STATE-OF-THE-ART REVIEW

The Burden of Dengue and Chikungunya Worldwide: Implications for the Southern United States and California

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ABSTRACT

Background: Dengue virus (DENV) spreads to humans through the bite of an infected *Aedes aegypti* or *Aedes albopictus* mosquito and is a growing public health threat to both industrialized and developing nations worldwide. Outbreaks of autochthonous dengue in the United States occurred extensively in the past but over the past 3 decades have again taken place in Florida, Hawaii, and Texas as well as in American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and the US Virgin Islands. As the *Aedes* vectors spread worldwide it is anticipated that DENV as well as other viruses also transmitted by these vectors, such as Chikungunya virus (CHKV), will invade new areas of the world, including the United States.

Objectives: In this review, we describe the current burden of dengue disease worldwide and the potential introduction of DENV and CHKV into different areas of the United States. Of these areas, the state of California saw the arrival and spread of the *Aedes aegypti* vector beginning in 2013. This invasion presents a developing situation when considering the state's number of imported dengue cases and proximity to northern Mexico as well as the rising specter of chikungunya in the Western hemisphere.

Findings: In light of the recent arrival of *Aedes aegypti* mosquito vectors to California, there is now a small but appreciable risk for endemic transmission of dengue and chikungunya within the State. It is likely, however, that if DENV or CHKV were to become endemic that the public health situation would be similar to that currently found along the Texas-Mexico border. The distribution of *Aedes* vectors in California as well as a discussion of several factors contributing to the risk for dengue importation are discussed and evaluated.

Conclusions: Dengue and chikungunya viruses present real risks to states where the *Aedes* vector is now established. Scientists, physicians, and public health authorities should familiarize themselves with these risks and prepare appropriately.

Key Words: arbovirus, antiviral, California, chikungunya, dengue, flavivirus, vaccine

INTRODUCTION

In terms of the population size at risk and economic burden, dengue remains the most globally important mosquito-transmitted viral infection.[1] Dengue virus (DENV) is a vector-borne flavivirus, a genus that also includes the West Nile (WNV), yellow fever, and Japanese encephalitis viruses. Dengue virions are spherical, approximately 50 nm in diameter, and feature a host-derived lipid bilayer containing a single copy of the approximately 11,000 base pair positive-sense single-stranded RNA genome coding for 3 structural (PrM, C, and E) and 7 nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5).[2,3] There are 4 antigenically distinct DENV serotypes in circulation among humans, DENV-1 through DENV-4.[4-6] A potential fifth serotype, DENV-5, was recently isolated from a patient in Borneo; however, it remains unclear if this virus is capable of sustained transmission between humans.[7] Although infection with a particular serotype will confer lifelong immunity to that strain, this protection is generally weak and short-lived against the other DENV serotypes, lasting around 2 to 3 months at most.[3,4,8] Indeed, infection with a heterologous subtype is correlated with more severe disease, likely as a result of antibody-dependent enhancement (ADE).[9-11] By this mechanism, antibodies raised against the previously

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encountered serotype bind to the new virus type and promote their entry into leukocytes harboring the Fc receptor glycoprotein on their surface.[12,13]

The majority of DENV infections are asymptomatic and consequently difficult to detect. When disease does become apparent, symptoms are generally self-limiting and range from lethargy, fever, and rash to organ failure and hemorrhage. Dengue cases may be classified as either (typical) dengue or severe dengue, with the latter characterized by severe plasma leakage (leading to shock, known as dengue shock syndrome, or fluid accumulation and respiratory distress), bleeding, and/or significant organ impairment.[3,4] The case fatality ratio for severe dengue has ranged from 20% in some outbreaks to less than 1%.[3,14] Up to 90% of severe dengue cases are the result of a secondary heterotypic infection, with the remaining percentage resulting from primary infections of infants younger than age 1.[15] The incidence of severe dengue in infants may be due to the maternal transmission of non-neutralizing antibodies that facilitate antibody-mediated enhancement, a hypothesis that was recently supported by in vivo experiments in mice.[16,17] Several other risk factors for severe dengue have been described and include virus strain, host genetics, female sex, obesity, youth, chronic disease, ethnicity, and heterosubtypic infection.[3,4]

The clinical course of dengue begins after a 3- to 7-day incubation period and may last for ≥10 days. Once symptoms begin, the patient is capable of transmitting the disease to an *Aedes* spp. mosquito vector. The initial febrile phase may last for up to a week and is characterized by a high fever (>38.5°C), arthralgia, headache, vomiting, rash, and/or mild hemorrhagic symptoms such as petechiae or bruising. Although the majority of cases will spontaneously recover following the febrile stage, a small number of patients, primarily children or young adults, will progress to the critical phase that is characterized by increased vascular permeability and resultant hemorrhage (severe dengue/dengue hemorrhagic fever or shock), leading to death. The critical phase generally begins around defervescence and may last ≤4 days. At the end of this phase, patients will enter the final period of spontaneous recovery during which they experience a rapid improvement of their condition.[3,4] There is some evidence for a "post-dengue syndrome" in patients recovering from apparent disease that is characterized by persistent fatigue, arthralgia, myalgia, and malaise ≤2 years after their illness.[18]

DISTRIBUTION AND GLOBAL BURDEN OF DISEASE

Dengue is, at its core, a global disease. Around 2.5 billion people, or 35% of the global population, live in a region where dengue is endemic.[1] The speed with which dengue spreads worldwide to become a global health concern is alarming: Before 1970, only 9 countries had reported outbreaks of severe dengue. By 2014, this number had grown to include >100 countries in Africa, North and South America, southeast Asia, Europe, and the Pacific reporting severe dengue outbreaks.[19] The World Health Organization (WHO) estimates that 50 million to 100 million dengue infections occur each year, around 500,000 of which will proceed to severe dengue resulting in >20,000 deaths, primarily among pediatric cases[9,19] (Fig. 1). The WHO figure of 50 million to100 million cases of dengue each year was derived by extrapolating from ratios of dengue cases to severe dengue cases and deaths resulting from severe dengue cases.[20] A more sophisticated approach involving data from the literature and online resources reporting areas of dengue occurrence yielded an approximation of 96 million apparent DENV infections out of 390 million overall infections per year.[21] Of the apparent infections, 70% occurred in Asia, with half of those infections occurring in India alone. Despite these estimations, some have argued that dengue is widely and acutely underreported across the subcontinent.[22] Africa and the Americas bore around 14% of the global total each; however, it is widely thought that surveillance in Africa is inadequate largely due to underreporting and the difficulty of the differential diagnosis versus other endemic viral diseases on that continent. Within the WHO southeast Asia region, which includes around half of the 2.5 billion people living in dengue-endemic countries, costs associated with dengue treatment and vector control averaged $950 million 2010 USD^{2010} per year between 2001 and 2010.[23,24] The economic and societal costs of dengue in the Americas is even steeper at an estimated at $1billion to $4 billion USD^{2010} each year.[25] Approximations of annual aggregate direct medical care costs in individual countries are large (all values are in USD^{2010}): India spends $521 million, the Philippines $328 million, Puerto Rico $38.7 million, and Malaysia $57 million.[26-29] In Singapore alone, the economic burden of dengue is around $1 billion USD^{2010}, half of which is spent solely on vector-control efforts.[30] Worldwide, estimates are as high as $39 billion USD^{2010} per year on the costs of medical care, surveillance, vector control, and lost productivity.[31] The direct and indirect costs of dengue are substantial and are likely an enormous burden on the developing tropical nations where dengue is most often endemic.

HISTORY OF DENGUE VIRUS AND DENGUE HEMORRHAGIC FEVER

Ancestral dengue virus arose 1000 to 2000 years ago among monkeys in either Africa or Asia; DENV-1 and DENV-2 probably emerged much more recently, perhaps within the past 3 centuries.[32,33] Descriptions of the disease have existed in the medical literature for ≥130 years and reports of a dengue-like illness are found in Chinese

documents dating to the third and fourth centuries CE.[32,34,35] Before the 19th century, the virus and vector were spread worldwide in drinking water reserves stored aboard sailing vessels, maintaining transmission cycles long enough to arrive at a virgin port where epidemics would generally follow introduction.[6,36,37] Dengue remained a globally inconsequential tropical illness until World War II, when extensive troop movements and ecological disruption served to spread both vector and virus, particularly the diverse subtypes, across the planet.[6] Indeed, by the late 1940s and early 1950s, large swaths of Asia were hyperendemic, or host to the 4 circulating serotypes.[38] As serotypes spread to areas where they were not previously encountered, the first reports of a more acute disease, termed dengue hemorrhagic fever or severe dengue, emerged, likely as a result of the increased chance of heterosubtypic infections.[37,39] Since then, jet travel, rapid urbanization of tropical regions, globalization, and inadequate vector-control efforts have allowed dengue to spread extensively across the globe and particularly in Africa and Asia, continents that are expected to undergo the most rapid growth over the next century.[5] This expansion is thought to have been accelerated in the Americas by the end of *A. aegypti* eradication programs in the 1970s, resulting is a return to pre-eradication population levels by 1995.[38] The burgeoning international trade in used tires also has been implicated in the spread of arboviral vectors, particularly *A. albopictus*, to previously uninhabited areas, setting the stage for possible dengue outbreaks.[40] Since exploding across the globe, sporadic epidemics of dengue, such as the 1998 outbreak in the Americas and Asia resulting in 1.2 million WHO-reported infections, will likely become more common as international commercial air travel facilitates travel of infected humans and vectors.[35,41] Other factors that may influence the incidence of epidemics include the level of herd immunity to a particular serotype and genetic changes in the virus that increase its epidemic fitness.[41]

VECTOR DESCRIPTION AND DISTRIBUTION

The urban-adapted, day-biting *A. aegypti* is the primary mosquito vector of dengue although transmission may also occur through a secondary vector, *A. albopictus*. *A. aegypti* is a cosmotropical species distributed worldwide between 35° N and 35° S, latitudes that roughly correspond to a 10°C winter isotherm, which appears to be the limit for what the species can tolerate while overwintering[3] (Figs. 1, 2). This species is highly adapted to urban environments, breeding in stagnant water found in manufactured containers, garbage heaps, and tires. Female infected mosquitoes transmit the virus, and DENV-naïve female mosquitoes feeding on an infected host will, after a 4- to 10-day incubation period, remain infectious for the duration of their life span.[19] The female *A. aegypti* prefers to feed just after daybreak or just before sunset, and is a promiscuous feeder capable of biting multiple individuals in a short period, often resulting in clusters of infections within the same household.[23] Due to the limited range of the mosquito vectors, often $\leq$500 m, movement of infected humans between households and communities is most likely responsible for driving virus spread.[23,42] The vector is not absolutely required for transmission as some cases of dengue have been traced to needlestick injury, blood transfusion, mucocutaneous contact, vertical transmission from mother to child, and, in one case, through bone marrow transplant, although these events are not very commonly reported.[14,43-46] Macroclimate is another important factor in predicting the range of *Aedes* mosquitoes and as climate change threatens to expand the area hospitable to this species, the need for vector-control efforts as well as novel vaccines and antiviral therapies for dengue and other flaviviruses will certainly grow.[47] The secondary vector, *A. albopictus*, has been implicated in previous outbreaks of dengue and chikungunya in more temperate climates; however, some research has suggested that this vector species is much less efficient at transmitting the virus than *A. aegypti*, perhaps due to native *Wolbachia* infection.[48,49] Alternatively, recent modeling approaches have suggested that *A. albopictus* may be even more efficient than *A. aegypti* at dengue transmission, particularly when considering the longer life span of this species.[50] Some have theorized that *A. albopictus* is implicated in maintaining the sylvatic and/or rural transmission cycles in endemic areas, and is thus less adapted to the urban environment than *A. aegypti*.[51] *A. albopictus* has spread globally and is now widely distributed throughout the Americas (excluding Canada), Europe, Asia, Africa, Australia, and the Pacific.[52]

DIAGNOSTICS, VACCINES, AND ANTIVIRALS

There are currently no FDA-approved vaccines or antiviral drugs for DENV infection, and treatment is limited to fluid replacement and palliative care.[3,4] The current rationale in drug design is based on the observation of 1- to 2-fold log differences in the plasma viremia of patients with severe (or hemorrhagic) dengue versus typical dengue, suggesting that inhibitors of viral replication will likely reduce the severity of disease by impacting this viremic state.[3,53,54] The lessons learned in the development of antivirals against another flavivirus, hepatitis C, are being exploited in the search for similar inhibitors of DENV proteins. Most work is focused on identifying inhibitors of the NS3 multifunctional nonstructural protein, NS2B/NS3 protease, and NS5 polymerase through cell culture—based high- or low-throughput approaches and in silico screening.[55-60] Host proteins required for viral replication or egress also are being explored as possible

targets for drug development.[61,62] For an excellent review of dengue drug development, see Lim et al. (2013).[63]

Dengue vaccine development has been hampered by safety concerns and challenges in eliciting a balanced and effective immune response. As the immune response is capable of exacerbating infection through ADE, it is important to develop a vaccine that is protective against all 4 serotypes. The most advanced candidate is Sanofi-Pasteur's CYD-TDV, a live-attenuated tetravalent formulation containing 4 recombinant yellow fever 17D vaccine strain viruses expressing the prM and E proteins from each DENV serotype. Two large Phase III trials of this preparation in Asia and South America were recently completed, demonstrating a vaccine efficiency ranging between 50% and 70% and, in 1 study, 80% effectiveness at preventing hospitalization, however, serotype-specific efficiencies were as low as 35% against DENV-2.[64,65] This vaccine will likely prove useful, even as a trivalent formulation, in an outbreak context and to begin reducing the enormous burden of apparent dengue infection worldwide while potentially decreasing hospitalizations, deaths, and associated costs.[66] Takeda's DENVax tetravalent vaccine using an attenuated DENV-2 and recombinant versions bearing prM and E proteins from DENV-1, -3, and -4 and the National Institutes of Health's TetraVax-DV combining 4 attenuated DENV strains have both shown promise in Phase II trials.[64,67,68] Several other candidates are currently in Phase I trials: Fiocruz, GlaxoSmithKline, and Walter Reed Army Institute of Research (WRAIR) are pursuing DPIV, a tetravalent purified, whole inactivated preparation. Merck & Co. is developing a purified recombinant subunit vaccine using truncated E proteins and the Naval Medical Research Center, WRAIR, and Vical are collaborating on a DNA vaccine.[69-71]

VECTORS IN CALIFORNIA

Both *Aedes* mosquito vectors of DENV are currently found in California. *A. aegypti* was absent before 2013, when breeding populations were located in the central counties of Fresno, Madera, and San Mateo.[72] By 2014, this species had spread to the adjacent Kern and Tulare counties and south to Los Angeles and San Diego counties[73,74] (Fig. 3). These populations are genetically diverse and were likely introduced from the southeastern United States rather than from nearby populations in Arizona and Mexico.[74] The ability of *A. aegypti* to spread across the state and survive the mild Californian winter presents a significant geographically expanding risk area for dengue or chikungunya outbreaks. *A. albopictus* was first introduced to California in 2001, most likely aboard container ships transporting live *Dracaena* bamboo from southern Chinese ports to Los Angeles; this original founder population has probably been supported by more recent introductions and remains entrenched in pockets across Los Angeles.[75] The restricted range of this species since introduction suggests that *A. albopictus* may not be entirely adapted to southern Californian climes or the highly developed urban landscape there.

Surveillance by state health authorities for dengue is ongoing and officials found no evidence of DENV in 214 *A. aegypti* mosquitoes captured across Fresno County in 2013.[76] Further testing of mosquitoes in all counties where *A. aegypti* has arrived is required, particularly in the heavily urbanized southern counties of Los Angeles and San Diego which will likely present the greatest chance of mosquito encountering a dengue case.

DENGUE AND CHIKUNGUNYA RISK IN CALIFORNIA

Outbreaks of locally acquired (or autochthonous) dengue in the continental United States were widespread in the past, with the first recorded outbreak in Philadelphia in 1780; several large epidemics occurred across the continent and Hawaii since then, including a 1922 outbreak in Texas that resulted in an estimated 500,000 to 600,000 cases. The last epidemic on the continent occurred in Louisiana in 1945.[77] The first autochthonous case of dengue in the United States following the 1945 outbreak was identified in 1980, in a young girl from the Texas-Mexico border region.[78] Since then, sporadic outbreaks have occurred have occurred in southern Texas, Hawaii, and Florida in addition to extensive transmission in Puerto Rico and the US Virgin Islands[77,79-84] (Fig. 2).

The Texas outbreaks present a unique case study when considering the risk for dengue importation into California. The cities of Laredo, Texas, and Nuevo Laredo, Tamaulipas state, Mexico are continuous and separated only by the international border. A 1999 serosurvey completed following an outbreak of dengue in the area found a much lower seroprevalence of anti-DENV antibodies in the Texan cohort (23% anti-DENV immunoglobulin [Ig] G positive in Laredo versus 48% in Nuevo Laredo) despite a much higher *A. aegypti* infestation and far more infested containers per household. The presence of air conditioning was correlated with a lower seroprevalence; the authors suggested that 55% of dengue cases in Nuevo Laredo were attributable to this factor.[79] In other words, socioeconomic differences across the border were largely predictive of infectious risk, an important consideration when evaluating the risk for dengue in California. A 2005 serosurvey in Brownsville, Texas, immediately adjacent to Matamoros, Mexico, showed 38% IgG seropositivity among the Texan cohort as opposed to 77% among Matamoros residents. Significantly, 25% of Brownsville residents with no reported travel outside of the United States were IgG or IgM positive.[80,85] Another study used preserved cerebrospinal fluid or serum samples collected

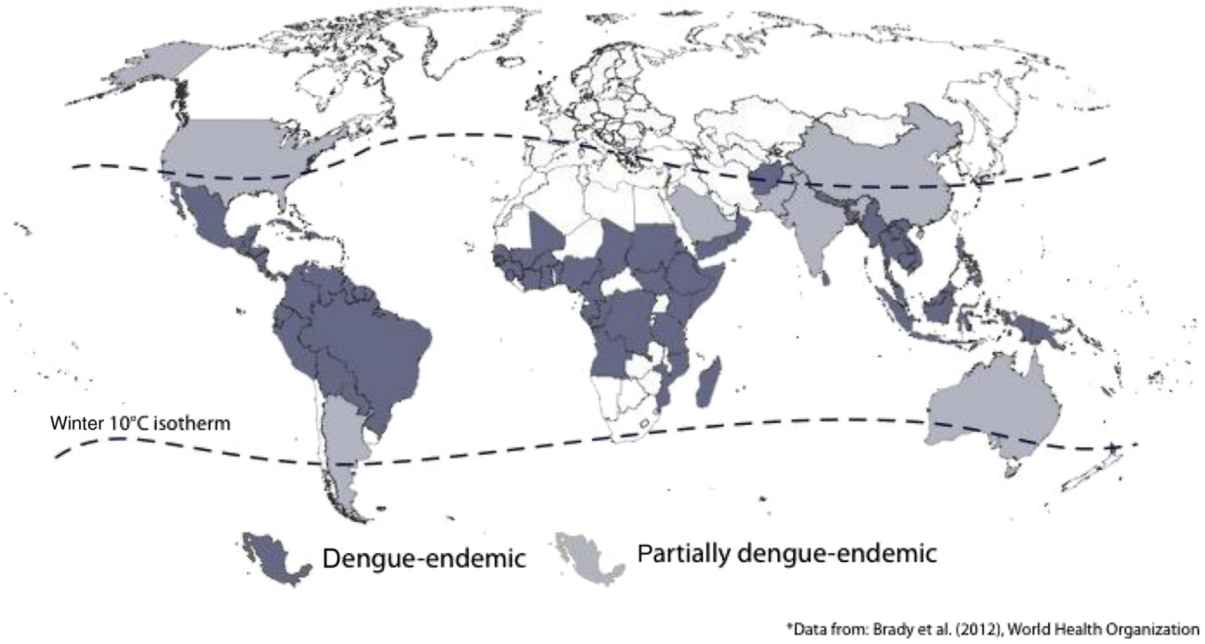

Figure 1. The global distribution, burden, and risk of dengue, 2010-2014. Distribution of dengue virus and disease is cosmotropical across the planet; however, it is also found in some temperate regions. Dark-shaded nations are considered to be widely endemic to dengue; light-shaded counties show a widespread transmission risk in only certain regions or counties. Hatched lines represent isotherms delineating an approximate 10°C winter minimum, the hypothetical lower limit for *Aedes* to survive and overwinter.

from Houston, Texas patients suffering from aseptic encephalitis or meningitis who had previously tested negative for WNV or St. Louis encephalitis viruses; they found that 1.2% of patients (n = 47) were positive for anti-DENV IgM antibodies, 2 of whom were also positive for DENV RNA via quantitative reverse transcriptase polymerase chain reaction.[86] Travel histories were obtained from 45% of the cohort, of whom 84% had no travel history to dengue-endemic areas. Some doubt has been cast on these findings with respect to demographics, assay sensitivity, and travel histories; however, it remains possible that some form of autochthonous transmission of dengue has occurred in Houston, a city along the Gulf of Mexico, >300 miles from the Mexican border.[87]

These studies are important when considering the dengue risk in California. Both Texas and California share an extensive border with Mexico. Dengue transmission is more widespread in the eastern Tamaulipas state bordering Texas than in Baja California state bordering much of California; however, Mexico is experiencing a nationwide progressive increase in the endemicity of dengue, possibly as a result of internal movements and the arrival of migrant populations from Central America that are transporting DENV to new parts of Mexico.[88,89] Furthermore, the *A. aegypti* vector in Mexico appears to be spreading into elevations and climes previously thought to be inhospitable.[47,89,90] Indeed, the first locally acquired cases of dengue in Baja California state, Mexico, were reported in November 2014 in addition to an above-average number of imported cases.[72] The socioeconomic differences that exist between Texas and Mexico that have been previously described as protective against a dengue outbreaks are likely also applicable to the cross-border situation in California; however, these factors are not entirely preventative.[79]

There are 2 mechanisms for an outbreak or establishment of dengue in California: spillover of mosquitoes harboring the virus from nearby Mexico or the arrival of infected humans in areas of California infested by the *Aedes* mosquito. Although both vectors are present in central and southern California, an outbreak cannot occur without a host that can transmit the virus to the vector in a natural transmission cycle. Spillover of infected mosquitoes is a theoretical risk for an outbreak of dengue within southern California when considering the amount of cross-border traffic. It appears, however, that importation of infectious *Aedes* mosquitoes from Mexico is not likely, considering that both *A. aegypti* and Californian dengue outbreaks were absent prior to the arrival of *A. aegypti* in 2013 despite frequent and extensive travel and commerce between southern California and Mexico.[74] Furthermore, the life span of an adult *A. aegypti* mosquito is 3 to 4 weeks thus an outbreak resulting from a single introduction of even several infected mosquitoes would be short-lived.[23]

Imported cases remain a concern. Californians traveling abroad are a constant and consistent source of imported dengue cases. In 2013, the California Department of Public Health reported 8 laboratory-confirmed and 117 suspected cases of dengue in the state, all of

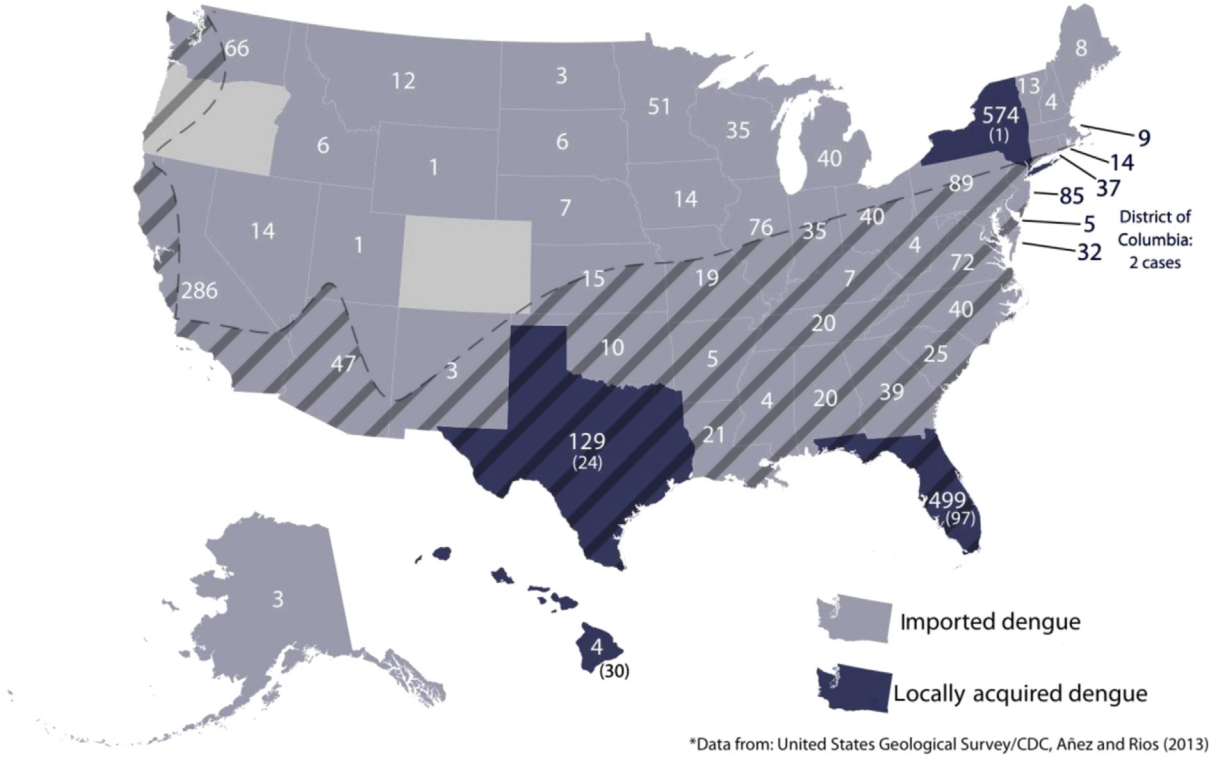

Figure 2. The distribution, burden, and risk of dengue in the United States, 2010-2014. Light-shaded states represent those where an imported case of dengue disease has been reported to and confirmed by the Centers for Disease Control and Prevention; dark-shaded states are those where a confirmed case of autochthonous dengue virus transmission has occurred. Values represent the number of imported cases over the 4-year period; numbers in parentheses represent cases of locally acquired dengue. The hatched area bordered by the dotted line represents geographic regions at risk for dengue outbreaks based on approximate vector distribution as of 2013.

which were occurred after recent travel to an endemic area.[76] There were 24 locally acquired cases in each of Texas and Florida as well as 8204 cases in Puerto Rico over that same period[91] (Fig. 3). Southern California appears to have the most significant risk in terms of the presence of vector, a nearby endemic area, and amount of both commercial and individual traffic (Fig. 2). Los Angeles International Airport was the sixth busiest airport in the world in 2013, with nearly 67 million passengers arriving or departing that year, while the Port of Los Angeles processed an additional 430,000 passengers in cruise ship traffic.[92] Gardner et al.[93] used a network-level regression model incorporating data on air travel, passenger volume, and infection rates to quantify the risk for the importation of dengue into the United States and found that Mexico-California airline routes presented the second highest individual risk nationwide, after Mexico-Texas. They postulated that Texas was most likely due to the high number of cases of dengue reported in Mexico as well as the length of this border and the volume of traffic crossing it; as these demographics change and dengue incidence increases across Mexico, the risk will surely increase. Considering the endemicity of dengue along the Texas-Mexico border and perhaps even within the Houston metro area, it appears likely that dengue will become endemic or perhaps already is endemic along the California-Mexico border extending from San Diego in the west to Yuma, Arizona on the east.

Daily commuters and both working and migrant populations from Mexico represent another significant population input from dengue endemic areas. The San Ysidro Border Crossing, where San Diego adjoins Tijuana along the California-Mexico border, is the world's busiest overland border crossing and processed >28 million pedestrians or vehicle passengers in 2013.[94] Furthermore, unauthorized border crossings by migrants represent another large but unregulated population of arrivals in California, the majority of whom are traveling from areas where dengue is endemic and widespread. The Customs and Border Protection US Border Patrol apprehended 414,397 individuals along the southwestern border in 2013, around 90% of whom were from Mexico, Guatemala, Honduras, or El Salvador, all countries that are among the top 30 most dengue-endemic nations in the world.[1,95] The apprehension rate along this border is estimated between 40% and 55%, providing an estimate of the real rate of immigration somewhere between 750,000 and 1 million individuals crossing this border each year.[96] The true number of those crossing the border into California specifically is likely much lower, as the Department of

*Data from: United States Geological Survey/CDC, California Department of Public Health.

Figure 3. The distribution, burden, and risk of dengue in California, 2010-2014. Light-shaded counties are those where an *Aedes aegypti* infestation has been reported; dark-shaded counties have reported both *A. aegypti* and *A. albopictus* infestations; only Los Angeles County, as of early 2015, reported a continued *A. albopictus* presence. Values represent the number of imported dengue cases to that county over the 4-year period. All cases must be laboratory confirmed before incorporation into the USGS/CDC-ArboNET database.

Homeland Security's apprehension figure includes repeat arrests of the same individual and only 10.4% of those apprehensions actually took place along the California-Mexico border. Even with these accountings in mind, up to 100,000 individuals entering each year from regions that are burdened by dengue presents another entry route for infected individuals beyond the establish commercial traffic pathways. Furthermore, Mexico is experiencing a gradient of increasing dengue incidence from south to north that has been hypothesized as the result of tourists and both working and illegal migrants arriving from Central America harboring dengue viruses from their nations of origin.[89] This mechanism will likely contribute to the establishment of dengue in these border regions and increase the likelihood that anyone crossing the border is exposed to dengue. Recognizing these risks, public health officials on both sides of the border as well as the US Centers for Disease Control and Prevention established the Border Infectious Diseases Project in 2003 with the goal of enhancing binational surveillance and response times to issues of infectious disease affecting the border region.[97] It remains to be determined if this program will prove useful in monitoring the arrival and spread of dengue along the US-Mexico border region.

Chikungunya presents another risk for importation now that *A. aegypti* populations have become established in central and southern California as the vector preferences are the same as dengue; recent modeling approaches forecasting the spread of chikungunya identified Los Angeles as a high-risk area for the importation of chikungunya cases but a low-risk area for local transmission.[98] In agreement with these predictions, a single case of chikungunya was identified in Los Angeles in a traveler returning from a visit to Haiti in 2013.[99] By the end of 2014, a total of 46 imported cases of chikungunya in California were reported to and confirmed by CDC.[100] The risks here appear real: A single chikungunya outbreak occurred in temperate northern Italy in 2007 that was transmitted by *A. albopictus* and sparked by the return of a single infected traveler from India.[101,102] A similar outbreak occurred in France in 2011.[103] As of 2014, cases of locally acquired chikungunya have been identified in Florida.[104] As *Aedes* populations spread across California and continue to successfully overwinter, the possibility of local transmission of both DENV and CHKV will surely increase. As it stands in the first days of 2015, it appears that the overall risk for the dengue becoming an endemic disease in southern California remains very low, as surveillance is robust and the state has an established plan for reporting and responding to an outbreak of dengue or chikungunya in the state.[105] However, it does seem likely that outbreaks of dengue or chikungunya will occur at some point, particularly if the *Aedes* vectors continue to overwinter, spread, and establish breeding populations across the state. In the event that these outbreaks take place, the state is expected to respond in a similar fashion as to the arrival of WNV in the early 2000s. WNV is an excellent case study for how California will move to control a mosquito-borne illness through a statewide surveillance program using sampling of mosquito traps and pools, sentinel chickens, and public health awareness to target vector-control efforts and identify outbreaks.[105-108]

CONCLUSION

The growth of dengue from a minor tropical illness to a disease of worldwide importance is a demonstration of the power that commerce, air travel, and globalization can have on global public health. Indeed, the emergence of dengue hemorrhagic fever is a testament to the unpredicted results of these phenomena. As the *Aedes* vectors continue to spread worldwide and within the United States, the risk for the establishment of DENV or CHKV within this country in areas where it had previously been eradicated or never present becomes more real. As DENV continues to spread in Mexico, there will certainly be a growing need for disease surveillance, vector-control efforts, antiviral drugs, and effective vaccines in the border regions of the United States and in particular California, Arizona, and Texas. Although the overall risk in California for large outbreaks or dengue becoming an endemic illness appears low, continued

efforts will be required to monitor *Aedes* populations, identify imported cases, and perhaps even begin regular serosurveys of residents on both sides of the border.

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