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Zika and chikungunya: mosquito-borne viruses in a changing world

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The reemergence and growing burden of mosquito-borne virus infections have incited public fear and growing research efforts to understand the mechanisms of infection-associated health outcomes and to provide better approaches for mosquito vector control. While efforts to develop therapeutics, vaccines, and novel genetic mosquito-control technologies are underway, many important underlying ecological questions remain that could significantly enhance our understanding and ability to predict and prevent transmission. Here, we review the current knowledge about the transmission ecology of two recent arbovirus invaders, the chikungunya and Zika viruses. We introduce the viruses and mosquito vectors, highlighting viral biology, historical routes of transmission, and viral mechanisms facilitating rapid global invasion. In addition, we review factors contributing to vector global invasiveness and transmission efficiency. We conclude with a discussion of how human-induced biotic and abiotic environmental changes facilitate mosquito-borne virus transmission, emphasizing critical gaps in understanding. These knowledge gaps are tremendous; much of our data on basic mosquito ecology in the field predate 1960, and the mosquitoes themselves, as well as the world they live in, have substantially changed. A concerted investment in understanding the basic ecology of these vectors, which serve as the main drivers of pathogen transmission in both wildlife and human populations, is now more important than ever.

Keywords: mosquito; climate change; *Aedes aegypti*; *Aedes albopictus*; chikungunya; Zika

Introduction

Mosquito-borne viruses, a specialized group of arthropod-borne viruses or *arboviruses*, are an emerging threat of significant impact for human health and well-being. Epidemics of dengue, chikungunya, and Zika are spreading explosively through the Americas, creating a public health crisis that places an estimated 3.9 billion people living in 120 different countries at risk. This pattern began with the growing distribution of dengue virus (DENV) over the past 30 years, which today infects an estimated 390 million people annually. The more recent invaders, chikungunya virus (CHIKV) and Zika virus (ZIKV), are rapidly following suit. CHIKV emerged in the Americas in 2013 and has caused 1.8 million suspected cases from 44 countries and territories[1] to date. In 2015–2016, outbreaks of ZIKV spread throughout the Americas, resulting in over 360,000 suspected cases, with likely many more going unreported.

The growing burden of these infections and the potential spread into new areas have incited fear and a flurry of research to understand the health outcomes associated with viral infection, arbovirus epidemiology, and control. There is a current flood of investment toward the development of therapeutics, vaccines, and novel mosquito-control technologies, such as release of sterile males, transgenic mosquitoes, or *Wolbachia*-infected mosquitoes. Yet some important, underlying ecological questions remain. Why are these viruses escaping transmission cycles in Africa and Asia? What features of their disease ecology facilitate rapid global spread? What is

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the potential for sylvatic reservoirs in regions where these viruses have appeared? Are temperate regions of the world at risk for seasonal outbreaks?

To address these questions, we need a more concerted investment in understanding the basic ecology of the mosquito vectors, as they serve as primary drivers of pathogen transmission in both wildlife and human populations. Interestingly, all three of these viral invaders are primarily transmitted by two mosquito species: *Ae. aegypti* (the yellow fever mosquito) and *Aedes albopictus* (the Asian tiger mosquito). These mosquitoes, their hosts, and the pathogens they transmit associate in a rapidly changing world, and the ecological relationships among them are sensitive to shifts in habitat, water quantity and quality, and climate. The resulting changes in vector distribution, abundance, longevity, contact rates with hosts, and vector and host susceptibility to pathogens can dramatically alter disease transmission. A better understanding of this shared transmission ecology will be crucial not only for addressing the questions posed above but also for implementing and evaluating the effectiveness of any arbovirus-control campaign.

In this review, we highlight current knowledge about the transmission ecology of the two most recent arbovirus invaders, CHIKV and ZIKV. In the first section, we introduce the viruses and the mosquito vectors (*Ae. aegypti* and *Ae. albopictus*). For the viruses, we focus on viral biology, historical routes of transmission, and viral mechanisms that facilitate rapid global invasion. For the vectors, we highlight their history of domestication, the factors that contribute to their global invasiveness, and the reasons why these mosquitoes are such efficient vectors. The second section explores how human-induced biotic and abiotic changes to the environment facilitate arboviral transmission. Finally, the third section highlights critical knowledge gaps and concludes with a research agenda to aid in filling these gaps.

The viruses and their mosquito vectors

Chikungunya

Chikungunya is a mosquito-borne febrile disease caused by a positive-sense single-stranded RNA alphavirus in the *Togaviridae* family. Chikungunya mortality is low (less than one in 1000, mostly in neonates, the elderly, and immunocompromised adults),[2,3] but it causes significant morbidity. The name chikungunya is originally from the Makonde language and means "that which contorts or bends up," describing the posture of patients afflicted by symptoms of severe arthritis and joint pain. Approximately 85% of people infected develop symptoms that include rash, high fever, headache, photophobia, and severe joint pain. A significant percentage (30–40%) of patients will suffer from chronic joint disease that can last weeks, months, or even years after initial infection.[4–6]

While chikungunya-like illness has been documented for centuries,[7] it was first recognized as an endemic disease in 1952 in East Africa.[5] Shortly thereafter, with the aid of newly developed viral diagnostic tools of the day, CHIKV was isolated from human sera in Tanzania,[8] and *Ae. aegypti* was identified as the main vector.[9] In 2005–2006, CHIKV spread to several islands in the Indian Ocean, with the French island, La Réunion, experiencing one of the largest outbreaks on record for the time, with approximately 40% of the island's population infected and 273 deaths.[5] Interestingly, *Ae. albopictus* was the predominant vector for the La Réunion outbreak. Subsequent research demonstrated that this primary vector switch coincided with selection for a single amino acid change from alanine to valine at position 226 in the CHIKV E1 envelope glycoprotein (E1-A226V) that increased midgut infection, replication, dissemination, and transmission in *Ae. albopictus*.[10,11] After the La Réunion outbreak, CHIKV continued to spread and cause large outbreaks. In 2006–2007, CHIKV reached India, with more than 1.5 million estimated cases.[9,12] At the same time, the first locally acquired cases in temperate regions occurred, with outbreaks in Italy[13] and France.[14] These outbreaks, again, were largely driven by *Ae. albopictus*. In 2013, CHIKV was introduced to the Caribbean island system, likely via infected travelers, and quickly spread throughout the Americas. Cases of locally acquired CHIKV occurred for the first time in Florida (2014) and Texas (2016) in the United States.[15] At the time of writing, local CHIKV transmission has been confirmed in more than 45 countries or territories, with over 1.7 million suspected cases.[1]

Zika virus

ZIKV is another positive-sense, single-stranded RNA virus. Unlike the alphavirus CHIKV, ZIKV belongs to the *Flaviviridae* family, which also

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includes the dengue, yellow fever, and West Nile viruses.[16] Symptoms of Zika infection are relatively mild and include low-grade fever, skin rash, conjunctivitis, headache, and arthralgia usually lasting up to 1 week;[17] however, 70% of Zika cases will have no symptoms at all. Despite the high rate of asymptomatic cases, Zika has been declared a public health emergency of international concern[18] and is widely feared, owing to the 20-fold increase of microcephaly in newborns, an increase in the probability of pregnancy loss, and brain and eye abnormalities in infants born from infected mothers. Additionally, there is a 19% average increase in autoimmune neurological complications (Guillain-Barré syndrome) associated with Zika infection in Brazil (www.cdc.gov).

Zika was first detected in 1947 in a sentinel *Rhesus* monkey from the Zika Forest of Uganda and was isolated from *Ae. africanus* in 1948.[19] The first human cases of Zika were detected in 1952 during a serological study of Ugandan and Tanzanian residents,[20] and 2 years later the first human ZIKV isolate was obtained from a 10-year-old girl in Nigeria.[21] In the following decades, the virus traveled across Africa and tropical Asia, occasionally causing dengue-like fever outbreaks. During this period, Zika was not considered a major public health concern and there were no reported links to microcephaly or other complications. That changed in 2007 when the first outbreak outside Africa and Asia occurred on the island of Yap.[22] This key epidemiological event was viewed as an isolated oddity by many scientists at the time, but it was quickly followed by movement of ZIKV across Oceania and the Pacific islands between 2013 and 2014.[23] The next year, Zika was detected in Brazil, and it is currently spreading throughout the Americas.[24] Recent research on ZIKV evolution supports the hypothesis that two lineages of ZIKV diverged into an African group and an Asian group; with the Asian genotype recently introduced to the Americas.[25]

Similar to CHIKV, ZIKV is thought to be primarily transmitted by *Aedes* mosquitoes. A major sylvatic cycle of the virus occurs in Africa, involving mostly nonhuman primates and *Aedes* mosquitoes, but some reports of other genera (*Mansonia, Anopheles,* and *Culex*) have been suggested (reviewed in Ref. 6). *Ae. africanus* is considered a major sylvatic vector and *Ae. aegypti* a major human vector (reviewed in Ref. 26). *Ae. albopictus* is an additional vector of importance in the Americas. Many questions remain regarding the presence of additional vector species and the epidemiology of sylvatic and urban cycles of ZIKV. One question of particular interest is the potential for emergence of sylvatic cycles in Asia and the Americas involving nonhuman primates or other animals. Another is the identification of key vector species involved in the zone of emergence from sylvatic to domestic cycles.

Challenges for management and control of chikungunya and Zika infections

The proportion of the human population infected (prevalence) and number of new cases (incidence) of people with CHIKV and ZIKV are extremely difficult to quantify and control, for a variety of reasons. First, for both viruses, there are many cases that go undetected. An estimated 15% and 80% of all people infected with CHIKV and ZIKV, respectively, are asymptomatic and never seek treatment, even though they may still be infectious to biting mosquito vectors.[22] Second, reliable techniques to diagnose infection accurately in symptomatic patients are limited. The clinical presentation of these diseases is nonspecific and overlap across CHIKV and ZIKV (as well as dengue). Without presentation of unique symptoms, it can be difficult for medical personnel to diagnose illness, especially in resource-poor settings where expensive testing is not available. Even when an antibody test is administered, neutralizing antibodies often cross-react with other closely related viruses (e.g., the flaviviruses: dengue, West Nile, yellow fever, and Zika), leading to inconclusive results. Third, virus evolution can result in sudden and unpredictable outbreaks. For example, with CHIKV, a mutation in the viral envelope protein allowed increased midgut infection and dissemination in a new, highly invasive and abundant mosquito species (*Ae. albopictus*).[11] Phylogenetic analysis has confirmed two main Zika lineages, African and Asian,[26] with the latter spreading out of Africa and into the Americas and contributing to both the birth and neurological disorders[25] associated with ZIKV infection. Fourth, there are multiple transmission routes. Along with the bite from an infectious mosquito, these arboviruses can be transmitted maternally, through blood transfusion, and, with Zika, through sexual contact.[27–29] Finally, there currently are no available therapeutics or licensed

vaccines for CHIKV or ZIKV. This leaves public health experts with only two options—vector control (e.g., insecticides) and public education (e.g., larval-source reduction, personal protection, and repellent use)—in the battle against these infections.

Aedes vectors of chikungunya and Zika

The rapid expansion of CHIKV and now ZIKV out of Africa has followed the global spread of two very important mosquito vectors, *Ae. aegypti* and *Ae. Albopictus*.[30] Both mosquitoes are highly invasive and have been transported out of their native ranges through human migration and trade to occupy global distributions. For current distribution maps for both of these vectors, see Kraemer *et al.*[31] There is sufficient evidence to suggest that both *Ae. aegypti* and *Ae. albopictus* are important vectors for these two arboviruses.

Aedes aegypti

Ae. aegypti originated from an ancestral zoophilic tree hole breeding mosquito in North Africa, *Ae. aegypti formosus*.[32] The arid environment may have selected for divergence from the generalist sylvatic form into the domestic, anthropophilic/phagic form,[33] as humans created an ideal larval habitat and shelter for these adult mosquitoes from the harsh environment while providing a constant high-quality blood source. Migration and trade between the 15th and 19th centuries—particularly the slave trade—likely spread *Ae. aegypti* globally.[34] This species is now well established throughout the tropical and subtropical regions of the world.[33] In the 1700s to 1800s, the U.S. *Ae. aegypti* distribution spanned as far north as Philadelphia and southwest to Louisiana. However, its range has diminished in recent decades, most likely due to vector-control campaigns of the 1900s and competition with the more recent invader *Ae. albopictus*.

Many aspects of the life history of *Ae. aegypti* make this mosquito a very efficient vector of human disease. They feed almost exclusively on human blood[35] and can exhibit high rates of multiple blood feedings per gonotrophic cycle.[36,37] Additionally, *Ae. aegypti* breeds in manmade containers, rests indoors, and is diurnally active, all of which translate to high human exposure. Eggs can resist desiccation for up to 8 months,[38] facilitating its dispersal and survival during dry periods. While there is no known cold egg diapause that would allow for overwintering for this species, recent reports cite suspected overwintering populations in the Washington, D.C. region, facilitated by belowground winter survival.[39]

Aedes albopictus

Ae. albopictus was originally a zoophilic forest species in Asia, and its native range bordered New Guinea, Madagascar, Beijing, Seoul, and Japan. It first expanded out of this range to the islands of the Indian and Pacific Oceans,[40] and in the 1980s it rapidly moved to Europe, the United States, and Brazil via shipments of used tires and lucky bamboo plants.[41–43]

Like *Ae. aegypti,* the life history of *Ae. albopictus* lends itself to efficient disease transmission. *Ae. albopictus* is also a diurnal feeder that often cooccurs with humans and breeds in artificial containers, although they can also thrive in natural containers, such as rain-filled coconut shells, leaf axils of water-holding plants, such as bromeliads, or tree holes.[41] *Ae. albopictus* is an aggressive biter, and while they feed on a wider variety of hosts than *Ae. aegypti*, human feeding fidelity in some regions can be high.[35,44,45] In addition to resisting desiccation, *Ae. albopictus* populations in temperate areas produce diapausing eggs with the ability to overwinter. Consequently, *Ae. albopictus* has a larger geographical distribution than *Ae. aegypti,* which spans tropical, subtropical, and temperate habitats and enhances the possibility of disease transmission in temperate regions of the world. *Ae. albopictus* has already been implicated in CHIKV outbreaks in temperate regions, such as Italy (2007)[47] and France (2010 and 2014).[14,48,49] Furthermore, owing to its ability to feed on a wider diversity of vertebrate hosts, *Ae. albopictus* could facilitate the establishment of enzootic arbovirus transmission cycles in the Americas as a bridge vector (e.g., involvement in spillover of dengue from sylvatic cycles in Asia[50,51]).

Arbovirus transmission in a changing world

The factors influencing arbovirus transmission are complex, spanning abiotic and biotic environmental factors, vector biology, and viral and host factors (Fig. 1).

Interactions with the abiotic environment

Climate change. Climatic factors, particularly temperature, relative humidity, and rainfall patterns, are strong environmental drivers of vector-borne disease transmission and determine

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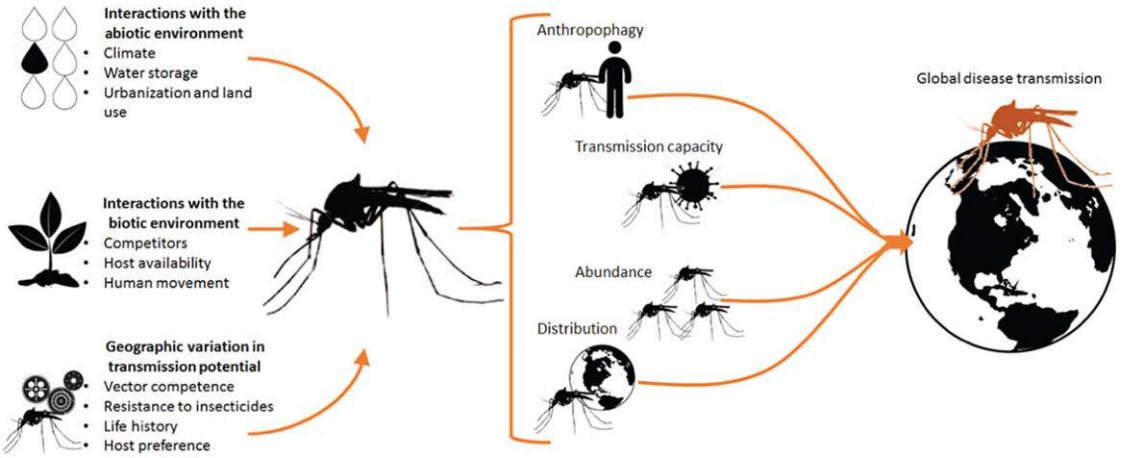

Figure 1. The complexity of interactions among mosquito vectors, arboviral pathogens, and transmission across environmental drivers.

the environmental suitability or potential for transmission.[52–61] Temperature has clear impacts on vector-borne diseases through effects on the insect vectors; mosquitoes are ectotherms and their internal body temperature varies considerably with variation in ambient temperature. Mosquito physiology (e.g., immunity),[62–64] life history (e.g., development, survival, reproduction, biting rates),[40,65–67] and arbovirus fitness (e.g., vector competence and extrinsic incubation periods)[68–72] are all directly affected by temperature variation. Future climate change will likely alter the climate conditions that mosquito vectors experience, but it remains unclear how mosquito vectors will respond. The mosquito and pathogen life history traits that determine transmission exhibit clear nonlinear relationships with temperature.[73–75] Rather, these traits typically show a parabolic relationship with temperature where performance is maximized at a thermal optimum, and a thermal minimum and maximum where performance of these traits is minimal. There is good evidence to suggest that warming in currently cool regions of the world has resulted in temperatures closer to the thermal optima and therefore increased vector-borne disease transmission (e.g., malaria[76]). However, in areas that are already conducive to transmission of mosquito-borne diseases, warming temperatures might move the environment away from the thermal optimum. Recent experimental and modeling work suggests that these areas could experience range contractions rather than range expansions of vector-borne diseases owing to this nonlinear relationship between transmission and temperature.[70,74,75]

Urbanization. *Ae. aegypti* and *Ae. albopictus* live with us in the habitat that we create. But this environment is not uniform, and different land use establishes a range of habitats that can vary in quality and suitability for these vectors. Of particular concern for mosquito-borne disease transmission is the potential for high population densities in urban areas. From 1960 to 2014, the proportion of people living in urban zones rose from 34% to 54%,[77] often resulting in sprawling, unplanned megacities. LaDeau[78] hypothesizes two main effects of urbanization on mosquito populations: urban heat islands raise mean temperatures and buffer temperature fluctuations, facilitating faster growth rates and viral replication rates, and the creation of additional container habitats supports immature mosquito life stages. Yet much of the work cited throughout LaDeau[78] used temperatures from laboratory studies to draw predictions from mathematical models.[79–82] Field studies explicitly testing changes in environmental variables associated with urbanization, such as temperature, are required to mechanistically link urbanization to changes in mosquito population dynamics and transmission potential.

While urbanization changes habitat and climate, the effect is rarely homogenous throughout a city.[83] Temperature, humidity, and the number of breeding sites vary depending on the economic status

of the landowner or resident, mosquito control, zoning, and cultural norms. Mosquito hotspots within a city can be particularly problematic following rapid increases in urbanization and unplanned growth. These factors may give rise to a lack of sanitation and infrastructure with little clean water, sewage, or waste management and therefore abundant mosquito habitat.[84]

Numerous studies have demonstrated that *Ae. aegypti* prefers urban areas; however, this trend is less clear for *Ae. albopictus*. Most studies conducted to date along an urban–rural gradient have conflicting results, demonstrating higher *Ae. albopictus* densities across all habitats: suburban,[85,86] urban,[87,88] and rural environments.[89–91] Only one published study found no correlation between urbanization and *Ae. albopictus* abundance.[92] Unfortunately, interpreting relationships between mosquito abundance and land-use patterns is difficult because researchers often use different rules to categorize landscapes. Some use percent vegetative cover, human population density, or a vague "general geography." Furthermore, quantifying these patterns across inappropriate scales, where large regions are lumped into different land-use classes, may obfuscate clear patterns because they may cover too broad a range of microclimate and available habitats. In order to refine our understanding of how heterogeneity in urban landscapes affects mosquito populations and virus transmission, we recommend that future studies use a more carefully defined classification of land use and economic status and work at finer scales more appropriate for the mosquito vector.

With an increasing proportion of the world living in urban environments, we may be inadvertently creating better habitats for vector species. While, in an ideal world, the ability to motivate and mobilize communities to participate in mosquito control could reduce transmission in urban environments, this approach requires significant financial resources, well-crafted educational messaging, and political will.

Water-storage practices. Water-storage practices driven by drought, infrastructure, and cultural norms may increase the abundance of *Ae.* mosquitoes by providing breeding habitat. The age-old practice of storing rainwater is common throughout tropical regions of the world where populations encounter a rainy season followed by long, dry seasonal periods with little to no rainfall. *Ae. aegypti* larval/pupal surveys in Colombia[93] and Peru[94] demonstrate how water-storage practices can influence mosquito dynamics. For example, in both countries, vector population size was determined by how often water-storage containers were emptied, which in turn was determined by climate and the availability of running water. Those authors found that people living in cities with unreliable plumbing tend to store water for the long term, while those living with reliable plumbing had short-term water storage containers that were emptied often. In cities with no running water, water-storage containers were regularly used, emptied, and refilled, reducing the probability of mosquitoes completing their life cycle to adulthood.

A review on drought and vector-borne disease by Brown[32] described how decreased rainfall in Australia led to government policies that encouraged the use of rainwater tanks for long-term water storage. This resulted in a substantial increase in households with water tanks (52.6% of households in some areas). While helping people store water over time, the tanks unintentionally provide an ideal mosquito larval habitat that could enable the reintroduction of *Ae. aegypti* from Queensland, Australia into more populated areas, such as New South Wales. Brown[33] also reviewed two studies in Yemen and Brazil where decreased rainfall in regions with little urban infrastructure caused residents to store water. This, in turn, provided habitat for *Ae. aegypti* and increased risk for dengue and chikungunya.

Water storage can be a sustainable and economic method to mitigate drought or a lack of water resources. But good intentions can have unintended consequences. Policies concerning water storage should be made with vector control in mind. Residents can be encouraged to cover the opening of containers to minimize access by egg-laying adult females.

Interactions with the biotic environment

Human movement. Throughout much of human evolutionary history, people have introduced exotic species into new geographic regions. With the relatively recent capability for long-distance travel, the spread of invasive species and pathogens have only increased in frequency and severity. Globalization has a profound impact on the flow of people and

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goods around the globe, with current transportation patterns in shipping and aviation illustrating a highly connected world. For both domesticated *Ae.* species, human transport of manmade containers contaminated with diapausing eggs and adult mosquitoes has facilitated their dispersal.[95] This is then followed by short-distance natural dispersal aiding range expansion at smaller scales.[95] Once mosquito vectors are present, people traveling from areas with ongoing arbovirus transmission can import viruses to these regions, as documented by Rezza[47] and Faria[96] with chikungunya to Italy and Zika to Brazil, respectively

At finer scales, individual biting risk is due more to human movement than to mosquito movement. *Ae. aegypti* tends to rest indoors, feed diurnally, does not disperse more than a few hundred meters,[97] and is distributed spatially in a heterogeneous pattern across communities.[98] Therefore, where and when a host spends its time daily (its "activity space") modulates its individual biting risk and potentially the dynamics of transmission within a community.[99] Unfortunately, individual activity space estimates for potential human hosts cannot be easily measured, may infringe on individual privacy, and must be linked with vector activity and feeding patterns[37] in order to be meaningful.

Human movement will continue to circulate vectors and pathogens. More thorough screening for vectors and pathogens, especially high-risk cargo arriving through global travel and shipping (or even at the point of departure), may reduce the frequency of accidental introductions. Much more research is needed to understand the fine-scale dynamics of human and mosquito movement and behavior and how abiotic and biotic drivers influence the biology of these dynamics.

Vertebrate hosts. Opportunities for human blood feeding for *Ae. aegypti* and *albopictus* differ on the basis of human population density and the relative densities of other hosts. What determines how often these vectors feed on humans? *Ae. aegypti* is established as a domesticated species with strong preference for human blood meals.[100,101] *Ae. albopictus* is traditionally considered a generalist and, in part because of this, a less important vector. This theory was based on earlier papers that identified a variety of mammal, bird, and reptilian hosts in wild-captured blood-fed females.[102,103] However, *Ae. albopictus* can be anthropophagic, especially in urban environments. Humans are often the primary host, followed by domesticated mammals.[104–110] In the United States, Singapore, Thailand, metropolitan Barcelona, and suburban Cameroon, *Ae. albopictus* feed almost exclusively on humans.[35,44–46,111]

Several studies identified a correlation between percent human blood meals and urbanization. Valerio[110] found that 79–96% of blood meals were human in urban sites, while only 22–55% were human in rural sites. Sivan[107] found that, in urban areas of the Andaman and Nicobar archipelago, 90.5% of blood meals were human. However, this percent decreased as vegetation increased to 8.7% in forested areas. Another study in Singapore found that 83.2% of blood meals from semiurban and rural areas were human, but 100% of blood meals were of human origin in urban areas.[107] In contrast, one study by Faraji[104] in New Jersey found the opposite trend, with higher relative *Ae. albopictus* blood meals from humans in suburban than urban environments, where proportionally more blood meals were from domestic pets. Few studies have explored *Ae. albopictus* feeding patterns on nonhuman primates, despite the potential importance of these hosts in sylvatic transmission cycles.

The extent to which *Ae. albopictus* host feeding represents patterns versus preference is unclear. Studies that incorporate blood-feeding analysis of wild-captured mosquitoes with environmental censuses of available hosts[35,112] could capture this information. Clearly, however, *Ae. albopictus* will feed on humans across its range and presents a risk for circulation and transmission of CHIKV and ZIKV.

Interspecific competition. As *Ae.* mosquito ranges expand, their habitats overlap with new sets of native species that present novel competition dynamics. Often, *Ae. aegypti* and *Ae. albopictus* encounter each other in the same larval habitat, resulting in either stable coexistence or competitive displacement of *Ae. aegypti* by *Ae. albopictus.* Competitive displacement likely occurs through larval resource competition, with *Ae. albopictus* generally outcompeting other species, including *Ae. aegypti* (see reviews by Juliano and Lounibos[113] and Lounibos[114]). However, some environments lead to stable coexistence. For example, in hot, dry climates, *Ae. albopictus* eggs may be more susceptible to desiccation, returning the competitive advantage to *Ae. aegypti.*[115] The outcome of larval competition

in the face of abiotic factors is complicated. Murrel and Juliano[116] demonstrated that the competition winner or even the presence of competition itself depended on the type of detritus in the larval environment. Competition can also enhance susceptibility of infection to arboviruses,[117] although, since competition also may shorten adult longevity,[118,119] the net effect of this interaction on vector competence remains unclear.

Adult mating competition between these two species also has been described. While hybridization of the two species has been explored for decades,[120] few studies have documented its importance in the field. Nasci *et al.*[121] described unidirectional crossmating of field strains of male *Ae. albopictus* with released *Ae. aegypti* females in Louisiana effectively sterilizing *Ae. aegypti* females, and more recent studies have named this phenomenon *satyrization*. Researchers have now demonstrated that substances transferred from the *Ae. albopictus* male accessory gland inhibit or reduce *Ae. aegypti* female fecundity,[39,109] and that this may occur in nature at very low rates (1.6–3% of field-collected females in Florida[109,122]). However, one study showed that satyrization may occur even without successful insemination.[123] More research is required in order to understand if this phenomenon plays a significant role in the displacement of *Ae. aegypti* in nature.

Displacement of vectors by another species may increase or decrease transmission risk for chikungunya and Zika. In the case of chikungunya, changes in vector species may form the evolutionary pressure for viral adaptation. For this reason, continued surveillance—even of established populations—is crucial to track shifting distributions. In addition, more research is necessary to understand when competition will result in displacement. Interactions of *Ae. albopictus* with other native and invasive species (e.g., *Ae. japonicus* in the United States) is not clearly understood, with varied and conflicting results to date (reviewed in Ref. 124). Identifying the most important behavioral, environmental, and genetic mechanisms driving competition may enable us to better predict range expansion and overlap with native competitors.

Geographical variation in transmission potential

Variation in vector competence. Work in a range of invertebrate–pathogen systems, spanning fruit flies,[125] daphnia,[126] and pea aphids,[127] shows that regional and locale-specific conditions are key to understanding disease transmission. Almost always, both the underlying genetics of the specific host–pathogen combination and the local environmental conditions shape transmission. Existing mechanistic models often use mixed-species data to parameterize transmission models, even though it is well known that important parameters are species specific.[74,128] Evidence from a diversity of systems[129–132] suggests that this assumption may be inappropriate. Different mosquito species, for example, vary in their ability to transmit disease and in their life history, all of which will integrate to differentially affect vectorial capacity. Additionally, transmission potential could vary across populations within a given vector species owing to adaptation to local environments. In the CHIKV and dengue systems specifically, there is growing evidence that variation in vector competence is influenced by both genotype $\times$ genotype (G $\times$ G)[130,133] and G $\times$ G $\times$ environment (G $\times$ G $\times$ E)[134] interactions. Thus, even a single-species approach to parameterizing transmission models may be inappropriate. Insights from these studies suggest that the viral mutation conferring increased transmission of CHIKV in *Ae. albopictus* may not be successful under all environmental conditions. [134] Alternatively, *Ae. albopictus* may become more permissive for *Ae. aegypti*–adapted CHIKV strains in certain environmental contexts. Finally, the above studies demonstrate that relationships constructed among temperature, extrinsic incubation period (EIP), and vector competence that were inferred from other classes of virus or geographically distinct climatic conditions may not be that informative for assessing arbovirus risk in other regions of the world. While less, in general, is known for ZIKV, a recent study demonstrating G $\times$ G interactions in *Ae. aegypti* and *Ae. albopictus* populations suggests that these factors are likely to be important in this system as well.[135]

The above research suggests that, in order to predict relative transmission risk within a given area, more empirical work is required on local mosquito–virus combinations under local environmental conditions. As a first step, more studies could focus on assessing how vector competence and EIP of CHIKV and ZIKV vary with different combinations of viral isolates and *Ae. aegypti* and

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Ae. albopictus populations collected from the field under a wider range of environmental conditions. These data could then be used to assess whether understanding this level of variation improves the transmission-risk predictions of current modeling efforts.

Variation in mosquito life history traits. Interpreting how *Ae. aegypti* and *Ae. albopictus* respond to change generally assumes intraspecific similarity. But disparate field populations become genetically distinct. This can translate to higher fitness in the local environment, which increases disease transmission. Revealing changing population dynamics in specific locations will show how these invasive species respond to novel environments while characterizing local disease-transmission risk.

Diapause in *Ae. albopictus* only exists in some strains, and critical photoperiod (Cpp) varies in relation to climate and latitude. Two studies exposed mosquitoes from North America and Japan to photoperiods and temperatures corresponding to different latitudes. Among Japanese strains, Cpp was adapted to geography. However, the relationship between latitude and Cpp was three times greater in Japan than in the United States.[136,137] This suggests that U.S. populations originated from a temperate Asian strain, and rapid dispersal resulted in populations that were not fully adapted to local conditions. Further experiments found strong clinal variation in diapause within the southern United States, confirming ongoing adaptation.[138] Three studies showed that diapause is a locally adapted trait along a latitudinal cline. Urbanski *et al.*[139] repeated Focks' and Pumpunni's experiments from the 1990s and showed that latitude and Cpp are now similarly related in the United States and Japan. Lounibos *et al.*[140] found that diapause exists within Florida along a cline, and Leisnheim *et al.*[141] showed higher egg-hatch rate for overwintering U.S. northern versus southern strains.

Other intraspecific fitness traits investigated include larval growth,[142,143] adult survival,[144] reproduction and fecundity,[142,144] and overwintering survival.[41] The mixed results from this work generally show that fitness varies between populations, but with no clear underlying spatial pattern. For example, larval development in populations from New Jersey, Texas, and Florida did not vary significantly by region. However, high variation within New Jersey strains overpowered any significance in the differences between regions.[142]

Variation in fitness is rarely studied between different geographic strains of *Ae. aegypti.* Sota and Mogi[145] compared egg-desiccation resistance and found minimal differences between strains, while Mogi[146] found similar results in adult desiccation survival. A study on competitive ability against a single population of *Ae. albopictus* by geographic origin did not find differences between strains.[144]

Research on intraspecific variation in life history for *Ae. aegypti* is almost nonexistent, and for *Ae. albopictus* it has generally been conducted under unrealistic laboratory conditions. It is unclear how often *de novo* adaptations occur, which are the most important drivers of adaptation, or how much gene flow spreads traits between populations. Large-scale population ecology and genetics studies would help predict adaptation as these species' ranges expand and more accurately quantify local disease-transmission risk. Future studies should explore these considerations in more detail, with an effort to understand geographic variation and local adaptation, especially for life history traits most important for estimating R_0.

Insecticide resistance. Insecticides are among the most important tools for controlling Zika and chikungunya vector populations, yet resistance in these mosquitoes is common and has been reported for every class of insecticide used. This topic was reviewed by Vontas *et al.*[147] Resistance to pyrethroids, dichlorodiphenyltrichloroethane, and temephos is widespread among *Ae. aegypti* and has been detected in *Ae. albopictus* populations. The genetic mechanisms of resistance in *Ae. aegypti* is due to mutations (sodium channel *kdr* knockdowns, GABA receptor) and/or overexpression of detoxification or cuticular resistance genes. Studies of the resistance mechanisms in *Ae. albopictus* are mostly inconclusive or report negative results. Significantly more data on common resistance mechanisms in the field, selective pressures, and how variation in resistance leads to mosquito control failures are sorely needed.

Furthermore, what remains somewhat unclear is how insecticide resistance affects the ability of the mosquito vector to transmit pathogens.[148] Owing to variation in the protective responses to different classes of insecticides in resistant mosquitoes,

Table 1. Key barriers and challenges impeding our ecological understanding of the transmission dynamics and vector biology for invasive arboviruses, such as dengue, chikungunya, and Zika

Inadequate understanding of basic mosquito ecology
Inadequate estimates for life history traits and how they vary geographically.
Inadequate tools for age-grading mosquitoes and tracking movement in the field.
Inadequate documentation of genetic diversity of mosquito populations.
Lack of understanding of geographic variation in transmission potential.
Lack of understanding of the role of insecticide resistance on ability of mosquitoes to transmit pathogens.
Lack of understanding of the role of human movement in dissemination of new viruses.
Lack of understanding of mosquito biting behavior in relation to environmental and temporal context.
Inadequate coordination of efforts and resources
Lack of surveillance data showing the current distribution and abundance of *Ae.* vectors in the Americas.
Lack of data sharing between private and public sector vector control.
Lack of broad-scale use of standardized surveillance methods to generate comparable data.
Lack of consideration of socioeconomic and demographic factors in mapping and predicting risk.
Misconceptions about the value and importance of investing research resources and effort in basic mosquito ecology.

the physiological environment that arboviruses experience could be significantly different than susceptible mosquitoes and mosquitoes resistant to different classes of insecticides. This can not only lead to changes in vector competence and pathogen burdens (e.g., malaria[149,150]), but also mosquito life history traits relevant for transmission (e.g., larval development, survival, fecundity, biting rates), mediated through physiological trade-offs with evolved resistant mechanisms. Thus, increases in insecticide resistance do not necessarily correspond to proportional increases in transmission, and this currently unmeasured source of variation could challenge our ability to predict overall transmission potential and the effectiveness of new mosquito-control technologies.

Conclusions/future research/unanswered questions

Important yet unanswered questions remain and serve as barriers for a more complete ecological understanding of the transmission dynamics and vector biology of these invasive arboviruses (Table 1). These unknowns affect our ability to predict and ultimately mitigate the factors influencing transmission risk and arbovirus emergence globally.

First, current modeling efforts for future vector distribution and disease transmission are limited by the low quality and quantity of available data.[134,151] Even in systems that have been relatively well studied (e.g., malaria (*Plasmodium falciparum*), DENV), key parameters are often estimated from just a few data points and are available only for laboratory-adapted vector–pathogen strains.[74] Only recently did our full realization of the artifactual effects of laboratory adaption on vectors and pathogens come into sharp focus. Much of our data on basic mosquito ecology in the field predates 1960, and the mosquitoes themselves, as well as the world they live in, have substantially changed. Nothing highlights this more than the major distributional shifts in U.S. mosquito vectors, with *Ae. aegypti* receding after the introduction of *Ae. albopictus* in the 1980s and the current southward invasion of *Ae. japonicus* in the United States. In addition, we do not have adequate estimates for many of the mosquito life history traits that are important for arbovirus transmission. For example, we do not have good estimates for mosquito life span (progress is hampered by our ability to age-grade mosquitoes in the field), fecundity (which can vary widely among geographic strains and environmental conditions), duration of gonotrophic cycles and biting frequency (critical to understanding EIP and transmission risk), propensity to feed on carbohydrates (e.g., nectar and honeydew, which can alter EIP drivers), variation in host blood sources (potentially altering vector fitness estimates), resting behavior and oviposition site selection (essential for surveillance and targeting control), mating behavior, and dispersal distance across natural landscapes (important for targeting control and understanding

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risk). As a result, predictive models are often forced to include ecologically questionable assumptions. Studying mosquitoes in their natural environment is challenging, but not impossible, and results can lead to much more rigorous estimates of transmission potential. In addition, open-field studies in conjunction with semifield setups can provide more accurate measures in a more controlled setting.

Second, while environmental conditions and vector behavior shape the potential distribution and magnitude of vector-borne diseases, socioeconomic and demographic factors determine the level of human exposure and the realized transmission risk.[152,153] Variation in wealth has been linked to human exposure in multiple vector-borne disease systems across resource-wealthy and resource-poor nations.[154,155] This is due, in part, to changes in mosquito breeding habitats around the home,[156] land cover,[157–161] availability of other food sources,[162–164] access to public health infrastructure (e.g., vaccines and therapeutics),[165] and access to education and to intervention strategies, such as bed nets.[166,167] The proportion of a population of a given age or sex can also influence exposure to vector-borne disease via age-, sex-, or even pregnancy-related differences in human behavior.[166–168] Current mapping efforts, which highlight the transmission risk of CHIKV and ZIKV globally, fail to incorporate these factors.[169,170] Thus, predicting the risk of CHIKV transmission in novel regions requires understanding the relative importance of the environmental and genetic determinants of transmission potential and the interactions among them and the socioeconomic and demographic predictors of human exposure.

Third, we do not have adequate data on the current distributions of potential vector species across much of the world. For example, in the United States, surveillance and mosquito control are often patchy, dictated by the unique demands and resources (or lack thereof) of local communities. This often results in inconsistent trapping methods across geographical regions and areas that are completely lacking in mosquito abundance data. In regions with no public mosquito-control efforts, mosquito control falls in the purview of the private sector, often resulting in a lack of publicly available records on current intervention strategies. Consequently, the scientific community and the federal government have very little capacity to design efficient intervention programs in response to emerging threats or to assess their effectiveness in controlling mosquito vectors and arbovirus transmission. To address these gaps, proactive rather than reactive strategies need to be adopted. Operationalizing a wide-scale surveillance program that utilizes a diversity of standardized mosquito-sampling techniques and methods would generate high-quality and comparable data on both the presence/absence and abundance of current mosquito vectors and would document the arrival and spread of any new invaders. A centralized database where mosquito abundance, virus isolation, sociodemographic, and intervention data could be stored and easily accessed in a standardized way would also be beneficial to integrate with mapping and mechanistic modeling efforts to predict arbovirus emergence and transmission risk. This all needs to be balanced, however, with the protection of individual and community confidentiality.

Unfortunately, the rewards of investing resources into mosquito surveillance and basic mosquito ecology are often perceived as relatively unimportant relative to rewards associated with the development of successful novel vector-control tools, drugs, and vaccines. Perhaps it is time to change this misconception for the benefit of public health. In addition, studies focusing on these efforts often do not survive the funding review process because they are not considered innovative. However, we argue here that we cannot assess the effectiveness of these better-funded technologies in mitigating transmission without a solid understanding of the transmission process, in which mosquitoes and their ecology are integral. We advocate that, in response to current and emerging mosquito-borne threats, it is time to begin funding necessary field-based science in order to address the knowledge gaps currently hindering our ability to predict transmission and enact effective intervention programs.

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Conflicts of interest

The authors declare no conflicts of interest.

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