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SUPPLEMENT ARTICLE

Zika Virus Mosquito Vectors: Competence, Biology, and Vector Control

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Zika virus (ZIKV) (Flaviviridae, *Flavivirus*) has become one of the most medically important mosquito-borne viruses because of its ability to cause microcephaly in utero and Guillain-Barré syndrome in adults. This virus emerged from its sylvatic cycle in Africa to cause an outbreak in Yap, Federated States of Micronesia in 2007, French Polynesia in 2014, and most recently South America in 2015. The rapid expansion of ZIKV in the Americas largely has been due to the biology and behavior of its vector, *Aedes aegypti*. Other arboviruses transmitted by *Ae. aegypti* include the 2 flaviviruses dengue virus and yellow fever virus and the alphavirus chikungunya virus, which are also (re)emerging viruses in the Americas. This mosquito vector is highly domesticated, living in close association with humans in urban households. Its eggs are desiccation resistant, and the larvae develop rapidly in subtropical and tropical environments. Climate warming is facilitating range expansion of *Ae. aegypti*, adding to the threat this mosquito poses to human health, especially in light of the difficulty controlling it. *Aedes albopictus*, another highly invasive arbovirus vector that has only been implicated in one country (Gabon), is an important vector of ZIKV, but because of its wide geographic distribution may become a more important vector in the future. This article discusses the historical background of ZIKV and the biology and ecology of these 2 vectors.

Keywords. Zika; *Flavivirus*; *Aedes aegypti*; *Aedes albopictus*; vector competence.

Zika virus (ZIKV) (Flaviviridae; *Flavivirus*) was considered a generally mild disease until it emerged in French Polynesia in 2013 and more dramatically in the Americas in 2015. It is almost exclusively transmitted by *Aedes* species mosquitoes, and it is neurotropic. These combined characteristics make this virus unusual; biologically it falls between the *Aedes*-transmitted hemorrhagic disease flaviviruses, such as dengue and yellow fever viruses that have nonhuman primates as their vertebrate hosts, and *Culex*-transmitted encephalitic flaviviruses, such as West Nile and St Louis encephalitis viruses, with birds as the amplifying hosts [1]. Therefore, ZIKV does not adhere to the classical separation of flaviviruses by disease association and epidemiology, generally correlated with the phylogenetic relationships among the flaviviruses. Another unusual aspect of ZIKV is its pathogenicity to fetuses, especially during the first trimester of pregnancy. While there are a number of teratogenic viruses, flaviviruses generally do not cross the placenta and cause disease in the developing human fetus.

ZIKV was initially isolated in 1947 from a rhesus macaque monkey caged on a tree platform in the canopy as a sentinel to detect yellow fever virus (YFV) in the Zika forest, Uganda [2]. The virus subsequently was isolated in 1948 from *Aedes africanus*, also from the Zika forest [2]. Isolation of virus from other *Aedes* species, specifically of the *Aedimorphus*, *Diceromyia*, and *Stegomyia* subgenera, in forested habitats include *Ae. africanus* and *Aedes apicoargenteus* (Uganda) [3, 4], *Aedes luteocephalus* (Nigeria) [5], and *Aedes furcifer and Aedes vittatus* (Senegal) [6], and several species have been demonstrated in the laboratory to be competent vectors [7–9].

Outside of Africa, *Aedes aegypti* (Linnaeus) is considered the predominant vector of ZIKV. In 1956, the first experimental studies indicated successful transmission of ZIKV by laboratory-infected *Ae. aegypti* to mice and monkeys [8], demonstrating that this virus could be transmitted in an urban as well as sylvatic cycle. And indeed, in 1966, ZIKV was isolated from this species in Malaysia [10]. In the laboratory, the extrinsic incubation period was estimated to be approximately 10 days, although virus titers remained high in the mosquito through 60 days.

Zika virus was reported to have emerged from its sylvatic cycle to a rural habitat in 2007 when disease was recognized on Yap Island, Federated States of Micronesia, in 2007. The vector is presumed to have been *Aedes hensilli*, the most abundant and widespread *Aedes* species mosquito in Yap State [11]. Although virus was not isolated from any mosquito on the island in spite of attempts made, *Ae. hensilli* has been demonstrated to be an efficient vector [12].

Also in 2007, ZIKV was detected for the first time in *Aedes albopictus* (Skuse), in Gabon, Africa, in an urban environment [13]. This species was first introduced into Africa in 1991, and found for the first time in Gabon in 2007; the same year, not

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only ZIKV, but also chikungunya virus (CHIKV) and dengue virus (DENV) were detected in the country. This finding was especially concerning because of the highly invasive nature of this mosquito species as evidenced by its geographic global expansion in Africa, Europe, and the Americas.

In 2013–2014, ZIKV was introduced into French Polynesia in the South Pacific, leading to an urban outbreak outside Africa for the first time [14]. The origin of this outbreak remains unknown, and the virus spread to other Pacific Islands from there, most likely from infected travelers. The 2 mosquito species thought to possibly be involved in this new location are *Ae. aegypti*, present on Pacific Islands, and the endemic species, *Aedes polynesiensis* [15]. Both species were found to be poorly competent, lending suspicion that other *Aedes* vectors may have been involved. The relatively low viral loads in patients infected with ZIKV with an order of magnitude of 1×10^5 copies/mL compared with 1×10^7 to 1×10^9 copies/mL for CHIKV [16, 17] suggest that vector competence may be critical—that is, the mosquito must be highly susceptible to infection to establish a human–mosquito transmission cycle.

ZIKV IN THE AMERICAS

The focus of attention on ZIKV vectors in the Americas has been on *Ae. aegypti*, the vector of DENV, CHIKV, and urban YFV. This species occurs in 2 distinct forms in its native country, Africa: the feral form, subspecies *formosus*, and the domesticated form, subspecies *aegypti* [18]. It is the latter form that has been inadvertently spread throughout the world, becoming established in receptive environments, specifically tropical and subtropical regions, not only as a consequence of accommodating temperatures in those regions, but also as a result of its highly domesticated nature leading to close association with urban households, and manmade perturbations on the environment. It was first introduced into the Americas in the 16th century. This species arguably poses the greatest threat for transmission of arboviral infections to mankind.

A potential secondary vector and even more invasive species is *Ae. albopictus*, which, like *Ae. aegypti*, is in the subgenus *Stegomyia* and is ecologically similar to *Ae. aegypti*, albeit with significant differences. Until recently, *Ae. albopictus* was found only in the Eastern Hemisphere, but became established in the United States in the mid-1980s [19]. *Aedes albopictus* distribution has expanded dramatically into temperate regions of Europe and North America, currently inhabiting 28 countries beyond its native tropical range in Southeast Asia, and is now found on every continent except Antarctica [20, 21]. A review of the vector status of *Ae. albopictus* (to 2004) examines its role in dengue and other arboviral outbreaks [22]. *Aedes albopictus* was the vector of the first CHIKV outbreak reported in Europe in 2007 when there were an estimated 254 human cases occurring in Italy [23]. CHIKV infection of *Ae. albopictus* was associated with a mutation in the envelope protein gene (E1-A226V), making this species competent. In addition, *Ae. albopictus* has been incriminated as likely the significant vector of ZIKV in Gabon [13] but also may play a secondary role in viral transmission in Mexico in the state of San Luis Potosi, as reported by the Pan American Health Organization/World Health Organization (WHO) in April 2016 [24] and elsewhere. But there is no definitive evidence it is playing a significant role in transmission in the current outbreak (since 2015 to July 2017) in other countries in the Americas. Whether this is due to behavioral differences, life table characteristics, vector competence, or lack of effective surveillance for this species is under study. Understanding this species' biology is critical, as *Ae. albopictus* may become significant vectors of ZIKV in the future if the virus were to adapt to them through genome microevolution as occurred with CHIKV in La Réunion 2005–2006 during the Indian Ocean outbreak [25].

Aedes aegypti and *Ae. albopictus* are holometabolous. Eggs withstand some degree of drying depending on the species, with *Ae. aegypti* eggs more resistant to drying than temperate *Ae. albopictus* [26, 27], giving the former an advantage under dry conditions. *Aedes aegypti* eggs actually need to dry as a stimulus for embryonation. In Florida, *Ae. aegypti* are regaining terrain previously lost to the more competitive *Ae. albopictus* (see below), moving north as temperatures have increased and environments have become drier, favoring their survival. An Australian study demonstrated 2%–15% *Ae. aegypti* egg viability following 1 year of desiccation and viability remaining >88% through 56 days of varying levels of dryness. Intraspecific variations in egg survival times were recorded, suggesting local adaptation [28]. In the laboratory, –3°C for 24 hours was identified as a threshold for viability of *Ae. albopictus* eggs [29].

The eggs hatch when submerged under water. The larvae pass through 4 instars followed by pupation and emergence of the adult. The 2 species share larval habitats where they coexist and experience interspecific resource competition. Larvae of *Ae. albopictus* appear to be more competitive under such conditions [30], giving them an advantage when both species are developing in the same container of water. It has been hypothesized that the increased success of *Ae. albopictus* is due to its ability to feed very quickly and not to stop feeding even in the presence of a predator, thereby selecting for mosquitoes ovipositing in predator-free containers. This seems to be true for both temperate and tropical forms of *Ae. albopictus* [31]. They also seem to be refractory to apparently toxic compounds, possibly because of their association with tires that have noxious leachates [32]. *Aedes albopictus* adults may have an advantage possibly as a result of satyrization, or asymmetric mating interference with *Ae. aegypti* [33]; furthermore, evolved resistance to this phenomenon results in reduced fitness, but the phenomenon appears to be rare in the field [34, 35]. For all these reasons, *Ae. albopictus* appears to be displacing *Ae. aegypti* except under dry conditions where superior egg survival of *Ae. aegypti* gives this species a distinct advantage.

Additional differences in the biology of *Ae. aegypti* and *Ae. albopictus* include life table characteristics, preferred habitat, and feeding and breeding differences. *Aedes aegypti* prefer urban habitats, and breed in any container that holds water around homes, taking blood meals from the inhabitants of these houses after emergence as adults, and often resting indoors. *Aedes aegypti* feeding habits are highly focused on humans, and the females take blood meals frequently (ie, more than once in each gonotrophic cycle), potentially transmitting virus with each blood meal [18, 36, 37]. *Aedes albopictus*, on the other hand, prefer suburban back yards and green parks rather than urban city centers. In addition, their feeding preferences are more catholic—they will feed on domestic animals and such mammals as squirrels and chipmunks as readily as on humans. Faraji and colleagues [38] found that in the northeastern United States, *Ae. albopictus* fed exclusively on mammalian hosts with >90% of their blood meals derived from humans and domesticated pets, and they fed from humans significantly more often in suburban than in urban areas. In southern Thailand, 100% of the *Ae. albopictus* blood meals were human, with a very low proportion of double blood meals [37]. In general, 6%–10% of *Ae. albopictus* blood meals have been reported to be double blood meals from multiple vertebrate hosts [39, 40].

Vectorial capacity, VC = [ma2 (I*T)pn]/–ln(p), incorporates biology of the mosquito and its ability to become infected and transmit virus, including m, the vector density in relation to the host; a, the probability that a vector feeds on a host in 1 day (ie, the host preference index multiplied by the feeding frequency); p, the probability that a vector survives 1 day; n, the duration of the extrinsic incubation period (EIP) in days; I (infection rate) * T (transmission rate) is equal to vector competence (b) or the proportion of vectors ingesting an infective meal that are later able to transmit the infection; and 1/–ln(p) is the duration of the vector's life in days after surviving the EIP. Frequency of feeding on the targeted host (host feeding [a]) is one of the most important components of vectorial capacity. *Aedes aegypti*'s focused feeding habits on humans partially explain the effectiveness of this species as a vector. While the ability of *Ae. aegypti* to become infected with and transmit YFV in Nigeria was demonstrated to be low, they sustained the outbreak due to both frequent blood feeding and high population density [41]. As will be discussed later, *Ae. aegypti* similarly appears to not be a highly efficient vector of ZIKV.

The current distribution of *Ae. aegypti* and *Ae. albopictus* in the continental United States is limited to the selected Atlantic and Gulf states (Figures 1 and 2) [42]. If *Ae. albopictus* were to become a significant vector of ZIKV in the United States through viral adaptation/mutation, as was the case for CHIKV in La Reunion [23, 43], Italy [44], France [45], and Asia [46], the United States and other temperate locations would be at greater risk of ZIKV transmission because the range of this species extends further north than that of *Ae. aegypti*, for example, north to New England and the lower Great Lakes in the United States (Figures 1 and 2). *Aedes albopictus* is increasing its range not only in the Americas, but also in Europe [47]. There have been multiple introductions of this species to the United States, first at the Port of Houston in 1985, and later in the Port of Los Angeles, and differences in genetics of distinct populations can be seen. (D. M. Fonseca, unpublished data). Used tires and "lucky bamboo" are 2 common culprits containing eggs [48]. The invasive success of both *Ae. aegypti* and *Ae. albopictus* [49] has been attributed to the "anthropogenically induced adaptation to invade" hypothesis of Hufbauer and colleagues [50].

Aedes species survive adverse climatic periods in the egg stage; thus, the ability of the eggs to withstand cold and desiccation (discussed above) is critical to perpetuation of the species and continued transmission of viruses such as ZIKV in temperate environments. Both temperate and tropical populations of *Ae. albopictus* have become established in the United States, with the temperate ones being more cold adapted, allowing them to become established in cooler environments. *Aedes aegypti* and possibly *Ae. albopictus* egg survivorship/hatching success is important in understanding and predicting future ZIKV transmission in the temperate environments of North and South America. It is also likely that *Aedes* can gradually adapt to cooler temperatures, which will affect the limits of their ability to expand north in North America, and south, in the Southern Hemisphere, as well as increase their distribution vertically in elevation. One study conducted with a population of *Ae. aegypti* at the limits of its distribution in Argentina, demonstrated larvae completed development during a simulated cold season, with a trend toward increased survival of late-hatching cohorts. Survival was 30% at 13.2°C and >90% at 20°C; development time was 49.4 days at 13.2°C and 17.7 days at 20°C. These levels of success are only meaningful if the emerged adults are able to mate and take blood meals successfully, but the greater success at development under cool conditions than those seen in other studies suggests adaptation to the cooler climate in the country [51].

VECTOR COMPETENCE

The many studies evaluating vector competence of *Aedes* species for ZIKV have been difficult to compare with each other as different populations of *Ae. aegypti* have been used, including both colonized and field populations, different strains of ZIKV, various doses in the infectious blood meal (unnaturally high and lower doses), blood meal presentation, and other differences (Table 1). In general, geographic origin of the virus and vector make a difference; the African strains of virus have been found to be more infectious for *Ae. aegypti* than American strains [52].

Since multiple introductions of *Ae. albopictus* have been suggested in the United States [53], with both temperate and tropical origins, vector competence assays should be conducted with multiple populations, as it is known that there

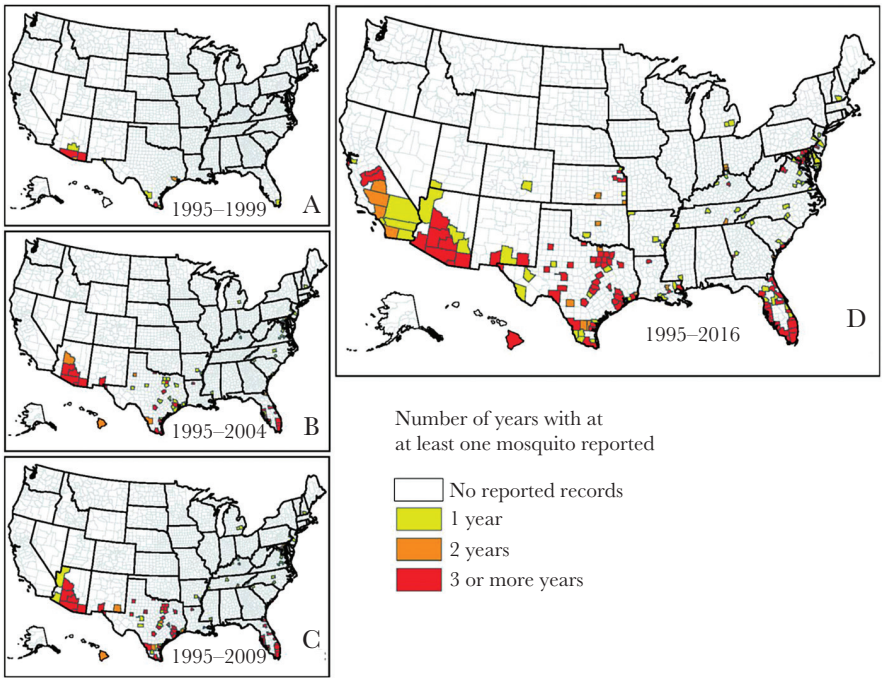

Figure 1. Maps showing the reported occurrence of *Aedes aegypti* by county between 1 January 1995 and March 2016 in the United States. Reported occurrence from 1 January 1995 through 1999 (*A*), from 1 January 1995 through 2004 (*B*), from 1 January 1995 through 2009 (*C*), and from 1 January 1995 through March 2016 (*D*), representing the best knowledge of the current distribution of this mosquito based on collection records. Counties shown in white had no reported *Ae. aegypti* presence records within the specified time period. Counties shown in yellow had *Ae. aegypti* presence records for 1 year within the specified time period, those shown in orange had 2 years of presence records within the specified time period, and those shown in red had ≥3 years of presence records within the specified time period. Adapted from Hahn et al [42].

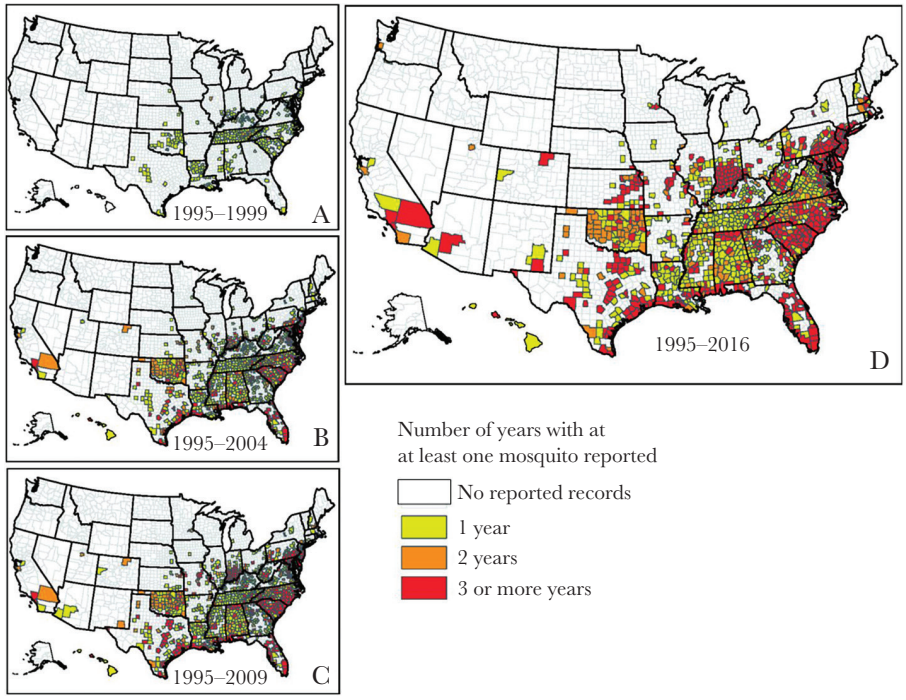

Figure 2. Maps showing the reported occurrence of *Aedes albopictus* by county between 1 January 1995 and March 2016 in the United States. Reported occurrence from 1 January 1995 through 1999 (*A*), from 1 January 1995 through 2004 (*B*), from 1 January 1995 through 2009 (*C*), and from 1 January 1995 through March 2016 (*D*), representing the best knowledge of the current distribution of this mosquito based on collection records. Counties shown in white had no reported *Ae. albopictus* presence records within the specified time period. Counties shown in yellow had *Ae. albopictus* presence records for 1 year within the specified time period, those shown in orange had 2 years of presence records within the specified time period, and those shown in red had ≥3 years of presence records within the specified time period. Adapted from Hahn et al [42].

Table 1. Studies on Vector Competence for Zika virus[a]

	Mosquito vector			Zika virus strain			Vector competence study		
Reference	Species	Origin	History	Strain	Origin	Lineage	Infection Route	Competence	Summary of results
Aliota et al., 2016 [54]	*Ae. aegypti*	Black eyed Liverpool	Lab colony	PRV ABC59	Human, Puerto Rico, 2015	Asian	Murine $10^{6.8}$ PFU 14 di	IR 100, DR 71, TR 24	*Ae. aegypti* and *albopictus* highly competent, *Ae. triseriatus* and *Cx. pipiens* incompetent.
	Ae. albopictus	Missouri 2002	Lab colony					IR 100, DR 67, TR 22	
	Ae. triseriatus	Iowa 2002	Lab colony					IR 31, DR 0	
	Cx. pipiens	Iowa 2002	Lab colony					IR 0, DR 0	
Amraoui et al., 2016 [57]	*Cx. pipiens*	Tabarka, Tunisia 2010	Lab colony	NC-2014–5132	Human, New Caledonia, 2014	Asian	BM; $10^{7.2}$ PFU 3 - 21 dpi (d 14 shown)	IR 0, DR 0, TR 0	*Culex* spp. incompetent
	Cx. quinq.	San Joaquin Valley, CA 1950	Lab colony					IR 17, DR 2, TR 0	
Boccolini et al., 2016 [58]	*Cx. pipiens*	Rome, 2015	Lab colony	H/PF/2013	Human, French Polynesia, 2013	Asian	BM: $10^{6.46}$ PFU 3–24 dpi (d14 shown)	IR 0, DR 0, TR 0	*Cx. pipiens* incompetent. *Ae. aegypti* moderately competent.
	Ae. aegypti	Reynosa, Mexico,1998	Lab colony					IR 50, DR 50, TR 38	
Boorman and Porterfield,1956 [8]	*Ae. aegypti*	Nigeria 1948	Lab colony	MR 766	Monkey, Uganda, 1947	E African	BM, $10^{6.7}$ LD_{50} 60 dpi	IR 100 TR 50	Transmission to mice
Chouin-Carneiro et al., 2016 [113]	*Ae aegypti*	French Guiana	F1	NC-2014–5132	Human, New Caledonia, 2014	Asian	BM 10^{7} $TCID_{50}$ per 0.03 ml 7 & 14 dpi	7 dpi: IR 100, TR 0	At 7 dpi high infection (low dissemination – not shown), no transmission by all vectors tested. At 14 dpi, Ae. albopictus and *Ae. aegypti* exhibited similar low transmission efficiency.
	Ae aegypti	Guadeloupe	F2					7 dpi: IR 87, TR 0	
	Ae aegypti	Martinique	F1					7 dpi I: IR 90, TR 0	
	Ae aegypti	Orlando, Florida	>F10					7 dpi: IR 93, TR nd	
	Ae aegypti	Tubiacanga, Brazil	F1					7 DPI: IR 83, TR nd 14 dpi: IR 77, TR 8	
	Ae. albopictus	Jurujuba, Brazil	F1					7 dpi: IR 23, TR nd	
	Ae. albopictus	Vero Beach, Florida	F7					7 dpi: IR 60, TR 0 14 dpi: IR 50, TR 2	
Ciota et al., 2017 [114]	*Ae. albopictus*	Suffolk, New York	F5-F7	HND 2016–19563	Human, Honduras, 2016, p2	Asian	BM, fresh, $10^{6.6-7.7}$ PFU 21 dpi	HND: IR 93 TR 20 CAM: IR 40 TR 10	*Ae. albopictus* IR≥ *Ae. aegypti*, but transmission efficiency higher for *Ae. aegypti*, indicating a transmission barrier in *Ae. albopictus*
	Ae aegypti	Poza Rica, Mexico	F5-F7	CAM FSS130325	Human serum, Cambodia, 2010, p4	Asian		HND:IR 47, TR36 CAM:IR 44, TR33	
Cornet et al., 1979 [9]	*Ae. aegypti*	Senegal 1971	Lab colony	ArD 24280	*Ae. luteocephalus,* 1976, Senegal	W African	IT dose unknown 7- 28 dpi	TR 91	*Ae. aegypti* highly competent following inoculation
Diagne et al., 2015 [7]	*Ae. aegypti*	Dakar, Senegal	Domestic F1	ArD 128000	*Ae. luteocephalus,* 1997, Kedougou,	W African	BM 6.4–7.6 log_{10} PFU 5–15 dpi (results shown for 15 dpi)	*Ae. aegypti,*Dakar:IR+, DR+ (4 strains), TR 0	All vectors tested were infected by all virus strains and exhibited dissemination with ≥2 strains. Only two vectors were able transmit virus (*Ae. vittatus* with HD 78788 and *Ae. luteocephalus* with MR766).
	Ae. aegypti	Kedougou, Senegal	Sylvatic F1	ArD 132912	*Ae. dalzieli,*1998 Kedougou, p4	W African		*Ae. aegypti* Kedougou: IR+ DR+ (4 strains), TR 0	
	Ae. unilineatus	Kedougou, Senegal	Sylvatic F1	ArD 157995	*Ae. dalzieli* 2001 Kedougou, p6	W African		*Ae. unilineatus:* IR+, DR+ (2 strains), TR 0	
	Ae. vittatus	Kedougou, Senegal	Sylvatic F1	ArD 165522	*Ae. Vittatus*, 2002 Kedougou, p5	W African		*Ae. vittatus:* IR+, DR+ (3 strains), TR 20 (HD787888)	
	Ae. luteocephalus	Kedougou, Senegal	Sylvatic F1	HD 78788	Human, Dakar, 1991	W African		*Ae. luteocephalus:* IR+, DR+ (5 strains), TR 10 (MR 766)	
				MR 766	Monkey, Uganda, 1947	E African			

Table 1. Continued

	Mosquito vector			Zika virus strain			Vector competence study		
Reference	Species	Origin	History	Strain	Origin	Lineage	Infection Route	Competence	Summary of results
Di Luca et al., 2016 [115]	*Ae. aegypti*	Mexico	Lab colony	H/PF/2013	Human, French Polynesia	Asian	BM $10^{6.4}$ PFU 3–21 dpi	IR 40, DR 40, TR 40	*Ae. aegypti* more competent than *Ae. albopictus*
	Ae. albopictus	Italy 2015	Lab colony					IR 20, DR 10, TR 10	
Dodson, et al., 2017 [63]	*An. gambiae*	NIH	Lab colony	MR 766	Monkey, Uganda, 1947	E African	BM, $10^{4.3\text{-}7.7}$ PFU 7–14 dpi (14 dpi shown)	IR 0	*Anopheles gambiae, Anopheles stephensi,* and *Cx. quinq* mosquitoes refractory to Zika virus infection.
	An. stephensi	Johns Hopkins	Lab colony					IR 0	
	Cx.quinq.	Wadsworth	Lab colony	MR 766	Monkey, Uganda, 1947	E African		IR 0	
				PRV ABC59	Human, Puerto Rico, 2015	Asian		IR 0	
Dutra et al., 2016 [116]	*Ae.aegypti*	Urca, Rio de Janeiro, Brazil	Lab colony, wMel neg	BRPE 243/ 2015	Human, Brazil, 2015	Asian	BM, fresh $5x10^6$ PFU 14 dpi	IR 100, DR 100, TR 100	Dramatically reduced infection, dissemination and transmission rates were observed in *Ae.aegypti* mosquitoes naturally infected with Wolbachia bacteria.
			Lab colony, wMel pos					IR 35, DR 10, TR 45	
			Lab colony, wMel neg	SPH/ 2015	Human, Brazil, 2015	Asian	BM, fresh $8.7x10^3$ PFU 14 dpi	IR 95, DR 95, TR ND	
			Lab colony, wMel pos					IR 30, DR 25, TR ND	
Fernandes et al., 2017 [69]	*Cx. quinq.*	Recife, NE Brazil	F1	ZIKVPE243	Human; Recife 2015	Asian	BM $10^{6.36}$ PFU	IR 0	*Cx. quinq.* from areas of SE Brazil were refractory to infection by ZIKV isolates from Brazil. *Ae. aegypti were* highly infected. 100% tested had positive salivary glands. Virus detected in salivary expectorates at level similar to *Ae. aegypti*
				ZIKVSPH2014	Human Sumare 2015	Asian	BM $10^{7.23}$ PFU	IR 0	
				ZIKU1/2015	Human Rio de Janeiro	Asian	BM $10^{6.56}$ PFU 7,14 dpi	7d: IR 5 DR 0 14d: IR 0 DR 0	
	Cx. quinq.	Campina Grande, NE Brazil	F1	ZIKVPE243	Human; Recife	Asian	BM $10^{6.36}$ PFU	IR 0	
				ZIKVSPH2014	Human Sumare 2015	Asian	BM $10^{7.23}$ PFU	IR 0	
				ZIKU1/2015	Human Rio de Janeiro	Asian	BM $10^{6.56}$ PFU	IR 0	
	Cx. quinq.	Rio de Janeiro, SE Brazil	F>10	ZIKVPE243	Human; Recife	Asian	BM $10^{6.36}$ PFU	IR 0	
				ZIKVSPH2014	Human Sumare 2015	Asian	BM $10^{7.23}$ PFU	IR 0	
	Cx. quinq.	Rio de Janeiro, SE Brazil	F1	ZIKVPE243	Human; Recife	Asian	BM $10^{6.56}$ PFU	IR 0	
				ZIKSPH2014	Human Sumare2015	Asian	BM $10^{7.23}$ PFU	IR 0	
	Ae. aegypti	Rio de Janeiro, SE Brazil	F>10	ZIKVPE243	Human; Recife		BM $10^{6.36}$ PFU	IR 68 DR 100	
				ZIKVSPH2014	Human Sumare 2015		BM $10^{7.23}$ PFU	IR 100 DR 100	
				ZIKU1/2015	Human Rio de Janeiro		BM $10^{6.56}$ PFU 7 dpi	IR 75 DR 60	
Guedes et al., 2017 [67]	*Ae. aegypti*	Fernando de Noronha, PE Brazil	F1 - F2	BRPE 243/2015	Human, Brazil 2015	Asian	BM 10^6 pfu 3,7,15 dpi day (15dpi shown)	IR 40 SR 0	*Cx. quinq.* positive salivary glands; virus detected in salivary expectorates at rate similar to *Ae. aegypti.*
	Cx. quinq.	Recife PE,Brazil	CqS Lab colony					IR 39 SR 28	
	Ae. aegypti	Recife PE,Brazil	Rec Lab colony					IR 44 SR38	

Table 1. Continued

	Mosquito vector			Zika virus strain			Vector competence study		
Reference	Species	Origin	History	Strain	Origin	Lineage	Infection Route	Competence	Summary of results
Guo et al., 2016 [66]	*Cx. quinq.*	Hainan province southern China, 2014	Lab colony	SZ01	Human, Samoa, 2016.	Asian	BM, $10^{5.48}$ PFU 2–18 dpi	16d: IR 60 SR 0 (20% SG pos) 10 d: TR 89% mice pos	*Cx. quinq.* transmitted to mice at 10 dpi, but no virus in saliva 16 dpi
Hall-Mendelin et al., 2016 [60]	*Ae. aegypti*	Queensland, Australia	F4	MR 766	Monkey, Uganda, 1947	E African	BM, $10^{6.7}$ $TCID_{50}$ 14 dpi	IR 57, DR 71, TR 27	*Ae. aegypti* competent. Three other Aedes species displayed none -moderate dissemination but no transmission. Three Culex species incompetent.
	Ae. notoscriptus	Queensland, Australia	Field collected					IR 57, DR 0, TR 0	
	Ae. procax	Queensland, Australia	Field collected					IR 33, DR 17, TR 0	
	Ae. vigilax	Queensland, Australia	Field collected					IR 57, DR 27, TR 0	
	Cx. annulirostris	Queensland, Australia	Field collected					IR 0, DR 0, TR 0	
	Cx. quinq.	Queensland, Australia	Field collected					IR 7, DR 0, TR 0	
	Cx. sitiens	Queensland, Australia	Field collected					IR 0, DR 0, TR 0	
Hart et al., 2017 [61]	*Cx. quinq.*	Gulf Coast, US	Lab colony	DAKAR41525	1985 Senegal	W African	BM 10^6 FFU 3–17 dp	IR 0, DR 0, TR 0	*Cx. quinq.* and *Ae. taeniorhynchus* from the US Gulf Coast refractory to infection. In previous experiments, *Ae. aegypti* was competent for these virus strains.
				FSS13025	2010 Cambodia	Asian		IR 0, DR 0, TR 0	
				MEX1–7	2015 Mexico	Asian		IR 0, DR 0, TR 0	
				MEX 1–44	2015 Mexico	Ásian		IR 0, DR 0, TR 0	
	Cx. quinq.	Houston	F2	FSS13025	2010 Cambodia	Asian	BM	IR 0, DR 0, TR 0	
				MEX1–7	2015 Mexico	Asian	Murine	IR 0, DR 0, TR 0	
				PRV ABC59	Human, Puerto Rico, 2015	Asian	Murine	IR 0, DR 0, TR 0	
	Ae. taeniorhynchus	Gulf Coast, US	Lab colony	MEX 1–44	2015 Mexico	Ásian	BM	IR 0, DR 0, TR 0	
Heitmann et al. 2017 [64]	*Ae. aegypti*	Bayer company	Lab colony	FB-GWUH-2016	Travel case (Mexico, Belize, & Guatemala)	Asian	BM 10^7 PFU/ml 14 & 21 dpi (14 dpi shown)	18°C: IR 55, TR 0 27°C: IR49, TR22	Aedes spp. colonies competent only at 27°C at 14 dpi with similar transmission rates. Three Culex species, collected in Germany were not competent for ZIKV.
	Ae. albopictus	Calabria, Italy 2016	F7					18°C:IR 63, TR 0 27°C:IR 71, TR13	
	Ae. albopictus	Freiburg, Germany 2016	F7					18°C: IR 13, TR 0 27°C: IR 65, TR 13	
	Cx. p. molestus	Heidelberg, Germany 2011	Lab colony					18°C: IR 29, TR 0 27°C: IR 24, TR 0	
	Cx. p. pipiens	Hamburg, Germany	Field collected					18°C: IR 47, TR 0 27°C: IR 8, TR 0	
	Cx. torrentium	Hamburg, Germany	Field collected					18°C: IR 31, TR 0 27°C: IR 11, TR0	

Table 1. Continued

	Mosquito vector			Zika virus strain			Vector competence study		
Reference	Species	Origin	History	Strain	Origin	Lineage	Infection Route	Competence	Summary of results
Huang et al., 2016 [55]	*Cx. pipiens*	Anderson, CA	F15	PRV ABC59	Human serum, Puerto Rico, 2015	Asian	BM $10^{6.52}$ $TCID_{50}$ 7 & 14 dpi	7 dp: IR 0, DR 0 14 dpi IR 0, DR 0	*Cx. pipiens* and *Cx. quinq.* incompetent
	Cx. pipiens	Ewing, NJ	F7					7 dp: IR 0, DR 0 14 dpi IR 0, DR 0	
	Cx. quinq.	Vero Beach, FL	F7					7 dp: IR 0, DR 0 14 dpi IR 0, DR 0	
Kenney et al., 2017 [56]	*Cx quinq.*	Florida 1988	Lab colony	MR 766	Monkey Uganda, 1947	E African	BM: 10^6 PFU 14 dpi	IR 1, DR 0	Minimal infection, but no dissemination. IT inoculation to bypass midgut: moderate infection but no transmission except by *Ae. aegypti*
							IT: $10^{6.7}$ PFU 7 dpi	IR 70, TR 0	
				PRV ABC59	Human, Puerto Rico, 2015	Asian	BM: $10^{7.1}$ PFU 14 dpi	IR 0, T 0	
							IT: 10^6 PFU 7 dpi	IR 15, TR 0	
				R103451	Human, Honduras 2016	Asian	BM: $10^{7.6}$ PFU 14 dpi	IR 0, TR 0	
	Cx pipiens	Chicago 2010	Lab colony	MR 766	Monkey, Uganda 1947	E African	BM: 10^6 PFU 14 dpi	IR 5, DR 0	
				PRV ABC59	Human, Puerto Rico, 2015	Asian	BM: 10^6 PFU 14 dpi	IR 10, DR 0	
							IT: 10^6 PFU 7 dpi	IR 61, TR 0	
	Ae aegypti	Poza Rica, Mexico	Lab colony	PRV ABC59	Human, Puerto Rico, 2015	Asian	IT: 10^6 PFU	IR 100, TR 67	
Ledermann et al., 2014 [12]	*Ae. (Stegomyia) hensilli*	Yap Island, Micronesia	F12- F15	MR 766	Monkey, Uganda, 1947	E African	BM, $10^{4.9}$ PFU 8 dpi	IR 86 DR 20 TR nd	*Ae. hensilli* exhibited high infection and moderate dissemination rates.
Li et al., 2012 [117]	*Ae. aegypti*	Singapore	Field	MR 766	Monkey, Uganda, 1947	E African	BM 10^7 $TCID_{50,}$ 1–14 dpi (14 dpi shown)	IR 100, DR 100, TF 100	*Ae aegypti* highly competent.
Richard et al., 2016 [15]	*Ae. aegypti*	Tahiti 2014	F16-F18	PF13/251013–18	Human, French Polynesia, 2013	Asian	Blood meal, 10^7 $TCID_{50}$ 2–21 dpi	IR 85, DR 85, TR 36	Polynesian *Ae. aegypti* highly competent. *Ae. polynesiensis* showed moderate infection and dissemination but no
	Ae. polynesiensis	Tahiti 2014	F16-F18					IR 36, DR 18 TR 0	

Table 1. Continued

	Mosquito vector			Zika virus strain			Vector competence study		
Reference	Species	Origin	History	Strain	Origin	Lineage	Infection Route	Competence	Summary of results
Roundy et al. 2017 [52]	*Ae. aegypti*	Salvador, Brazil	F2	DAK AR 41525	Senegal	W African	BM/murine 10^{4-6} FFU/mL 4–14 dpi (results shown for 14 dpi 10^{6}/mL)	BM: IR 100 TR 100	Transmission highest for Senegal strain. Blood meals from viremic mice were more infectious than artificial blood meals of comparable doses.
				FSS 13025	Cambodia	Asian		BM: IR 75 TR 0 Murine: IR 100 TR 40	
				MEX1-7	Mexico 2015	Asian		BM: IR 75 TR 0	
	Ae. aegypti	Dominican Republic, Caribbean	F6	DAKAR 41525	Senegal	W African		BM: IR 100 TR 100	
				FSS 13025	Cambodia	Asian		BM: IR 100 TR 18	
				MEX1–7	Mexico 2015	Asian		BM: IR 90 TR 20	
	Ae. aegypti	RioGrande Valley, Texas, US	F4	DAKAR 41525	Senegal	W African		BM: IR 100 TR 30	
				FSS 13025	Cambodia	Asian		BM: IR 40 TR 0	
				MEX1–7	Mexico 2015	Asian		BM: IR 65 TR 0	
Weger- Lucarelli et al., 2016 [62]	*Ae. aegypti*	Poza Rica, MX	F11-13	PRV ABC59	Human, Puerto Rico, 2015	Asian	BM, Fresh $10^{6.3}$ PFU 14 dpi	IR 95, DR 92, TR 70	ZIKV efficiently transmitted by *Ae.aegypti* from Mexico. Compared to frozen preparations, blood meals containing fresh virus resulted in higher infection and dissemination rates especially at early dpi. Fresh virus did not infect the three Culex species.
							BM, Frozen 4 hr 10^{72} PFU 14 dpi	IR 95, DR 80, TR 65	
							BM, Frozen 1 wk 10^{72} PFU 14 dpi	IR 60, DR 40, TR 22	
				DAKAR 41525	*AE Africanus*, Senegal, 1984	W African	BM, Frozen 10^{72} PFU 14 dpi	IR 75, DR 60, TR 55	
				PRV ABC59	Human serum, Puerto Rico, 2015	Asian		IR 60, DR 40, TR 25	
				MR 766	Monkey, Uganda, 1947	E African		IR 58, DR 40, TR 37	
	Cx. quinq.	Florida1988	Lab colony	PRV ABC59	Human serum, Puerto Rico, 2015	Asian	BM, Fresh $10^{6.7}$ PFU 14 dpi	IR 0	
	Cx pipiens	Pennsylvania 2002	Lab colony					IR 0	
	Cx. tarsalis	California 1953	Lab colony					IR 0	
	Ae. aegypti	Poza Rica, MX	F11-13					IR 96	
Wong et al., 2013 [118]	*Ae. albopictus*	Singapore	Field	MR 766	Monkey, Uganda, 1947	E African	BM, fresh $10^{7.5}$ $TCID_{50,}$ 10 dpi	IR 83, DR 100, TR 100	*Ae. albopictus* highly competent.

Abbreviations: *Ae.*, *Aedes*; *An.*, *Anopheles*; BM, mosquitoes fed by artificial blood meal; *Cx.*, *Culex*; Cx. *quinq*, Cx. *quinquefasciatus*; d or dpi, day post-infection; DR, dissemination rate, percentage of engorged females with virus in legs, head, and/or salivary glands; ID_{50}, 50% infectious dose; IR, infection rate, percentage infected at 14 dpi unless otherwise stated; IT, intrathoracic inoculation; nd, not done; NIH, National Institute of Health; SR, salivary rate; TR, transmission rate, percentage of engorged females with virus in saliva at 14 dpi unless otherwise noted; murine: mosquitoes infected by feeding on an infected mouse; BM: mosquitoes fed on artificial blood meal; blood meal titers expressed as PFU (plaque forming unit), FFU (fluorescence focus units), $TCID_{50}$ (50% tissue culture infectious dose), ID_{50} (50% infectious dose), per mL; temperature (°C): extrinsic incubation temperature.

[a]Data in Table 1 is the best estimate of IR, DR, TR determined as proportion of all engorged females in the experiment, but because raw data was not available, slight differences from the actual results may be present.

is intraspecific variation. Such variation may be behind the findings that *Culex pipiens* and its sibling species, *Culex quinquefasciatus*, are not competent ZIKV vectors in a total of at least 11 experimental laboratory studies [54–64] among others reviewed in [65]; but *Cx. quinquefasciatus* was demonstrated to transmit to mice when a population from Hainan province of southern China was infected with a 2016 isolate from Samoa [66], and the presence of ZIKV RNA and infectious virus in 3 of 80 pools of *Cx. quinquefasciatus* collected in field studies in Recife, Brazil, a hotspot for ZIKV [68]. In addition, laboratory studies demonstrated the presence of viral RNA in the saliva of perorally infected *Culex* [67, 68]. Other Brazilian scientists differ in their findings, concluding that *Cx. quinquefasciatus* has not played a role in the Rio de Janeiro outbreak; experimental studies with *Cx. quinquefasciatus* from areas with the highest incidence of microcephaly associated with ZIKV infections in the Northeast Region of Brazil demonstrated they are refractory to ZIKV [69]. One possible explanation for the discrepancy in results is mosquito population genetics, which are known to vary for *Cx. quinquefasciatus* populations [70], and virus genetics, which are known to affect vector competence. While this explanation seems unlikely, and *Cx. pipiens*/*Cx. quinquefasciatus* do not appear to play a significant role in ZIKV transmission, one cannot rule out that with some combinations of virus and vector strains, *Cx. quinquefasciatus* may possibly serve as secondary vectors.

VIRUS PERPETUATION

ZIKV is maintained primarily by transmission between humans and *Aedes* species mosquitoes. Some *Aedes* species capable of transmitting ZIKV and other viruses are likely to live year-round across certain tropical areas in the Americas, Africa, and Asia. However, in less suitable habitats, the virus may persist in the environment through alternative mechanisms. While there is no requirement for an enzootic amplification cycle, similar to DENV, CHIKV, and YFV once virus emerges from its sylvatic habitats, sylvatic transmission between nonhuman primates and forest-dwelling mosquitoes may serve to maintain the virus during periods of low urban transmission either due to climatic conditions or to high herd immunity in the human population. Antibody to ZIKV has been detected in other vertebrates besides nonhuman primates in Africa and Asia, but because of extensive cross-reactions among flaviviruses even in serum neutralization assays, these serologic assays are not confirmatory [71]. However, more studies are needed as experimental infections demonstrated susceptibility of diverse vertebrate species. The role of sylvatic virus in directly causing disease in humans is under investigation with DENV [72], and clearly occurs with YFV [73].

Another mechanism of viral maintenance is vertical transmission, which may serve to facilitate maintenance during low transmission seasons/years. Infection of male *Ae. furcifer*, a forest vector, has been reported [6]. ZIKV vertical transmission in *Ae. aegypti* mosquitoes was demonstrated in F1 adults following intrathoracic inoculation, yielding a minimum filial infection rate of 1:290 [74]. These investigators did not observe vertical transmission by *Ae. albopictus* similarly tested. But intrathoracic inoculation is not a natural means of infection. Following peroral infection of *Ae. aegypti* with 8.9–9.3 $\log_{10}$ plaque-forming units/mL ZIKV (Honduras), resulting in >93% disseminated infections, a filial infection rate (FIR) of 11.9 (range, 4.9–24.6) was found, equal to approximately 1:84, a rate higher than that generally observed for flaviviruses. *Ae. albopictus*, similarly tested, was determined to have an FIR of 11.8 (range, 1.7–134.8), thus also capable of vertical transmission [75]. Finally, alternate vectors must be considered as playing a role in maintenance of ZIKV. Little research has been done evaluating mosquito species other than *Ae. aegypti* and *Ae. albopictus*, with the exception of the studies mentioned above on *Cx. quinquefasciatus*.

ABIOTIC FACTORS

Mosquitoes are particularly susceptible to climate variability and climatic change as they are poikilothermic organisms; despite its domestic habits, *Ae. aegypti* is no exception. There have been numerous studies on association between temperature and development, current and future geographic distribution, and population dynamics of *Ae. aegypti* mostly in relation to DENV transmission [76, 77], but also looking specifically at impact on the vector itself [78, 79]. Temperature and precipitation affect both the immature stages of the mosquito, a holometabolus organism with immature stages confined to water-containing environments, and the adult stage. However, adults have a greater ability to survive in ostensibly inhospitable environments by moving to protected areas, (eg, cellars, sewers). That being said, *Ae. aegypti* larvae also have been found to breed very successfully in subterranean habitats, such as wells and service manholes in Australia [80]. Septic tanks in Puerto Rico have been demonstrated to be productive for *Ae. aegypti* larvae [81]. Such protected habitats allow *Ae. aegypti* to maintain DENV during the dry season. The identification of such habitats is especially important as *Aedes* control campaigns are directed at surface habitats primarily. New habitats more biologically accommodating to the vectors are also created by warming climates. For example, *Ae. aegypti* is now found at elevations up to 1420 m above sea level in Mexico, where elevations >1200 m above sea level had been prohibitive in the past [82]. Similarly, Lozano-Fuentes [83] commonly found *Ae. aegypti* at elevations as high as 1700 m, and occasionally from 1700 to 2130 m above sea level, in Mexico.

Other factors besides climate contribute equally, if not more, to increasing risk of infection with viruses such as ZIKV transmitted by *Ae. aegypti*. Such factors fall into social, economic, and epidemiologic groups. Passenger travel has increased

significantly, allowing viremic individuals to travel with increasing speed to receptive environments containing susceptible mosquitoes. The estimated number of passengers flying internationally increased from 227 million in 1980 to 1.2 billion people in year 2016 [84, 85]. It is anticipated that by 2030, the number of people flying across international borders will exceed 1.8 billion per year. Because individuals with DENV, ZIKV, CHIKV, and YFV infections are infectious during the viremic phase for *Ae. aegypti* mosquitoes, these viruses may move even more frequently around the globe in the future. Furthermore, not only human travel, but also increased movement of goods around the world, creates an environment where eggs are transported inadvertently with cargo between regions. The vectors *Ae. aegypti* and *Ae. albopictus* are spreading geographically as a consequence of their invasiveness as container breeders and the ability of their eggs to withstand dry conditions. Anthropogenic changes increase breeding habitats and increase contact between humans and mosquitoes in increasingly dense urban population centers with substandard housing and lacking infrastructure to support the number of people living there.

PREVENTION AND CONTROL

With the continued expansion of DENV and the recent introduction of ZIKV to the Americas, there has been a new impetus for vaccine development and antivirals against flaviviruses. Nonetheless, control of arboviral activity still rests largely with vector control at this time. This is problematic with the growing prevalence of insecticide resistance, particularly to commonly used organophosphates and pyrethroids, as well as carbamates and organochlorines and growing intolerance of the community to the use of such toxic agents, diminishing effectiveness of such intervention strategies. Moyes and colleagues [86] recently provided a comprehensive assessment of the geographical distribution of insecticide resistance in *Ae. aegypti* and *Ae. albopictus*, against the backdrop of environmental suitability for these species [87]. Figure 3 points out the locations of populations that have been bioassayed. This makes control of *Ae. aegypti* and *Ae. albopictus* and the diseases they cause a particularly grand challenge.

In the early 20th century, systematic elimination of *Ae. aegypti* breeding sites successfully led to vector suppression and consequent control of yellow fever [88]. In the 1950s, DDT (dichlorodiphenyltrichloroethane) was used to spray infested containers and solid surfaces to further control *Ae. aegypti* [89]. By the early 1960s, the species was declared absent from 22 countries. But when control efforts ceased, *Ae. aegypti*, which likely had not been completely eliminated by the earlier efforts, reemerged in force repopulating cities in Central and South America. Today, *Ae. aegypti* continues to pose a major public health threat.

The field of vector control is moving forward rapidly with promising new approaches. But the behavior and biology of *Ae. aegypti* and *Ae. albopictus* make these species particularly difficult to control over the long term. Specifically, their propensity to breed in artificial and natural containers in close proximity to people's homes, where in addition the adults have access to protected resting sites, diminishes exposure to treatment. The number, diversity, and distribution of containers make it logistically difficult to treat all existing habitats to eliminate breeding. Furthermore, control of *Ae. aegypti*–transmitted pathogens is exacerbated by this species' habit of feeding often and almost exclusively on human blood, thereby increasing the efficiency of transmission (R0) of each individual female [36].

As a consequence, a broad multifaceted approach to control is needed. With integrated pest management, a combination of methods is applied in concert, addressing prevention of transmission, reduction of the vector population, and the elimination of conditions that lead to mosquito infestations [90]. One aspect of this approach is adoption of personal protection measures by the community, education on *Ae. aegypti* and *Ae. albopictus* habits and on how to prevent mosquito bites, and source reduction. But such effort on its own has not been very successful in controlling disease. Additionally, ultra–low volume sprays and fogging with US Environmental Protection Agency–registered pesticides, generally conducted by mosquito control organizations or companies using aircraft or truck-mounted sprayers, have been used. But this method of control is fraught with problems not only because of indoor resting behavior of the vector, but also insecticide resistance, insecticide persistence in the environment, toxicity of the compounds for nontarget species, and public opinion. While peridomestic and indoor residual spraying may have been successful in the past, this approach is no longer acceptable to most people in an urban environment.

Biopesticides are being used as larvicides to circumvent the problem of resistance to and toxicity of chemical compounds. Examples include microbial control agents—for example, *Bacillus thuringiensis* (Berliner) [91] and *Bacillus sphaericus* Neide [92]—and insect growth regulators such as methoprene, pyriproxyfen, and diflubenzuron, which are chitin synthesis inhibitors [93, 94]. Pyriproxyfen not only inhibits the development of the adult mosquito, but in addition, when an adult mosquito comes in contact with this agent it can inadvertently transfer it to other containers [95]. It has been demonstrated in the field that low doses are effective in inhibiting *Aedes* and the residual activity can be maintained for 11–15 weeks [96]. But in the laboratory, resistance to some chitin synthesis inhibitors develops within a few generations [93]. Excellent thorough reviews on microbial control agents have been published and should be read for comprehensive information (eg, [97, 98], among many others). But it must be kept in mind that any introduced lethal agent, whether chemical or biological, affects the entire ecosystem because of the interdepence of all life.

Physical approaches to mosquito control include lethal ovitraps, insecticide-treated clothing, mosquito coils, and other such measures (see Ogoma and colleagues [99] for a review of spatial repellency testing methodologies). But both cultural and

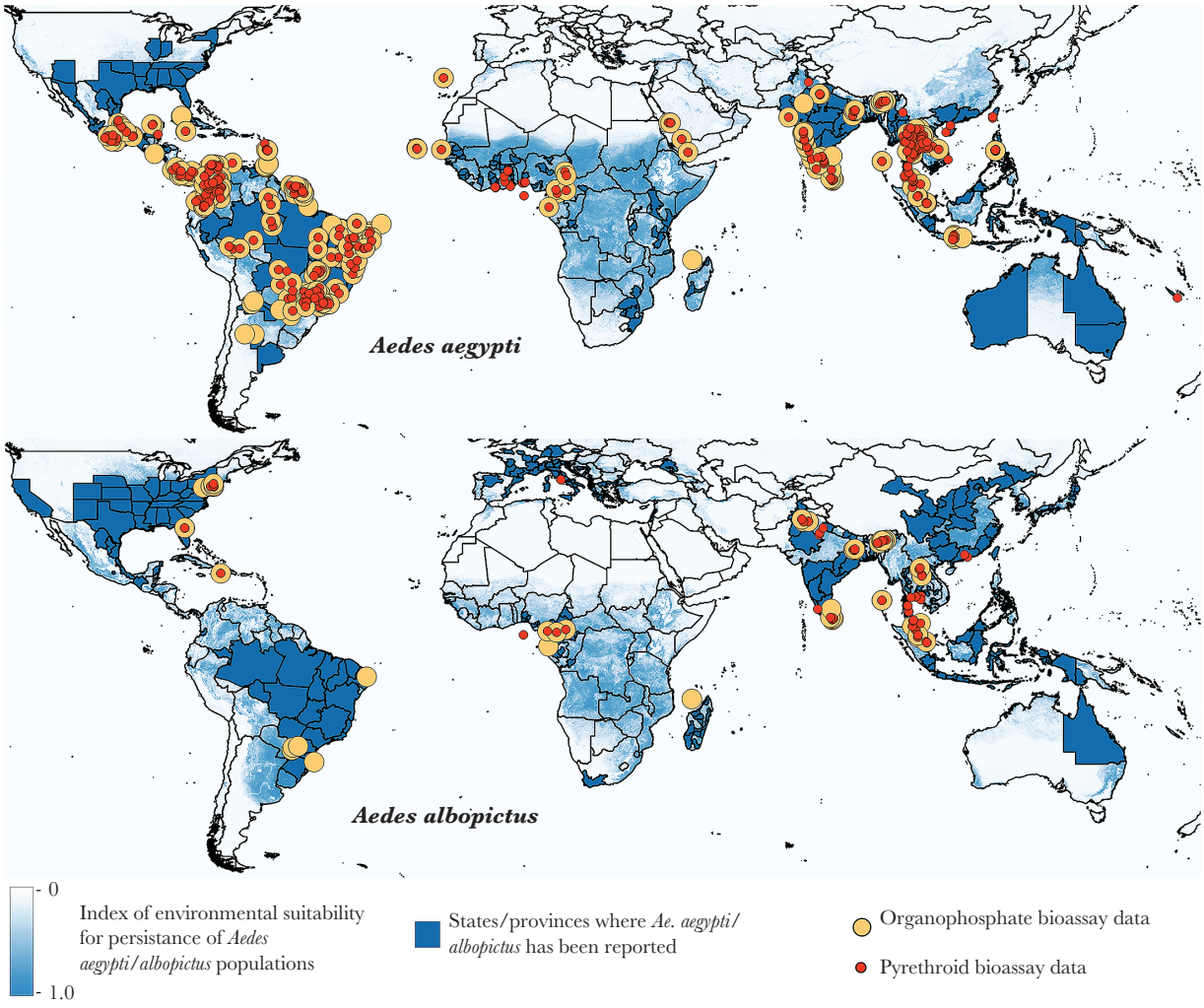

Figure 3. Locations of bioassay data for the organophosphates and pyrethroids, 2006–2015. Locations of populations that have been bioassayed (susceptibility and dose response, adult and larval) are shown for both insecticide classes, overlaid on maps of environmental suitability for *Aedes aegypti* and *Aedes albopictus*. Adapted from Moyes et al [86] and Kraemer et al [87].

biological factors hinder integrated pest management methods, making development of novel methods a priority. To name a few such factors, people are hesitant to allow biological or chemical agents to be added to their drinking water; many breeding sites are cryptic and cannot be easily located; and breeding habitats may be ephemeral, making biological control ineffective.

Exciting novel approaches under development and in trial circumvent chemicals and biologicals and can be incorporated into an integrated vector control program. These approaches attack the adult stage of the mosquito and use the manipulated male mosquito as the delivery vehicle. They include sterile insect technique (SIT) [100], a modification of SIT where genetically engineered males carrying dominant lethal genes (release of insects carrying dominant lethal gene [RIDL]) are released into the wild [101], and release of *Wolbachia*-infected mosquitoes. Each of these approaches will be discussed briefly below.

Sterile Insect Technique

In this autocidal approach to mosquito control, large numbers of irradiated or chemosterilized males are released into the environment where they compete with wild-type males to ultimately suppress the F1 population of that species. Because SIT control is based on mating behavior, this approach is species-specific. But in field tests, the sterilized males lack competitiveness; furthermore, mated females may move into the area and lay eggs, further diminishing effectiveness. Repeated releases of the sterilized males is necessary as the procedure is not self-sustaining, but it is only native species that are being introduced, making the technique environmentally friendly. This technique has been extremely successful in eradicating the screw-worm fly (*Cochliomyia hominivorax*) from North and Central America [102].

Release of Insects Carrying Dominant Lethal Gene

Suppression is basically a modification of the SIT where, in place of irradiation or chemosterilization, a dominant lethal transgene is inserted during the embryonic stage. Its expression is artificially repressed during rearing in the laboratory but functional following release of the engineered males in the wild; any wild female mating with a RIDL male will produce offspring, all of which carry 1 copy of the RIDL system. All the female progeny will therefore die from the female-specific lethality. The male progeny, on the other hand, will survive, and because they carry 1 copy of the RIDL system, half of the next generation's female progeny will die, and so on [101].

Oxitec (Oxitec Limited, Oxford, United Kingdom) has developed its own version of RIDL where the male mosquitoes are engineered to contain a self-limiting gene that causes their offspring to die, but allowing Oxitec insects to live and reproduce normally when they are fed a diet containing tetracycline (in the rearing facility). The self-limiting gene, tTAV (tetracycline repressible transactivator variant), is a gene variant that has been optimized to only work in insect cells. In the wild, offspring that contain the self-limiting gene make a nontoxic protein that ties up the cell's machinery so its other genes are not expressed and the insect dies [103]. Field studies in the Cayman Islands led to a suppression of 80% of the natural population [104] and, in Brazil, a suppression of 78%–95% of the natural population [105].

Wolbachia

Wolbachia is an endosymbiotic bacteria that is naturally found in many arthropod species, with the exception of *Ae. aegypti* [106]. Infection of *Ae. aegypti* with *Wolbachia* has been shown to inhibit DENV and CHIKV replication [107] as well as ZIKV [108]. Contributing further to the effectiveness of *Wolbachia* is the phenomenon of cytoplasmic incompatibility [109], allowing it to spread efficiently in caged populations [110] and in the environment, as demonstrated in Australia with the release of *Ae. aegypti* infected with wMel *Wolbachia*. The frequency of these *Wolbachia*-infected *Ae. aegypti* remained at >90% for 3 years [111] demonstrating that *Wolbachia* is a highly efficient gene drive mechanism.

A pressing question is what level of population suppression of *Ae. aegypti* is necessary for elimination of virus transmission to humans, the target host. Since *Ae. aegypti* may take multiple interrupted blood meals in each gonotrophic cycle, mosquito populations with few infected females may still be effective in maintenance of the virus transmission cycle. Other issues that need to be addressed include lack of acceptance by the community, logistics of release, and certainty that nontarget insects are not harmed.

CONCLUSIONS

Aedes aegypti and *Ae. albopictus* are widely distributed globally and 2 of the most important vectors of human pathogens involved in the transmission of medically important arboviruses such as DENV, ZIKV, CHIKV, and YFV. This review has discussed some of the factors that have contributed to the ecological success of these species, including rapid development, desiccation-resistant eggs, resistance to the principal insecticide classes currently available on the market, preference for the urban environment and consequently proximity to humans, globalization (ie, increase of trade and travel), lack of effective surveillance, and lack of efficient control. Furthermore, *Ae. albopictus* demonstrates ecological plasticity and a strong competitive ability [112]. Relationships between climate and vector ecology and the social, economic, and epidemiological factors involved in virus transmission remain unclear. Models have not accounted for local microclimate effects, leading to difficulty interpreting results. But socioeconomic factors, including adequate healthcare and sanitation, may affect the current geographic distribution and human incidence of many diseases more significantly than climate. Clearly, integrated management approaches to control *Ae. aegypti* and *Ae. albopictus* must be undertaken if there is any hope of controlling these 2 important mosquito vectors.

Notes

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