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Aedes (Stegomyia) aegypti in the Continental United States: A Vector at the Cool Margin of Its Geographic Range

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ABSTRACT After more than a half century without recognized local dengue outbreaks in the continental United States, there were recent outbreaks of autochthonous dengue in the southern parts of Texas (2004–2005) and Florida (2009–2011). This dengue reemergence has provoked interest in the extent of the future threat posed by the yellow fever mosquito, *Aedes (Stegomyia) aegypti* (L.), the primary vector of dengue and yellow fever viruses in urban settings, to human health in the continental United States. *Ae. aegypti* is an intriguing example of a vector species that not only occurs in the southernmost portions of the eastern United States today but also is incriminated as the likely primary vector in historical outbreaks of yellow fever as far north as New York, Philadelphia, and Boston, from the 1690s to the 1820s. For vector species with geographic ranges limited, in part, by low temperature and cool range margins occurring in the southern part of the continental United States, as is currently the case for *Ae. aegypti*, it is tempting to speculate that climate warming may result in a northward range expansion (similar to that seen for *Ixodes* tick vectors of Lyme borreliosis spirochetes in Scandinavia and southern Canada in recent decades). Although there is no doubt that climate conditions directly impact many aspects of the life history of *Ae. aegypti*, this mosquito also is closely linked to the human environment and directly influenced by the availability of water-holding containers for oviposition and larval development. Competition with other container-inhabiting mosquito species, particularly *Aedes (Stegomyia) albopictus* (Skuse), also may impact the presence and local abundance of *Ae. aegypti*. Field-based studies that focus solely on the impact of weather or climate factors on the presence and abundance of *Ae. aegypti*, including assessments of the potential impact of climate warming on the mosquito's future range and abundance, do not consider the potential confounding effects of socioeconomic factors or biological competitors for establishment and proliferation of *Ae. aegypti*. The results of such studies therefore should not be assumed to apply in areas with different socioeconomic conditions or composition of container-inhabiting mosquito species. For example, results from field-based studies at the high altitude cool margins for *Ae. aegypti* in Mexico's central highlands or the Andes in South America cannot be assumed to be directly applicable to geographic areas in the United States with comparable climate conditions. Unfortunately, we have a very poor understanding of how climatic drivers interact with the human landscape and biological competitors to impact establishment and proliferation of *Ae. aegypti* at the cool margin of its range in the continental United States. A first step toward assessing the future threat this mosquito poses to human health in the continental United States is to design and conduct studies across strategic climatic and socioeconomic gradients in the United States (including the U.S.–Mexico border area) to determine the permissiveness of the coupled natural and human environment for *Ae. aegypti* at the present time. This approach will require experimental studies and field surveys that focus specifically on climate conditions relevant to the continental United States. These studies also must include assessments of how the human landscape, particularly the impact of availability of larval developmental sites and the permissiveness of homes for mosquito intrusion, and the presence of other container-inhabiting mosquitoes that may compete with *Ae. aegypti* for larval habitat affects the ability of *Ae. aegypti* to establish and proliferate. Until we are armed with such knowledge, it is not possible to meaningfully assess the potential for climate warming to impact the proliferation potential for *Ae. aegypti* in the United States outside of the geographic areas where the mosquito already is firmly established, and even less so for dengue virus transmission and dengue disease in humans.

KEY WORDS United States, *Aedes aegypti*, climate, dengue, geographic range

Important vectors of microorganisms that cause disease in humans or domestic animals are the subjects of extensive field and laboratory studies to better understand their life histories and the dynamics of pathogen transmission. Field studies understandably tend to focus on the geographic areas where the problems caused by these vectors are most severe, typically at the core(s) of the geographic distribution of a given vector species, where it is most abundant and pathogen transmission is most intense. Likewise, laboratory experiments most commonly expose vector species to environmental conditions representative of such core distributional areas. However, in recent decades, we have experienced both expansions of the geographic ranges of already established vector species, potentially driven by environmental change, and introductions of vector species into new geographic areas. Examples of well documented range expansions include the spread of *Ixodes* vectors of Lyme borreliosis spirochetes northward in Canada and Scandinavia, and to higher elevations in central Europe (Materna et al. 2008, Jaenson et al. 2012, Leighton et al. 2012). Notable introductions of important mosquito vectors or nuisance biters include the arrivals and subsequent establishment and spread of the Asian tiger mosquito [*Aedes (Stegomyia) albopictus* (Skuse)] and *Aedes (Finlaya) japonicus* (Theobald) in the Americas and Europe (Moore and Mitchell 1997, Peyton et al. 1999, Medlock et al. 2012). The introduction of *Ae. albopictus* to the continental United States in 1985, and its subsequent rapid spread throughout the southeastern part of the country, is especially troubling because it is a vector of several arboviruses, including dengue and chikungunya viruses (Moore and Mitchell 1997, Moore et al. 1988, Moore 1999, Gratz 2004, Kuno 2012). Such range expansions and species introductions raise questions about the potential for pathogen transmission at the margins of the geographic distribution of a vector species, where environmental conditions may be only borderline-suitable for development and survival of the vector, and knowledge of its natural history accumulated through field or laboratory studies often is lacking or minimal. This forum article addresses these issues through a case study focusing on the yellow fever mosquito, *Aedes (Stegomyia) aegypti* (L.), one of the world's most important and intensely studied vector species, at the cool margin of its range within the continental United States. A key question is how climate warming may impact the range of the mosquito and its associated arboviruses, especially dengue virus, in the United States in coming decades.

Ae. aegypti: A Formidable Threat to Human Health

Ae. aegypti is the primary urban vector of dengue and yellow fever viruses and is an important vector of chikungunya virus (Gratz 1999, Gubler 2004, PIALOUX et al. 2007, Halstead 2008). Dengue is the most important arboviral disease in the subtropics and tropics, with 50–100 million dengue virus infections estimated

to occur annually (Gubler 1998, Kyle and Harris 2008, WHO 2009, Brady et al. 2012). Yellow fever is still a public health concern, with sporadic outbreaks occurring in resource-constrained settings with low vaccine coverage (Gubler 2004, Barrett and Higgs 2007). Chikungunya virus recently caused large disease outbreaks on islands in the Indian Ocean as well as in India and Southeast Asia, and it is a significant threat to the naïve population of the Americas should the virus emerge here (Staples et al. 2009).

The broad geographic distribution of *Ae. aegypti* is considered, in part, to be limited by cold temperatures: the low-latitude areas equatorward of the average 10°C winter isotherms in the northern and southern hemispheres are thought to approximate the climatic boundary for establishment and proliferation of the mosquito (Christophers 1960, Hopp and Foley 2001, WHO 2009). The mosquito is closely associated with human habitation and ubiquitous in populated areas of the subtropics and tropics with a suitably warm and humid climate, where it can be found in settings ranging from small rural villages to megacities. A wide range of water-holding natural and artificial containers in and around human dwellings are exploited as sites for oviposition of eggs and development of immatures (Focks and Alexander 2006, Tun-Lin et al. 2009). The females commonly rest and feed indoors, and they can be encountered in homes as well as other indoor environments, such as schools or work places (García-Rejón et al. 2008, 2011; Halstead 2008). *Ae. aegypti* makes creative use of a wide range of building types, including high-rise buildings, where it has been found to readily move vertically among floors (Liew and Curtis 2004). Collections within the domicile often produce the greatest numbers of *Ae. aegypti* adults from bedrooms (Macdonald 1956, Davila et al. 1991, García-Rejón et al. 2008), where the mosquito likely rests in secluded places such as in closets or under furniture. Use of intact screening and air conditioning (to minimize the opportunities for the mosquito to penetrate buildings via open doors or windows) may reduce the risk of indoor biting by *Ae. aegypti*, as these factors were found to be protective in recent studies on the risk for exposure to dengue virus (Reiter et al. 2003, Brunkard et al. 2007, Ramos et al. 2008).

The tremendous potential for range expansion and proliferation of *Ae. aegypti* within geographic areas with favorable conditions was inadvertently demonstrated when the mosquito reclaimed lost territory across the Americas in the decades after the cessation in the early 1970s of an intensive hemispheric campaign, led by the Pan American Health Organization, to eliminate this mosquito and prevent yellow fever virus transmission (Gubler 1998, 2004; Isturiz et al. 2000; Brathwaite Dick et al. 2012). Between 1948 and 1962, *Ae. aegypti* was eliminated from 21 countries in the Americas, and by 1970 its geographic distribution was limited to the southeastern United States, islands in the Caribbean, and the northeastern corner of South America (Venezuela, Guyana, Suriname, and French Guiana). However, by 2004 the mosquito had reclaimed all lost territory and today it is established

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from Argentina in the south to the United States in the north (Gubler 2004, Darsie and Ward 2005, WHO 2009). This establishment was accompanied by the reemergence of dengue from the 1980s to present time, with co-circulation of multiple and sometimes all four dengue virus serotypes (hyperendemicity) now occurring in many parts of the subtropics and tropics of the Americas (San Martin et al. 2010, Brathwaite Dick et al. 2012).

The spread of *Ae. aegypti* undoubtedly is facilitated by human transport of containers infested by eggs or immatures. Urbanization, especially uncontrolled growth with poor sanitary services, is considered a key factor underlying the proliferation of *Ae. aegypti* across the tropical world (Gubler 1998). Indeed, this mosquito may now be more widely distributed and more abundant than at any time in the past (Halstead 2008). Moreover, the difficulty in controlling *Ae. aegypti* in today's complex and rapidly growing subtropical and tropical urban areas is evident from recent decades of intensive but largely unsuccessful mosquito control efforts aiming to reduce dengue virus transmission (Gubler 1989, Reiter and Gubler 1997, Heintze et al. 2007, Erlanger et al. 2008, Esu et al. 2010). Instead, epidemic dengue is on the rise throughout the subtropics and tropics of the Americas (San Martin et al. 2010, Brathwaite Dick et al. 2012).

Some aspects of the feeding behavior of *Ae. aegypti* have important implications for its role as a pathogen vector. The female feeds predominantly on human blood (Scott et al. 1993b, 2000a), making this mosquito an effective vector of pathogens for which humans are important reservoir or amplification hosts, such as dengue virus. Moreover, females frequently take multiple partial bloodmeals within a single gonotrophic cycle, including from different individual humans, not only increasing the likelihood of feeding on an infectious human but also leading to single infectious females potentially feeding on and infecting multiple humans within a relatively short time period (McClelland and Conway 1971; Gubler 1988; Scott et al. 1993, 2000a; de Benedictis et al. 2003). Finally, the day-biting habit of *Ae. aegypti* females (Christophers 1960, Trpis et al. 1973, Chadee and Martinez 2000) leads to humans potentially being bitten in a wide range of indoor and outdoor environments.

Ae. aegypti at the Cool Margins of Its Geographic Range in the Americas

Ae. aegypti, considered to have originated in Africa (Tabachnick 1991, Barrett and Higgs 2007, Brown et al. 2011), likely was introduced from West Africa into the Americas in the wake of the European "discovery" of the new world and the subsequent emergence of a transatlantic slave trade (Dyar 1928; Christophers 1960; Guerra 1966, 1993; Picó et al. 1969). The first clearly described yellow fever outbreaks in the Americas, with the likely involvement of *Ae. aegypti* as the virus vector, occurred in Barbados and Mexico's Yucatan Peninsula in 1647–1648 (Patterson 1992). The mosquito itself, originally described by Linnaeus in

1762 as *Culex aegypti* L. and later reassigned to *Aedes aegypti* (L.) (Dyar 1920, 1928), was first described from the Americas (West Indies) in 1805 as *Culex fasciatus* F. (Christophers 1960). However, as indicated by the above-mentioned yellow fever outbreaks, for which *Ae. aegypti* most likely served as the virus vector, the mosquito probably has been present in the western hemisphere at least since the 1640s.

Large portions of the Americas, including the southernmost part of the eastern United States, the Caribbean, Central America, and lower elevation areas in Mexico and South America (excluding the southern parts of Argentina and Chile), enjoy warm and humid climates well suited for proliferation of *Ae. aegypti* (WHO 2009). The northern cool margin of the mosquito's range is in the southeastern United States, where the "usual range" (permanent range) is considered to include the Gulf Coast states (Florida, Alabama, Mississippi, Louisiana, and southeastern Texas) and adjoining states (South Carolina, Georgia, and southeastern Arkansas) (Darsie and Ward 2005). *Ae. aegypti* also is established locally in the southwestern United States, i.e., the southern parts of Arizona and New Mexico (Darsie and Ward 2005, Hayden et al. 2010, Walker et al. 2011), but this area should not necessarily be viewed as a cool margin because arid conditions may be a key limiting factor here. The southern cool margin of the mosquito's range is in central Argentina (Buenos Aires and La Pampa provinces), and it also was recently collected in the southern part of the country (Neuquén Province in the Patagonia region) (Rossi et al. 2006, Grech et al. 2012, Díaz-Nieto et al. 2013). Additional cool margins occur at high elevations in the Andes in western South America and in Mexico's central highlands, where the elevation ceiling for *Ae. aegypti* (i.e., the elevation above which it cannot establish and proliferate) appears to be in the range of 1,600–2,200 m above sea level (Suarez and Nelson 1981, Ibanez-Bernal 1987, Herrera-Basto et al. 1992, Lozano-Fuentes et al. 2012). These cool margins of the geographic range of *Ae. aegypti* are of increasing interest based on the idea that climate warming may make them more suitable for the mosquito and ultimately allow for local dengue virus transmission, and also because large human populations reside near them, for example just above the current elevation ceiling for *Ae. aegypti* in Mexico (e.g., Mexico City and Puebla City) or Ecuador (Quito) and to the north of the current range margin in the eastern United States (e.g., New York and Philadelphia).

A History of *Ae. aegypti* and Its Associated Diseases in the Continental United States

Ae. aegypti was first described from the continental United States (Savannah, GA) in 1828 as *Culex taeniatatus* Wiedemann (Christophers 1960). However, as indicated by the yellow fever and dengue outbreaks outlined below, for which *Ae. aegypti* most likely served as the vector, the mosquito probably has been present, permanently or intermittently, in the continental United States at least since the 1640s. The ear-

liest appearances of yellow fever in what is now the United States occurred in 1649–1650 in Spanish Florida and in 1668 in New York and Philadelphia, and the last outbreak occurred in 1905, affecting New Orleans, Pensacola, and scattered Gulf Coast towns (Patterson 1992, Reiter 2001). Notable outbreaks of yellow fever during the 18th and 19th centuries, with cases numbering in the hundreds or thousands, occurred in Charleston (range, for outbreak years with >100 cases, 1699–1871), Philadelphia (1699–1805), New York (1702–1822), Pensacola (1765–1905), Baltimore (1794–1819), New Orleans (1796–1905), Boston (1798), Norfolk (1800–1853), Mobile (1819–1853), Savannah (1820–1876), Galveston (1839–1867), Baton Rouge (1853), and Memphis (1867–1879) (Patterson 1992, Reiter 2001). Likely reasons for the demise of yellow fever in the United States include changes to ship design and sailing patterns; urban improvements (particularly to piped water supplies); increasing use of window screens; and, after the realization in 1900 that a mosquito transmits the causative agent of yellow fever, mosquito control efforts (Patterson 1992). In this respect, it is interesting to note that major outbreaks in the northernmost-affected cities (Baltimore, Boston, New York, and Philadelphia) did not occur after the 1820s, whereas cities to the south still experienced outbreaks in the latter part of that century. This difference may, in part, have been related to dramatically altered shipping and trade between southern and northern states during and after the U.S. Civil War in the 1860s.

For dengue, an outbreak of “bilious remitting fever,” possibly caused by dengue virus, occurred in Philadelphia in 1780, and major dengue outbreaks occurred in southeastern cities in 1827–1828 (most notably Charleston, Pensacola, New Orleans, and Savannah), 1848–1851 (Augusta, Charleston, Mobile, New Orleans, and Savannah), 1873 (New Orleans), and 1879–1880 (Augusta, Charleston, New Orleans, and Savannah) (Ehrenkranz et al. 1971, Reiter 2001, Brathwaite Dick et al. 2012). After 1880, there was a westward shift of major dengue outbreaks in the United States, possibly related, in part, to increased transcontinental railroad traffic to growing western cities. Major dengue outbreaks occurred in Texas in 1885–1886 (Galveston and Austin), 1897 (statewide), and 1907–1908 (Brownsville, Galveston, and Houston), and in Florida in 1898–1899. In the period between World Wars I and II, there were three waves of major dengue outbreaks in the southeastern United States, including in 1922 (Florida, Georgia, Louisiana, and Texas), 1934 (Florida and southern Georgia), and 1941–1945 (port cities in Texas and Louisiana) (Ehrenkranz et al. 1971, Hayes et al. 1971). After a long period without recognized endemic dengue virus transmission in the continental United States, small outbreaks of autochthonous dengue occurred in southern Texas in 2004–2005 and southern Florida from 2009 to 2011 (Brunkard et al. 2007, Adalja et al. 2012, Radke et al. 2012). Reasons for why dengue outbreaks persisted for decades after the last yellow fever virus outbreak in 1905, despite a shared human–*Ae. aegypti* transmission cycle

in the continental United States and the absence of a vaccine against yellow fever virus until the 1940s, are not clear. One possible contributing factor is the susceptibility of the human population; exposure to yellow fever virus leads to long-term protection against subsequent exposures, whereas there are four different dengue virus serotypes for which infection with one serotype fails to confer long-term cross-protection against the other serotypes.

The realization in 1900 that *Ae. aegypti* can transmit yellow fever virus (Service 1978) generated interest in understanding the geographic distribution of the mosquito, primarily for the purpose of controlling it. Early collection records are summarized by Howard and Dyar (Howard 1905, Dyar 1928). Systematic multi-state surveys for *Ae. aegypti*, coordinated by the Public Health Service, were conducted in the continental United States from 1942 to 1964 (Hayes and Tinker 1958, Tinker and Hayes 1959, Morlan and Tinker 1965). In summary, *Ae. aegypti* was commonly encountered in the southernmost states (Florida, South Carolina, Georgia, Alabama, Mississippi, Louisiana, and Texas) and occasionally recorded from bordering states to the north (North Carolina, Virginia, Arkansas, and Tennessee). The surveys failed to produce *Ae. aegypti* in Oklahoma, Kansas, Missouri, Kentucky, and the southern parts of Arizona and New Mexico. The most extensive survey was carried out from June to September 1964, in preparation for an *Ae. aegypti* eradication program in the United States that was funded by Congress in 1963 and initiated in 1964. The survey included >90,000 premises in 639 counties across 11 states (Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, and Texas) (Morlan and Tinker 1965, Schliessmann 1967, Schliessmann and Calheiros 1974). This survey produced *Ae. aegypti* from 203 counties (32%) and 10 of the 11 states, the lone exception being Oklahoma (Morlan and Tinker 1965). States from which $\geq 50\%$ of examined counties yielded *Ae. aegypti* included Alabama, Florida, and Georgia. The program to eradicate *Ae. aegypti* from the continental United States never reached its ultimate goal and was terminated in 1969 because of lack of funds (Slosek 1986). No subsequent surveillance effort in the southeastern United States has come close to rivaling the intensity of the 1964 survey for *Ae. aegypti*.

The most recent generalized distribution map for *Ae. aegypti* in the continental United States was presented by Darsie and Ward (2005) and separates the distributional area in the eastern United States into two subareas: one area to the south, constituting the “usual range,” referred to as the “permanent region” in older distribution maps; and a second adjoining area to the north, constituting an “extreme range,” referred to as the “temporary summer region” in older maps. The usual range includes Florida, South Carolina, Georgia, Alabama, Mississippi, Louisiana, southeastern Texas, and southeastern Arkansas. The extreme range extends through Arkansas, Tennessee, Kentucky, North Carolina, Virginia, Maryland, and Delaware and also includes the eastern parts of Texas and Oklahoma and

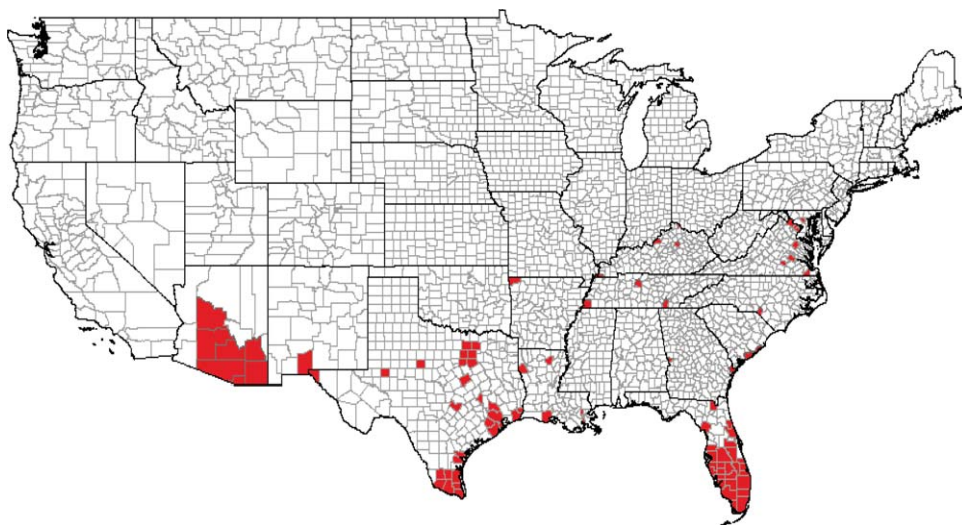


Fig. 1. Counties in the continental United States with collection records of *Ae. aegypti* from 1986 to 2010 (shaded red), based on information from a database for invasive mosquito species curated by C. G. Moore of Colorado State University. This database includes data from the Centers for Disease Control and Prevention ArboNet initiative, as well as reports from state and local public health and vector control programs, university researchers, and others. (Online figure in color.)

southern portions of Kansas, Missouri, Illinois, Indiana, Ohio, and Pennsylvania. There also is an isolated focus noted for coastal New Jersey, New York, Connecticut, and Rhode Island (Darsie and Ward 2005, VectorMap 2012). Collections of *Ae. aegypti* within the extreme range, especially from its northern edge, typically comprise low numbers of specimens (Chandler 1945, Bell and Benach 1973, Cookman and Lebrun 1986, Berry et al. 1988, Sweeney et al. 1988, Donnelly 1993, Hutchinson et al. 2008) and likely represent warm-season introductions of the mosquito, for example, through movement of scrap tires infested with eggs, to areas where it may proliferate during the warm months but then fails to overwinter.

Current Distribution of *Ae. aegypti* in the Continental United States

Specific resources containing collection records for *Ae. aegypti* in the continental United States include the Centers for Disease Control and Prevention (CDC) ArboNet initiative, the Walter Reed Biosystematics Unit's VectorMap initiative (VectorMap 2012), and a database for invasive mosquito species curated by C. G. Moore of Colorado State University. Figure 1 shows counties with collection records of *Ae. aegypti* from 1986 to 2010 based on the data in C. G. Moore's database that includes the data from ArboNet as well as reports from state and local public health and vector control programs, university researchers, and others. However, we caution that data extracted from these resources, as well as resulting maps showing mosquito distributions (see example in Fig. 1), should be viewed as compilations of records based on convenience sampling rather than a representation of systematic surveys, with the notable exception of subsets of data obtained through local surveys specifically targeting

Ae. aegypti. In the absence of a systematic sampling effort, the distribution map for a given mosquito species may reflect the intensity of collection efforts rather than the true distribution of the mosquito itself; stated differently, it may best represent the distribution of mosquito collectors.

We also caution against attempts to draw conclusions based on comparisons of the map presented in Fig. 1 with previously presented maps. Our map, based on a depiction of counties with collection records of *Ae. aegypti* from 1986 to 2010, should not be viewed as directly comparable either to maps presenting a generalized distribution of the mosquito rather than specific locations or counties of collection (e.g., Darsie and Ward 2005) or to county-based map presentations from earlier time periods (e.g., Morlan and Tinker 1965), based on differences in the intensity and spatial coverage of the surveillance effort and the collection methods used.

Linking *Ae. aegypti* and Dengue to Weather or Climate

The linkage between weather or climate and dengue disease in humans is indirect, in that weather conditions directly impact the mosquito vector but only indirectly impact the intensity of dengue virus transmission in the mosquito-human cycle (with the notable exception of influencing the extrinsic incubation period for the virus in the mosquito). Moreover, the intensity of dengue virus transmission is strongly influenced by the ever-changing dengue virus serotype-specific susceptibility of the human population (Gubler 1988, Scott and Morrison 2010, Oki and Yamamoto 2012). Studies that attempt to directly link weather or climate conditions to the occurrence of human dengue cases, including numerous studies

from the Americas (Chowell and Sanchez 2006; Hurtado-Diaz et al. 2007; Brunkard et al. 2008; Fuller et al. 2009; Johansson et al. 2009a,b; Degallier et al. 2010; Herrera-Martinez and Rodriguez-Morales 2010; Chowell et al. 2011; Colon-Gonzalez et al. 2011; Lowe et al. 2011; Machado-Machado 2012), should be interpreted with caution, as the observed association in reality is the result of multiple underlying separate relationships, including the impact of weather on mosquito population dynamics, the likelihood of human-mosquito contact, and the force of virus transmission among mosquitoes and susceptible humans. It therefore is not surprising that a recent systematic review of studies from the Asia-Pacific region that attempted to model the impact of weather or climate on dengue led to the conclusion that, although climate change is likely to affect the seasonal and geographic distribution of dengue, empirical evidence linking dengue to weather or climate patterns is inconsistent across geographic locations (Banu et al. 2011). Based on these considerations, caution also should be exercised when interpreting findings from models of the potential impact of climate change on dengue, some of which include the Americas or parts thereof (Jetten and Focks 1997, Patz et al. 1998, Hales et al. 2002, Erickson et al. 2012).

A simplified approach is to develop models for the impact of weather or climate factors on the distribution and abundance of the mosquito vector itself, thus focusing on relationships that are more direct and readily understandable. This approach is especially pertinent at the cool margins of the current geographic range of *Ae. aegypti*, where the effects of a changing climate can be expected to be most pronounced. Field, laboratory, or modeling studies to determine the effects of temperature on different life-history traits of *Ae. aegypti* (e.g., egg survival, larval developmental time and success rate, adult longevity, and the length of the female's gonotrophic cycle) or the dynamics of virus transmission (e.g., the length of the extrinsic incubation period) are abundant for the temperature ranges under which the mosquito thrives (Christophers 1960, Focks et al. 1993, Halstead 2008, Farnesi et al. 2009, Yang et al. 2009, Azil et al. 2010, Barbazan et al. 2010, de Almeida Costa et al. 2010, Barrera et al. 2011, Richardson et al. 2011, Chan and Johansson 2012, Chaves et al. 2012, Chen and Hsieh 2012, Tsai et al. 2012). Up to certain thresholds, increased temperatures lead to more rapid mosquito development (shortened generation time) and intensified virus transmission. However, similar studies are rare (and mostly date back to the early part of the 20th century) for the temperature conditions encountered at the cool margin of the geographic range of *Ae. aegypti* (Davis 1932, Bliss and Gill 1933, Rozeboom 1939, Derrick and Bicks 1958, Christophers 1960, Weissman-Strum and Kindler 1962, McCray and Schoof 1972, Chang et al. 2007, Weaver and Reisen 2010, Fischer et al. 2011). There also is a growing recognition that diel fluctuations in temperature impact both life-history traits of and virus transmission by *Ae. aegypti* (Lambrechts et al. 2011, Carrington et al. 2013), making past studies using constant temper-

ature regimes more difficult to interpret with regard to field relevance. Moreover, the impact of diel temperature fluctuations likely is most pronounced at the cool margin of the range of *Ae. aegypti*, where the mosquito is near the limit of its temperature tolerance and even small fluctuations may impede development or reduce the likelihood of survival. To conclude, our understanding of how temperature limits population buildup of *Ae. aegypti* at the cool margins of its range is very limited, including whether bottlenecks are associated primarily with winter survival of overwintering eggs or the active life stages during the warmer part of the year.

With the notable exception of a recent study from Mexico (described later in this section), systematically collected presence or abundance data for *Ae. aegypti* from the cool margins of its range are scarce in the Americas, including in the continental United States. Moreover, models for associations between weather or climate factors and mosquito presence or abundance that are developed based on data collected over broader climate ranges should not be assumed to apply to the narrower climate range at the cool margin, where the nature of the association (e.g., the slope of a regression line) may differ compared with the broader climate range. This difference highlights the critical need for collection of field data for *Ae. aegypti* from the cool margins of its range. In this respect, it also should be stressed that the unique biology of *Ae. aegypti* calls for unique collection methodology. Surveillance efforts that target other mosquitoes, such as *Culex* West Nile virus vectors, and make use of collection methods that only occasionally produce *Ae. aegypti*, for example CDC light traps, do not yield useful surveillance data for *Ae. aegypti* (Service 1992), although they can produce intriguing collection records (VectorMap 2012). We thus face a scenario where our technological capacity for modeling far outstrips the availability of high-quality data for the target mosquito species, and researchers need to be very cautious with the development of models for the cool ranges of *Ae. aegypti* if the field mosquito data the models are based on were not collected through sampling efforts specifically designed to support the modeling activity.

A recent study conducted at the cool margin of the geographic range of *Ae. aegypti* in Mexico (along an elevation and climate gradient in the states of Veracruz and Puebla that spanned local climates ranging from suitable to marginal or unsuitable for establishment and proliferation of *Ae. aegypti*) is a rare example of a study where field mosquito data were systematically collected at the cool margin for *Ae. aegypti* to support weather- and climate-based modeling of mosquito presence and abundance (Lozano-Fuentes et al. 2012). Importantly, this study collected data for mosquito immatures from households along the elevation and climate gradient that represented reasonably uniform socioeconomic conditions. The results showed strong linkages between climate factors and field-derived estimates for the abundance of *Ae. aegypti* immatures at the examined cool margin, including for winter average minimum daily temperature and

warm-season average minimum daily temperature, base 10°C cumulative growing degree-days, and rainfall. This linkage underscores the value of generating and using high-quality field mosquito data at the cool margin of the range of *Ae. aegypti*, within a geographic area with reasonably comparable socioeconomic conditions, to link mosquito abundance with weather or climate factors. Follow-up work is underway to develop a multivariate model to predict abundance of *Ae. aegypti* along the examined elevation and climate gradient and then to examine how current climate change projections for the study area may impact the abundance of the mosquito in the future (an undertaking that is facilitated by the fact that the availability of water-holding containers is comparable throughout the study area).

Potentially Confounding Impacts of Access to Larval Developmental Sites and Competition Among Container-Inhabiting Mosquito Species

Although weather and climate factors are important drivers for population buildup of *Ae. aegypti* as well as *Ae. albopictus* at the cool margins of their ranges (Lozano-Fuentes et al. 2012, Mogi et al. 2012), these mosquitoes also depend on the presence of water-filled containers for oviposition and larval development. This dependence includes the complex issue of the role of rainfall versus human action to fill water-holding containers (Halstead 2008), making the impact of rainfall on local population buildup of *Ae. aegypti* difficult to assess and model. Studies to assess how the distribution of *Ae. aegypti* in Australia might change in the future, based on current climate change projections and accounting for containers (larval habitat) as a limiting factor for persistence, indicate that water-storage practices likely will be a more important driver of mosquito populations than weather conditions in the arid environment characteristic of most of the continent (Beebe et al. 2009, Kearney et al. 2009, Williams et al. 2010). The availability of water-filled containers therefore should be viewed as a critical confounder if models for associations between weather or climate factors and presence or abundance of *Ae. aegypti* are 1) based on field mosquito data collected across a wide range of socioeconomic conditions, for example over a sampling transect extending from northern Mexico into the southern United States; or 2) applied outside of the socioeconomic conditions for which the mosquito data were collected, for example by applying a model developed in the central highlands of Mexico to geographic areas in the United States with comparable climate conditions.

Competition with other mosquito species that exploit containers as larval developmental sites, most notably *Ae. albopictus*, also can impact local population buildup of *Ae. aegypti* (Hobbs et al. 1991; O'Meara et al. 1992, 1995; Juliano 1998; Braks et al. 2004; Juliano et al. 2004; Lounibos et al. 2010; Bagny Beilhe et al. 2012) and thus may be a confounder in climate only-based models for this mosquito. However, some factors may counteract such competition occurring un-

der natural field conditions. First, *Ae. aegypti* and *Ae. albopictus* may be segregated across the human landscape, with *Ae. aegypti* being most common in the highest density human population settings and *Ae. albopictus* most common in lower density human population settings (O'Meara et al. 1995, Braks et al. 2003, Rey et al. 2006, Tsuda et al. 2006, Honorio et al. 2009, Leisnham and Juliano 2009). Second, populations of *Ae. albopictus* in the continental United States may be unlikely, especially to the north, to reach levels where competition for larval habitat is intense enough to impact *Ae. aegypti*, even in areas where these mosquito species co-occur. Additional studies are needed to assess the extent of the potential for range restriction of *Ae. aegypti* in different parts of the continental United States by other container-inhabiting mosquitoes under natural field conditions.

What Is the Future Threat Posed by *Ae. aegypti* to Human Health in the Continental United States?

The previously mentioned outbreaks of autochthonous dengue in southern Texas in 2004–2005 and southern Florida from 2009 to 2011 have provoked interest in the extent of the future threat posed by *Ae. aegypti* (and *Ae. albopictus*), and by dengue virus, to human health in the continental United States (Moren and Fauci 2008). Speculation of an increasing threat is based, in large part, on the geographic range and potential for population growth of *Ae. aegypti* (and of *Ae. albopictus*) likely being limited by cold temperatures in the continental United States, and thus potentially affected by climate warming. However, based on our current state of knowledge, the most reasonable answer to the intriguing question posed in the heading above is that we do not know.

Existing studies, with direct relevance to the continental United States, of the linkages between yellow fever or dengue disease and weather or climate factors (Jetten and Focks 1997, Patz et al. 1998, Diaz and McCabe 1999, Hales et al. 2002, Brunkard et al. 2008), or directly between mosquito vectors and weather or climate factors (Hopp and Foley 2001, Erickson et al. 2012), present thought-provoking findings but have minimal predictive value for geographic areas outside of the range in the continental United States where *Ae. aegypti* currently is firmly established. This situation results from our very poor understanding of how weather drivers may impact population buildup of *Ae. aegypti* at the cool margin of its range in the continental United States, and how such population buildup is affected by human-related factors, particularly the availability of water-filled containers and the extent of indoor mosquito–human contact, which is thought to contribute substantially to dengue virus transmission (Gubler et al. 2001, Reiter 2001, Halstead 2008, Ooi and Gubler 2009). It cannot be overemphasized that findings from field-based studies focusing solely on the impact of weather or climate factors on the presence and abundance of *Ae. aegypti* apply only to the prevailing socioeconomic conditions examined in the field. Consequently, results from field-based

studies at the high altitude cool margins for *Ae. aegypti* in Mexico's central highlands or the Andes in South America cannot be assumed to be directly applicable to geographic areas in the United States with comparable climate conditions (Reiter et al. 2003, Brunkard et al. 2007, Ramos et al. 2008). Moreover, the introduction through human travel of specific dengue virus serotypes and genotypes, in relation to the ever-changing serotype-specific susceptibility of the human population, presents further complicating factors to understanding local virus transmission dynamics in the continental United States (Gubler 1998, Kyle and Harris 2008, Wilder-Smith and Gubler 2008, Scott and Morrison 2010).

Although there is no question that a substantially warmer climate would increase the basic potential for proliferation of *Ae. aegypti* within its extreme range in the United States, including northern cities such as Philadelphia and New York that suffered yellow fever outbreaks in the past, mosquito population buildup in the present is counteracted by improved housing and municipal sanitation and minimal need for indoor or outdoor water storage. Indeed, one can speculate that the cessation of major yellow fever outbreaks in the 1820s in these northern cities (Patterson 1992) suggests that by that time a critical point had already been reached where improving sanitation combined with a less than optimal climate prevented *Ae. aegypti* from achieving population buildup to levels resulting in human-mosquito contact of an intensity to drive major disease outbreaks.

Assuming the likely historical presence of *Ae. aegypti* in Philadelphia and New York, during a time in the past when socioeconomic conditions still favored the mosquito in these cities, Halstead (2008) raised the intriguing question of which specific climate conditions limit the mosquito if all other factors are in place to support its proliferation. Moreover, it is not clear whether the mosquito successfully overwintered in these cities in the past or if it was reintroduced each year through human transport of infested containers. We therefore need to determine the cool margin climate conditions that 1) limit the ability of *Ae. aegypti* to establish stable populations that persist over multiple years (which could be related to overwinter survival of eggs, developmental success of immatures, or survival of females while engaged in host-seeking or reproduction) and 2) prevent population buildup even during the warm part of the year.

A first step toward the goal of assessing the extent of the future threat this mosquito poses to human health in the continental United States is to design and conduct studies across strategic climatic and socioeconomic gradients in the United States (including the U.S.-Mexico border area) to determine the permissiveness of the coupled natural and human environment for *Ae. aegypti* in the present. This approach will require experimental studies and field surveys that focus specifically on climate conditions relevant to the continental United States. These studies also must include assessments of how the human landscape, particularly the impact of availability of larval devel-

opmental sites and the permissiveness of homes for mosquito intrusion, and the presence of other container-inhabiting mosquitoes that may compete with *Ae. aegypti* for larval habitat (e.g., *Ae. albopictus* and *Ae. japonicus*) affect the ability of *Ae. aegypti* to establish and proliferate. Until we are armed with such knowledge, it is not possible to meaningfully assess the potential for climate warming to impact the proliferation potential for *Ae. aegypti* in the United States outside of the geographic areas where the mosquito is already firmly established, and even less so for dengue virus transmission and dengue disease in humans.

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