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Flavivirus transmission focusing on Zika

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Abstract

Flaviviruses are among the most diverse viruses with over 85 species recognized. Taxonomically, this genus is one of the 4 recognized genera within the family *Flaviviridae*. Most flaviviruses of human public health significance, e.g. dengue, yellow fever and Zika viruses, are arthropod-borne (arboviruses) and have two evolutionarily and ecologically distinct transmission cycles: a sylvatic transmission cycle, where the virus circulates between zoonotic vertebrate reservoir and amplification hosts and arboreal mosquitoes; and an urban transmission cycle, where the virus circulates between humans and peridomestic *Aedes* spp. mosquitoes. Zika virus (ZIKV), a flavivirus closely related to West Nile, dengue, Spondweni, Japanese encephalitis and yellow fever viruses, remained in obscurity since its discovery in 1947, but has recently emerged to cause a series of epidemics in the South Pacific, and most recently reaching nearly pandemic levels with its introduction in the Americas. Available epidemiologic and experimental evidence points to *Aedes aegypti* as the principal urban vector, possibly supplemented by *Ae. albopictus* in some locations. Unfortunately, the former is one of the most difficult mosquitoes to control owing to its highly anthropophilic behavior.

Introduction

Zika virus (ZIKV), a flavivirus closely related to West Nile, dengue and yellow fever viruses, remained in relative obscurity since its discovery in 1947 in Ziika (note original forest spelling was inadvertantly changed for the virus) Forest preserve, Uganda [1]. A year later the virus was isolated from arboreal *Aedes africanus* mosquitoes [1] and the first described human cases following ZIKV infection were reported in Nigeria in 1952 [2]. The first direct detection of ZIKV outside Africa and the first evidence of transmission by a domestic (urban) vector occurred when the virus was isolated from *Ae. aegypti* mosquitoes

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in Malaysia in 1966 [3]. A decade later, the first human infections in Asia were diagnosed in Indonesia in patients presenting with fever, malaise, stomach ache and anorexia [4]. However, throughout this time period no estimates of incidence in Africa or Asia were available. In 2007 ZIKV re-emerged to cause a series of epidemics in Africa, Southeast Asia [5–7], and more recently has reached nearly pandemic levels with its introduction into the Americas in 2013 [8,9].

Flaviviruses like dengue (DENV) and yellow fever viruses (YFV), are closely related and remarkably similar in some aspects of their natural history to ZIKV (Figure 1). All belong to the genus *Flavivirus*, family *Flaviviridae*. All of the approximately 80+ recognized species of flaviviruses share an approximately 10.7 kb, single-stranded, positive sense RNA genome, comprising three structural protein genes and seven non-structural protein genes. Species in this genus cluster within one of four major clades based upon the taxonomy of their hosts and their mode of transmission [10–13]: (i) transmission among vertebrate hosts by mosquitoes, (ii) transmission among vertebrate hosts by ticks, (iii) transmission among vertebrates without any known vector (no known vector), and (iv) restricted host range transmission among arthropods (insect-specific) without the involvement of vertebrates. Viruses of public health importance cluster within the mosquito-borne group and belong to a subgroup primarily transmitted by A*edes* spp. mosquitoes. As discussed below, all of these viruses originated in sylvatic, enzootic cycles (Figures 1, 2), in Asia and Africa respectively, maintained in non-human primates and forest-dwelling *Aedes* mosquitoes, and have a history of successful emergence into sustained transmission among humans by *Ae. aegypti* (reviewed in [14–18]).

Transmission Cycles

ZIKV circulation has been documented in two ecologically and evolutionarily distinct transmission cycles: an enzootic, sylvatic cycle, where the virus circulates between arboreal *Aedes spp*. mosquitoes and non-human primates; and a human or urban cycle, between humans and peridomestic/domestic *Aedes spp.* mosquitoes. The former has been documented in Africa [1] and there is indirect and unconfirmed evidence that ZIKV may be circulating in forests of Southeast Asia [19]. Until 2007, our knowledge of ZIKV derived almost exclusively from the sylvatic transmission cycle. The first documented ZIKV isolation was from *Ae. (Stegomyia) africanus* mosquitoes in Uganda [1,20], and subsequently in the Central African Republic [21] (CAR) and Senegal [22] from this species, suggesting its central role as a principal enzootic vector [the other being *Ae. (Stegomyia) luteocephalus*](Figure 2). ZIKV has been also isolated from *Ae. (Stegomyia) opok* in the CAR [21], *Ae. (Stegomyia) apicoargenteus* in Uganda, [23] *Ae. (Stegomyia) luteocephalus* in Nigeria [24] and Senegal [25] and *Ae. (Fredwardsius) vittatus*, *Ae. (Diceromyia) furcifer*, and *Ae. (Stegomyia) aegypti formosus* in Côte d'Ivoire [26] and Senegal [22]. In addition to these mosquitoes, ZIKV has also been isolated from other *Aedine species* [e.g. *Ae. (Aedimorphus) dalzieli*, *Ae. (Aedimorphus) hirsutus*, *Ae.* (*Stegomyia*) *unilineatus*, *Ae.* (*Stegomyia*) *metallicus*], as well as non-*Aedene* species mosquitoes such as, *Anopheles (Meigen) coustani* and *Mansonia (Mansonioides) uniformis*, mosquitoes that inhabit various rural ecotypes. Lastly, there is a report of isolation from a single pool of *Culex (Culex) perfuscus* mosquitoes, an observation that requires further

verification [22]. The isolation of ZIKV from *Ae. (Fredwardsius) vittatus* mosquitoes sampled in an agricultural village within the 'zone of emergence' supports its putative role as a bridge vector of enzootic ZIKV strains into the human transmission cycle [22] (Figure 2).

ZIKV transmission in the urban cycle mainly involves the anthropophilic *Ae. (Stegomyia) aegypti* mosquito, as documented by limited field surveillance [3,4,9] and experimental studies with geographically diverse populations [27–34]; *Ae.* (*Stegomyia*) *hensilli* [35] and/or *Ae.* (*Stegomyia*) *polynesiensis* [7,31] may serve as secondary vectors in niche ecotypes. However, experimental studies have yielded mixed results, with some suggesting relative refractoriness of *Ae. aegypti* mosquitoes [33]. This has led to speculation that other mosquitoes common in tropical cities, such as *Ae. (Stegomyia) albopictus, Ae. (Protomacleaya) triseriatus* [36] and *Cx. (Culex) quinquefasciatus*, could be potential ZIKV vectors.

Aedes (Stegomyia) albopictus [37] was implicated as a vector of peridomestic transmission in Gabon in 2007, and subsequent experimental studies [38] supported the role of Asian *Ae. albopictus* populations as competent ZIKV vectors. *Aedes albopictus* is a highly invasive species, fueled by global trade. This species expanded significantly its global geographic distribution in tropical as well as temperate settings, thus positioning it to become a significant ZIKV vector if conditions permit.

To explain the spectacular global spread of ZIKV, it was suggested that ZIKV underwent adaptive evolution for more efficient urban transmission by *Ae. aegypti* mosquitoes. Although phylogenetic analyses [9,39] suggest that this adaptive evolution could have occurred in Southeast Asia or the South Pacific where the virus has been circulating since the 1960's [3], experimental infections with laboratory colonies [32] or feral populations [34] of *Ae. aegypti* from diverse geographic settings fail support this hypothesis. While both studies have demonstrated that various strains of ZIKV (from either Asian/American or African lineages) have the capacity to infect and replicate in American *Ae. aegypti* populations, none have exhibited an enhanced replicative fitness or virus adaptation to these mosquito populations [32,34]. Thus, the extent and intensity of ZIKV transmission in the Americas may be influenced by other factors, certainly including the immunologically naïve human populations.

Although a perspective publication [40] and unsubstantiated reports in the Brazilian news media suggested that *Cx. quinquefasciatus* mosquitoes may be competent vectors of ZIKV, several peer-reviewed studies utilizing mosquito populations from Brazil [41], Italy [42], Tunisia [43], the U.S. [36,43,44] demonstrated that these mosquitoes as well as *Cx. pipiens* are refractory to ZIKV infection and incapable of transmission. However, a recent report by Guo et al. [45] suggested that Chinese *Cx. quinquefasciatus* are competent vectors in the laboratory setting. While this report contradicts other experimental studies, it is possible that factors such as the mosquito virome and/or microbiome or genetic differences in geographic mosquito populations may contribute to the conflicting results. Also, laboratory vector competence is only meaningful if a mosquito species repeatedly feeds on humans, and

widely divergent results have been obtained by studies of *Cx. quinquefasciatus* feeding patterns [46–49].

In summary, several experimental studies have demonstrated that *Culex* spp. mosquitoes are incompetent vectors of ZIKV transmission, and no evidence of natural transmission during outbreaks in the Americas [9], Southeast Asia [5] and Africa [37] has been reported.

Challenges to vector control

The absence of licensed vaccines and therapeutics indicates that very limited options exist in the short term to control the explosive global spread of ZIKV. The only currently viable methods include reduction of contact between the vector and susceptible humans, and the elimination and/or reduction of mosquito populations. While historical attempts to eradicate *Ae. aegypti* were successful, today they are considered to be environmentally unacceptable due to the highly toxic nature of the persistent insecticides used, such as DDT. Fueled by uncontrolled urban development and weakening of vector control measures, many neotropical cities are now fully reinfested with *Ae. aegypti*, and the prospects for renewed eradication efforts face formidable and probably overwhelming challenges. Reductions in *Ae. aegypti* populations can most feasibly be accomplished by the use of cost-effective approaches such as: community engagement and personal responsibility for eliminating or treating larval habitats, e.g. standing water in flower pots, water storage containers and refuse that holds standing water; use of larvicides to eliminate mosquito larvae from these habitats; application of insecticide aerosols within homes or other places where people are exposed to biting vectors and thus virus infection (although penetration of aerosols applied from trucks or airplanes into indoor resting sites favored by the adult females is challenging); release of genetically modified mosquitoes that express a dominant lethal gene resulting in the death of all offspring from mating with wild females, thus eliminating the risk for persistence of the transgene in nature; release of *Ae. aegypti* harboring the endosymbiotic *Wolbachia* bacteria, which suppress viral transmission by interfering with replication in the mosquito; and use of use of inexpensive and relatively maintenance-free lethal traps (reviewed in [39,50–52]). Collectively all these methods may be faced with logistical, technical and financial challenges and regardless which source(s) of vector reduction are implemented, they will need to be sustained over a long period of time if they are to be successful in reducing the risk of human exposure to human arboviruses.

Conclusion and future directions

Various *Aedine* spp. are the main vectors of ZIKV transmission in either sylvatic or urban transmission cycle, whereas *Culex* species are generally refractory for transmission. Given the recent controversy surrounding the role of *Culex* species in ZIKV transmission, other factors influencing vector competence, such as the mosquito gut mibrobiome and/or virome, should be investigated further. Moreover, the introduction of ZIKV and the explosive epidemic underway in the Americas beg the question whether the peridomestic *Ae. (Stegomyia) albopictus* has a potential role in ZIKV transmission in urban and rural settings, especially in temperate regions where *Ae. aegypti* cannot survive the cold winters. This vector has been implicated in Asia as a potential bridge vector for sylvatic DENV into the

urban cycle (reviewed in [15,53]). Thus could *Ae. (Stegomyia) albopictus* serve as a bridge vector for spillback infections from humans to nonhuman primates, leading to establishment of an enzootic ZIKV transmission cycle in the Americas [54]? Several arboreal New World mosquitoes involved in the enzootic transmission of yellow fever virus, including *Haemagogus albomaculatus, Hg. spegazzini, Hg. janthinomys, Sabethes chloropterus, Sa. albipivus, Sa. glaucodaemon, Sa. soperi,* and *Sa. cyaneus*, *Psorophora ferox* and *Ae.* (*Ochlerotatus*) *serratus* (reviewed in [53]) could serve as enzootic ZIKV vectors and should be evaluated experimentally. Importantly, establishment of a ZIKV sylvatic transmission cycle in the Americas would render future eradication efforts practically impossible, and also might inhibit our ability to control the ongoing outbreak of congenital Zika syndrome.

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Highlights

- Zika virus is a member of the genus *Flavivirus*, family *Flaviviridae*
- Transmitted in two ecologically and phylogenetically distinct transmission cycles
- Vectored mainly by *Aedes spp.* mosquitoes in either transmission cycle
- Its host range recently expanded to include the Western Hemisphere

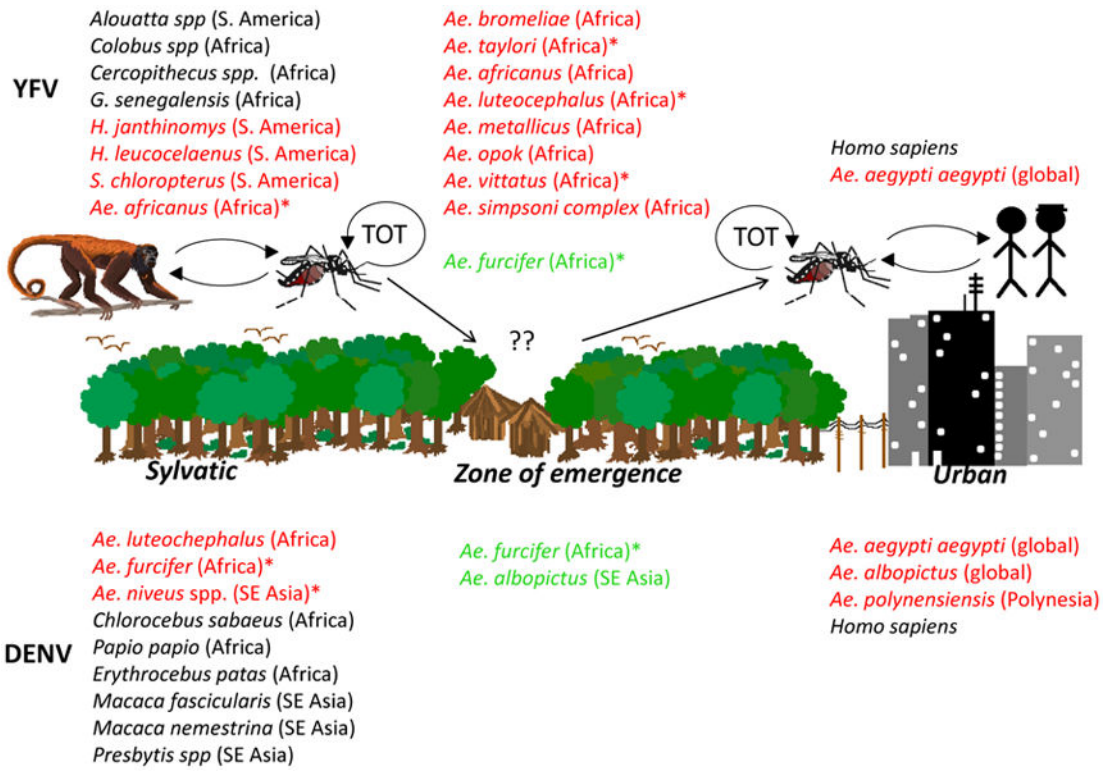

Figure 1.

Transmission cycles of dengue and yellow fever viruses, flaviviruses with significant human health impact. TOT – transovarial transmission; *-indicates major vectors; in red: vectors in either transmission cycle; in green: vectors implicated as bridge vectors

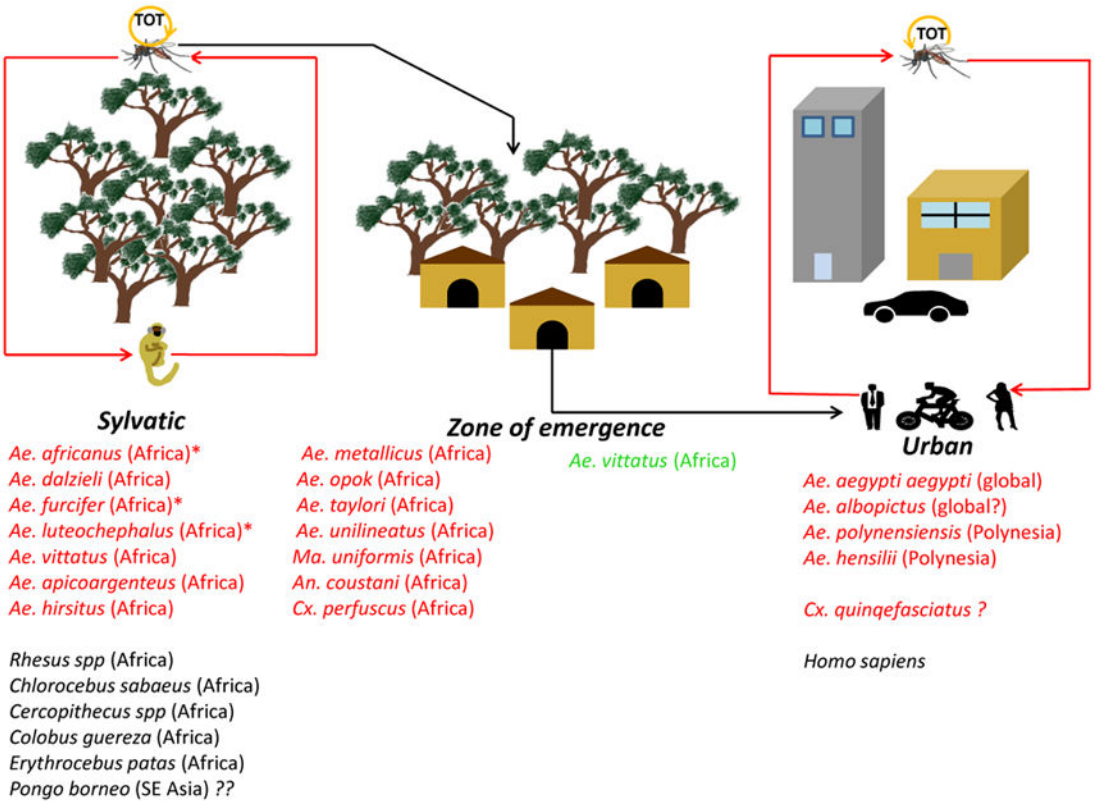

Figure 2.

Transmission cycles of Zika virus. TOT – transovarial transmission; *-indicates major vectors; in red: vectors in either transmission cycle; in green: vectors implicated as bridge vectors