidence in the Magdalena River watershed in Colombia. Storage tanks containing water may be more common during the dry periods than during periods of heavy rainfall as water scarcity may encourage people to save water in tanks, thus increasing the abundance of mosquito larval rearing sites even in the absence of rain. Conversely, the excessive rainfall could overflow water containers. A fast water change in rainy seasons may not allow for larvae to complete development to adults, but dry periods might lead to longer water retention times, and thus to more opportunity for the mosquito life cycle to be completed.

Socioeconomic Factors

Sociocultural Practices:

The transmission of viruses by *Ae. aegypti* is aided by low socioeconomic-related conditions (Reiter et al. 2003, Ramos et al. 2008, Hagenlocher et al. 2013). Such conditions are commonly associated with the absence of air conditioning (thus higher temperatures indoors), presence of open (i.e., non-screened) windows (more in-and-out access for mosquitoes), and sociocultural practices such as water storage (Chareonviriyaphap et al. 2003, Eisen et al. 2014). The latter is an important sociocultural practice in response to the lack of piped water systems (Padmanabha et al. 2010). However, increasing the piped water supply may complicate matters, if the supply is intermittent, because people tend to store more water when they have the knowledge that supply may stop unexpectedly (Padmanabha et al. 2010, Colón-González et al. 2013) (Fig. 2).

The aforementioned sociocultural practices related to low socioeconomic status are highly unlikely to occur in developed countries, such as the United States. However, it is important to consider other practices that do occur in the United States that may provide favorable conditions for these vectors to survive. Steam tunnels and other subterranean habitats associated with modern cities could provide constant stagnant water at favorable temperatures for vectors even during winters in northern states, as has been reported for the Washington D.C. area (Lima et al. 2016).

Mosquito Control Practices and Elimination of *Ae. aegypti*-Transmitted Viruses:

Control efforts, triggered by the finding of the Walter Reed experiments in 1901 in Cuba that *Ae. aegypti* was the means by which the yellow fever was spread, reduced the number of cases of yellow fever in the Caribbean region. In turn, this reduced the likelihood of introduction of both *Ae. aegypti* and the virus into the United States. At the beginning of the 20th century, based on the knowledge that mosquitoes were responsible for diseases such as malaria and yellow fever, and are painful, annoying pests, numerous anti-mosquito programs were initiated across the United States (Patterson 2009). These, in turn, led to the establishment of mosquito control/abatement districts becoming established in many states in the United States. This initiative, in addition to the introduction of screening and improved standard of living, was an important contributing factors to the elimination of yellow fever in this country. However, despite the eradication of yellow fever from the United States after 1905 (Patterson 1992), dengue outbreaks still occurred in the country until the 1940s (Eisen and Moore. 2013). A major anti-*Ae. aegypti* control program organized by the Pan American Health Association (PAHO) and supported by the Centers for Disease Control in the United States was responsible for great reductions in the numbers of *Ae. aegypti* (Patterson 2009, Dick et al. 2012), and the eventual eradication of dengue from the United States. The program was mostly successful, with the eradication of *Ae. aegypti* from 18 continental countries declared in 1962. The program was discontinued in 1970, resulting in a re-emergence of *Ae. aegypti* and dengue in the Americas since 1971 (Dick et al. 2012), with small, locally transmitted dengue outbreaks reappearing in southern Texas (2004) and southern Florida (2009) (Brunkard et al. 2007, Adalja et al. 2012, Radke et al. 2012).

Urbanization and Globalization:

In general, urban settings provide a variety of potential larval rearing sites for peridomestic *Ae. aegypti* (Lozano-Fuentes et al. 2012). In addition, the proximity of people in cities to these sites may facilitate transmission of these anthroponotic viruses (Lounibos 2002). Furthermore, these viruses are increasingly more likely to arrive to new urban settings because of the increasing globalization and ease of travel and transportation of goods (Tatem 2014). Urbanization and globalization have been attributed as major factors explaining the re-emergence of dengue in the Americas after the failure of the PAHO campaign (Pinheiro and Corber 1997, Gubler 2011). Similarly, the Zika outbreak in the Americas may also be explained by the adaptation of the virus to urban cycles involving humans and domestic *Aedes* mosquito vectors (Gubler and Musso, 2016) and by the increase in recreational travel by people between areas where these viruses are endemic and areas where vectors and an immunologically naïve population were located. The fact that commerce and travel were characteristics of the U.S. port cities where yellow fever outbreaks occurred during the 18th and 19th centuries (Patterson 1992, Crosby 2006) may forecast the threat represented by the growing globalization and urbanization in our current society.

Perhaps the most traditional means by which globalization has spread pathogens from source habitats to new habitats have been ships. The transition from sailing and other more primitive ships (that carried large numbers of *Ae. aegypti*) to modern shipping and changes in routes have also been proposed as contributing factors for the disappearance of yellow fever in the United States (Patterson 1992). However, modern cargo ships are still introducing large numbers of vectors inside containers used to transport merchandise, commodities, and goods (Lounibos 2002). Therefore, despite the change in shipping practices and ships and planes may still bring in large numbers of mosquitoes and infected people, respectively. This makes developing countries' socioeconomic-related conditions such as efficient mosquito control practices, sanitation, and continuous supply of piped water to be a concern to developed countries, as these developing countries may serve as a source of imported pathogens and even new vectors.

New Vectors

An additional concern regarding the risk of traditionally transmitted *Ae.* aegypti viruses in the present-day United States compared with that in the period of the large yellow fever outbreaks described by Patterson (1992) is the invasion of new vectors. *Aedes albopictus* (Skuse), which arrived into the United States in 1987 (Moore and Michell. 1997), has been reported to be a more competent experimental vector than *Ae. aegypti* for both dengue (Brady et al. 2014) and chikungunya (Turell et al. 1992) viruses. Furthermore, it was reported as the primary chikungunya vector in a major outbreak that occurred during the 2004-2007 outbreak on islands in the Indian Ocean, where vertical transmission was demonstrated in two out of 500 pools of larvae tested (Delatte et al. 2008). It has also been shown to be a competent experimental vector for Zika virus (Wong et al. 2013, Aliota et al. 2016, Chouin-Carneiro et al. 2016). *Ae. albopictus* is predicted to reach a further northern distribution than *Ae. aegypti* (Kraemer et al. 2015a, Kraemer et al. 2015b), because it is able to enter an egg diapause and withstand colder temperatures (Chang et al. 2007). Essentially the same statements can be made about *Aedes japonicus* (Theobald). It was first detected in New York and New Jersey in 1998 (Peyton et al. 1999) and is a competent vector of dengue and chikungunya viruses (Schaffer et al. 2011). However, because these are more general feeders than *Ae. aegypti*, with *Ae. albopictus* taking only between 24 and 58% of its blood meals derived from humans (Faraji et al. 2014, Richards et al. 2006) and *Ae. japonicas* taking only 36% of its blood meals from humans (Molaei et al. 2009), they are less likely to feed repeatedly on humans, resulting in a lower vectorial capacity (Richards et al. 2006, Lambrechts et al. 2010). This might explain why *Ae aegypti* is still believed to be the main vector of dengue virus and potentially also of Zika virus in the contiguous United States (Petersen 2016). As is the case with *Ae. aegypti*, modeling studies have also shown the climatic suitability of the contiguous United States for the presence of *Ae.*

albopictus (Messina et al. 2016, Kraemer et al. 2015a, Kraemer et al. 2015b, Monaghan et al. 2016).

Risk in the United States

As long as the current housing situation and contact with mosquitoes are maintained in the contiguous United States, no large-scale locally transmitted outbreaks of yellow fever, dengue, chikungunya, or Zika viruses are likely to occur. However, there remains potential for small outbreaks to recur in certain southern areas in Florida, Louisiana and Texas. This could be due to the longer warmer season in these areas as well as to relatively lower socioeconomic conditions in localized places and by the stronger ties of its populations with countries where these diseases may be prevalent, thus the likelihood of importing the viruses from those countries into local populations of mosquitoes. As of 12 October 2016, 128 cases of locally transmitted mosquito-borne Zika have been reported in Florida (CDC, 2016b). In contrast, with an average of 2,500 human cases of West Nile disease reported each year for the past 10 years (CDC 2016c), zoonotic diseases, such as West Nile fever and St. Louis encephalitis involving amplifying hosts other than humans, continue to be active in the United Sates. Nevertheless, due to globalization and travel, it is likely that cases of *Ae. aegypti*-transmitted diseases, imported from areas where these viruses are currently being transmitted, would continue to occur (Bogoch et al. 2016). In fact, as of 12 October 2016, >3,800 imported cases of Zika have been reported in the United States (CDC 2016b).

Conclusions and Recommendations

Although *Ae. aegypti*-transmitted viruses were once common in the United States, it seems clear that the main factors keeping outbreaks of these diseases from occurring today are socioeconomic such as lifestyle, housing infrastructure, and good sanitation. Whereas such conditions are maintained, it seems unlikely that large scale local transmission will occur, particularly in northern states. However, the increasing globalization, urbanization, and travel coinciding with global warming and increasing El Niño fluctuations may be a worrying combination of cultural and climatic conditions that is favorable for mosquito-transmitted diseases to spread from endemic countries. Such combinations make it likely that cases of these diseases will continue to be imported from areas where these viruses are currently being transmitted. This increases the risk of the occurrence of not only *Ae. aegypti*-transmitted viruses, such as yellow fever, dengue, chikungunya, and Zika viruses, but also other exotic pathogens. The growing interconnection of our global society makes global public health-related issues, such as sanitation and the lack of a continuous supply of piped water in developing countries, an important concern to developed countries, as these developing countries may serve as a source of imported cases of disease.

The prior outbreaks of yellow fever indicate that the climate of the United States is suitable to support outbreaks of *Ae. aegypti*-transmitted viruses but the current lifestyle and infrastructure essentially prevent any large-scale outbreaks. However, there remain some concerns. It is important to consider that if the isolation between humans and *Ae. aegypti* mosquitoes in the United States is primarily caused by lifestyle and living infrastructure associated with socioeconomic conditions; these could be threatened by massive natural disasters, or any other event that disrupts the current infrastructure. Consequently, it is important that appropriate disaster preparedness plans be in place to address this potential issue.

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Figure Legends

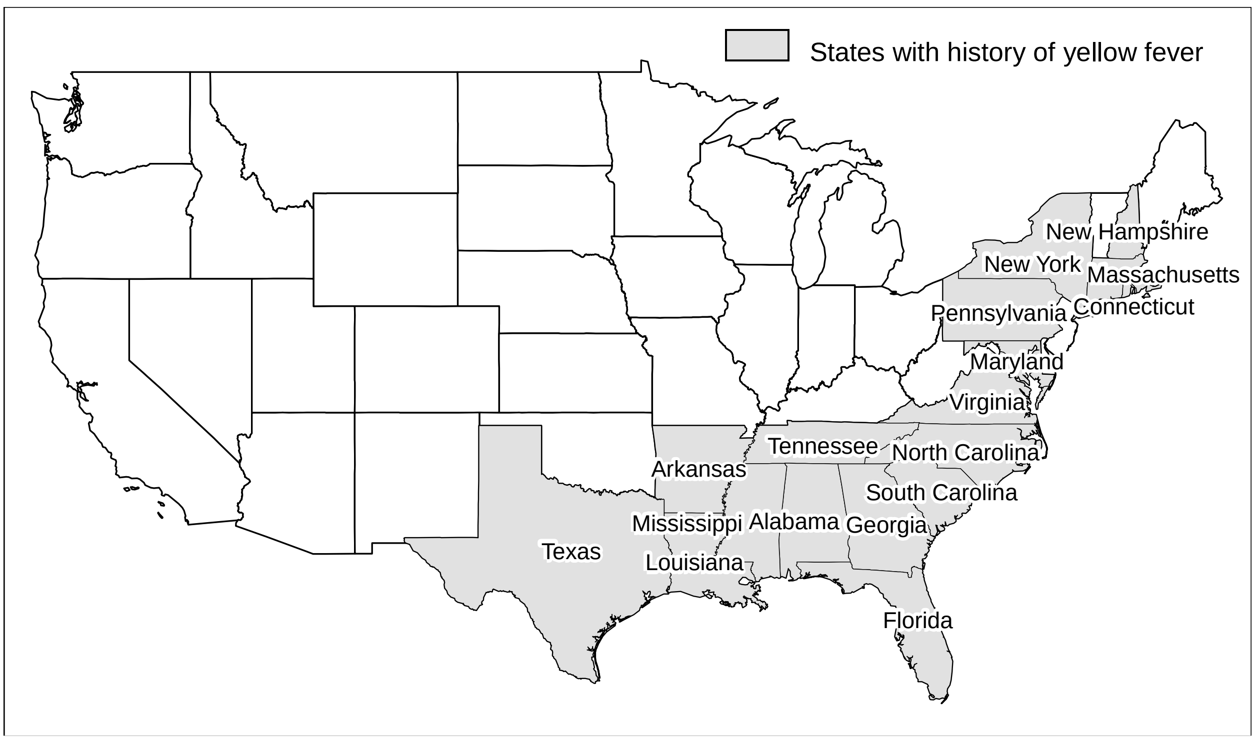

Fig. 1. Map of the Contiguous United States indicating states where local transmission of yellow fever occurred in the 1600's to 1800's based on Arnebeck (2008) and Patterson (1992). Therefore, the shaded states would be climatically suitable (at least during the summer) to allow *Ae. aegypti* to transmit yellow fever, chikungunya, dengue, or Zika viruses. Note that non-shaded states at equivalent latitudes did not report outbreaks during the given time period. This is likely due to the much lower human population densities in these areas and lack of trade with the Caribbean Islands at that time.

Fig. 2. This picture, taken in Mahates, Colombia, (a town with intermittent supply of piped water) shows water storage tanks filled from a hose. This was the municipality where in 2014 the first cases of chikungunya were reported in Colombia (El Tiempo, 2014). The growing interconnection of our global society makes global public health related issues, such as sanitation and the lack of a continuous supply of running water in developing countries to be an important concern to developed countries as these developing countries may serve as a source of imported cases of disease.