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Vector-borne transmission and evolution of Zika virus

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ABSTRACT:

Zika virus (ZIKV), discovered in the Zika Forest of Uganda in 1947, is a mosquito-borne flavivirus related to yellow fever, dengue and West Nile viruses. From its discovery until 2007, only sporadic ZIKV cases were reported with mild clinical manifestations in patients. Therefore, little attention was given to this virus before epidemics in the South Pacific and the Americas that began in 2013. Despite a growing number of ZIKV studies in the past three years, many aspects of the virus remain poorly characterized, particularly the spectrum of species involved in its transmission cycles. Here, we review the mosquito and vertebrate host species potentially involved in ZIKV vector-borne transmission worldwide. We also provide an evidence-supported analysis regarding the possibility of ZIKV spillback from urban to a zoonotic cycle outside Africa, and we review hypotheses regarding recent emergence and evolution of ZIKV. Finally, we identify critical remaining gaps in the current knowledge of ZIKV vector-borne transmission.

INTRODUCTION

Zika virus (ZIKV) is an arthropod-borne flavivirus related to yellow fever, dengue and West Nile viruses¹. ZIKV was first reported in East Africa in 1947 and expanded from the ancestral enzootic cycle in Africa to Asia several decades ago (Fig. 1). At the beginning of the 21st century, the virus expanded into the South Pacific and the Americas, triggering a pandemic that led to 48 countries reporting active ZIKV transmission by 2017². Prior to this expansion, there was little scientific research on this virus³.

In this paper, we review the natural history of ZIKV and current knowledge about ZIKV vector-borne transmission along with the mosquito and vertebrate host species potentially involved worldwide. Furthermore, we discuss the possibility of ZIKV spillback into an enzootic cycle outside Africa, and we review hypotheses regarding ZIKV recent global emergence and evolution. Finally, we identify research priorities for filling remaining gaps and challenges in our understanding of ZIKV.

Zika Virus Natural History

The virus was first isolated from a sentinel Rhesus Macaque and from *Aedes (Stegomyia) africanus* mosquitoes in the same Ugandan location. Surveillance efforts identified immune people in at least 25 African countries from 1945-2014 (reviewed by ⁴) and in 7 Asian countries or territories from 1952-1997 (Fig. 1). However, many of the serologic tests employed in this surveillance are cross-reactive among flaviviruses, so these results must be interpreted with caution. Nevertheless, direct detection of ZIKV in countries including Senegal, the Ivory Coast, Burkina Faso, Nigeria, the Central African Republic, Uganda, Thailand, Malaysia, Indonesia and the Philippines (reviewed in ⁵) confirmed its widespread distribution for many decades.

The first evidence of possible interhuman urban transmission came from Malaysia in 1966, when ZIKV was detected in the domesticated, anthropophilic mosquito, *Ae. (Stegomyia) aegypti aegypti*. However, between 1966 and 2013, there was no direct evidence of ZIKV transmission by this species, which may reflect limited urban transmission or simply a lack of surveillance and diagnostics to detect endemic or epidemic circulation.

The first ZIKV outbreaks were documented in Gabon ⁶ and Yap^{7,8} in 2007. In 2013, a major outbreak started in French Polynesia involving approximately 100,000 infected persons, and providing the first evidence of severe disease, Guillain Barré syndrome, associated with ZIKV infection⁹. This was followed by spread throughout the South Pacific and eventually to the Americas, where a massive epidemic ensued and congenital microcephaly was first associated with maternal ZIKV infection² (Fig. 1). Millions of ZIKV cases have now been reported from 86 countries, including the expanded forms of congenital infection that comprise congenital Zika syndrome (CZS) and Guillain Barré syndrome²³.

ZIKV VECTORS: EVIDENCE IN THE WILD AND FROM THE LABORATORY

To properly incriminate a ZIKV vector, the virus must be isolated from field-collected mosquitoes, and laboratory studies must ascertain their ability to transmit the virus (vector competence) (Supplementary Figure 1). Field surveys allow investigation of a large number of mosquito species but do not deliver proof of transmission because non-disseminated infections may occur, or residual virus may be detected in a partially digested blood meal. Experimental vector competence studies can demonstrate transmission potential, but practical constraints limit the number of species for which this can be performed, and competent species may not have proper contact with hosts to transmit the virus in nature. Consequently, combined information from both type of study is critical to the definition of the most plausible ZIKV vectors involved in sylvatic and urban transmission cycles (Fig. 2a).

Field Investigations

Our literature search conducted in April 2018 reported 31 wild-caught mosquito species infected with ZIKV worldwide (Supplementary Table 1). These mosquitoes belong to five genera: *Aedes* (22 species), *Culex* (four species), *Anopheles* and *Eretmapodites* (two species each) and *Mansonia* (one species) (Fig. 3). Among the *Aedes* mosquitoes, *Stegomyia* is the major subgenus from which ZIKV has been isolated (9 species). This distribution suggests the *Aedes* genus as the most important mosquito taxon involved in ZIKV transmission. Most ZIKV-infected mosquito species (25) have been caught in sylvatic

settings, while in urban contexts only six species have been reported to be infected with ZIKV: *Ae. aegypti*^{4,10-20}, *Ae. (Stegomyia) albopictus*^{6,11,21}, *Cx. (Culex) quinquefasciatus*^{14,19,22}, *Ae. (Aedimorphus) vexans*¹⁹, *Cx. (Culex) coronator*¹⁹ and *Cx. (Culex) tarsalis*¹⁹. With the exception of *Ae. albopictus* mosquitoes, ZIKV has been detected in salivary gland pools of all of these mosquito species caught in urban settings in Mexico¹⁹. Nevertheless, the viral titers associated with these detections were often not compatible with transmission-competence. To incriminate a vector, ZIKV titers consistent with transmission-competence are necessary, but viral loads have only been measured by quantitative reverse transcription PCR (RT-qPCR) on five occasions, in *Ae. aegypti*, *Ae. vexans*, *Ae. albopictus*, *Cx. tarsalis*, *Cx. coronator* and *Cx. quinquefasciatus* mosquitoes^{14,15,19,21,29}.

Field collection of ZIKV-infected mosquitoes has been performed in fifteen countries: nine in epidemic regions and six in regions with enzootic ZIKV circulation (Fig. 3). The sylvatic species that have been more frequently found infected with ZIKV in the field are: *Ae. (Stegomyia) luteocephalus*, *Ae. (Diceromyia) furcifer*, *Ae. (Aedimorphus) dalzieli*, *Ae. aegypti*, *Ae. africanus*, *Ae. (Fredwardsius) vittatus* and *Ae. (Diceromyia) taylori*. In urban settings, *Ae. aegypti* has been most frequently found ZIKV-infected and is the most widely distributed, with ZIKV detection in Africa, America, Asia and Oceania (Supplementary Table 1). *Ae. africanus*, *Ae. furcifer* and *Ae. luteocephalus* are also broadly distributed in Africa. Finally, 14 species have been reported infected with ZIKV only once: *An. (Cellia) gambiae* s.l., *Ae. (Stegomyia) apicoargenteus*, *Ae. (Diceromyia) flavicollis*, *Ae. (Neomelaniconion) taeniarostris*, *Er. inornatus*, *Er. quinquevittatus*, *Ae. (Neomelaniconion) jamoti*, *Ae. (Mucidos) grahamii*, *Ae. (Aedimorphus) hirsutus*, *Cx. (Culex) perfuscus*, *Ae. (Stegomyia) unilineatus*, *Ae. vexans*, *Cx. coronator* and *Cx. tarsalis* (Supplementary Table 1). Although ZIKV detection in field-collected mosquitoes does not prove their role as vectors, the distribution and frequencies of infected mosquitoes suggest that *Ae. africanus*, *Ae. furcifer*, *Ae. luteocephalus*, *Ae. vittatus*, *Ae. dalzieli* and *Ae. taylori* are involved in sylvatic ZIKV transmission cycles, and *Ae. aegypti* is implicated in urban ZIKV cycles. The latter is supported by anthropophilic and anthropophagic behaviors of *Ae. aegypti* and the high abundance of this species in urban environments nearly throughout the tropics^{24,25}.

Vector competence

Our April 2018 literature survey identified 45 appropriate ZIKV vector-competence studies involving 25 mosquito species: 13 *Aedes* or *Ae. (Ochlerotatus)* spp (*Ochlerotatus* is elevated to a genus by some authors), 8 *Culex* spp. and 4 *Anopheles* spp. (Supplementary Table 1). Eight of these species have been found to be able to transmit ZIKV in laboratory conditions, as infectious virus has been found in mosquito salivary glands or saliva: *Ae. aegypti*, *Ae. albopictus*, *Ae. vexans*, *Ae. (Rampamyia) notoscriptus*, *Ae. (Ochlerotatus) camptorhynchus*, *Ae. vittatus*, *Ae. luteocephalus* and *Cx. quinquefasciatus*.

Among the sylvatic mosquitoes examined, *Ae. vittatus* and *Ae. luteocephalus* were competent ZIKV laboratory vectors, in agreement with the high frequency and distribution of ZIKV-infected specimens from these species found in the field. This suggests their implication in sylvatic cycles in Africa. Outside Africa, many publications have recognized the role of *Ae. (Stegomyia) hensilli* and *Ae. (Stegomyia) polynesiensis* in the Yap Island and French Polynesia ZIKV outbreaks, respectively, because of their high abundances in households^{7,8,30}, although these species have never been found infected in the field^{4,5,31,32}. Vector competence assays have proved their ability to develop disseminated ZIKV infections, but have not confirmed transmission^{7,33}. Thus, further studies are needed in order to fully evaluate the role *Ae. hensilli* and *Ae. polynesiensis* in urban ZIKV cycles.

The *Culex* spp. controversy

Despite field reports of ZIKV infection in four *Culex* species (Fig. 3, Supplementary Table 1) and experimental oral infection assays highlighting that *Cx. quinquefasciatus* is susceptible to ZIKV with viral detection in saliva^{14,34,35}, there are so far no reports of naturally infected mosquitoes during outbreaks with viral loads consistent with transmission-competence. Even if the infection rates of mosquito populations in nature are very low³⁷ - which means that ZIKV detection will be strongly dependent on the study sampling effort - the majority of field investigations where *Cx. quinquefasciatus* mosquitoes were captured did not find any ZIKV infection in this species^{4,6,7,13,15,20,36}.

Vector-borne transmission in natural conditions (known as vectorial capacity) is also determined by the abundance of the vector and its ecological traits, which are quantitatively more important than vector competence (although competence is a requirement for transmission). This may explain why some “poor vectors” can mediate outbreaks regardless of limited vector competence ³⁹. *Cx. quinquefasciatus* are a highly abundant species that sometimes bite humans frequently in urban settings ⁴⁰, which favors the human-vector contact that is critical to vectorial capacity ³⁹ and thus may occasionally transmit ZIKV. Nevertheless, efficient ZIKV transmission by *Cx. quinquefasciatus* would require sequential feedings on human hosts, and this species is more often associated with avian than human bloodmeals ⁴¹. Taken together, the collected evidence suggests that *Culex* species does not play an important role on ZIKV transmission.

ZIKV vertical/venereal transmission reports

Vertical transmission of arboviruses in mosquitoes (from an infected female mosquito to her offspring) has been suggested as a mechanism that ensures maintenance of ZIKV during conditions adverse for horizontal transmission among vertebrate hosts (such as harsh winters, drought conditions, inter-epidemic stages limited by herd immunity), and also as a potential influence on the epidemiology of arbovirus infection ⁴². Vertical or venereal ZIKV transmission has been demonstrated for the mosquitoes *Ae. furcifer* ^{36,43}, *Ae. aegypti* ^{15,19} and *Cx. quinquefasciatus* ¹⁹ under natural conditions, since adult males have been caught infected with ZIKV in the field (Supplementary Table 2). In addition, ZIKV has been detected in *Ae. albopictus* eggs collected in Brazil ²¹, and in adult *Ae. (Stegomyia) bromeliae*, *Ae. unilineatus* and *Ae. vittatus* reared from field-collected eggs (reviewed in ⁵), suggesting the occurrence of natural vertical transmission in these species. Experimental studies have demonstrated vertical ZIKV transmission in *Ae. aegypti* ^{44–46} and *Ae. albopictus* ⁴⁶, while venereal transmission has been observed in both directions (male-to-female and vice versa) in *Ae. aegypti* ^{47,48} (Supplementary Table 2). These findings reveal the complexity of vector-borne ZIKV transmission dynamics (Fig. 2b). Although these inter-vector transmission modes guarantee the spread and maintenance of the virus in vector populations, its contribution to the mosquito-human

transmission chain and epidemiology continues to be a knowledge gap, since no infectious virus has been reported in saliva of vertically or venereally infected female mosquitoes.

ZIKV POTENTIAL HOST SPECIES

Vertebrate animals are also major players in the ZIKV maintenance in nature as ZIKV circulates in a sylvatic transmission cycle between non-human primate hosts and arboreal mosquitoes in tropical Africa ⁴⁹ (Fig. 2a). Our literature review identified 42 publications reporting ZIKV-infected animals, either in natural and experimental conditions.

At least 79 animal species have been identified as naturally infected or experimentally susceptible to ZIKV infection (Supplementary Table 3). Mammals and especially primates are the most represented taxonomic group, although birds, reptiles and amphibians have also been identified, indicating the potential diversity of ZIKV hosts and no clear association between ZIKV and particular animal taxa (Fig. 4, Supplementary Table 3). Among these species, 63 have been found as naturally 'infected', while *Macaca mulatta*, *Cercopithecus aethiops*, *Cercopithecus ascanius*, *Callithrix jacchus*, *Eidolon helvum* and *Capra aegagrus* have been recognized as susceptible to ZIKV infection in both natural and experimental conditions. However, the serological assays generally used to assess ZIKV exposure and susceptibility are of limited specificity and could result in overestimation of the number of species susceptible to ZIKV infection.

The incrimination of such animals in ZIKV transmission chains (either sylvatic or urban) will depend on their viremia levels and duration, their spatial coincidence with competent ZIKV vectors, and the feeding preferences of the latter. So far, viremia levels sufficient for transmission have only been detected in five monkey species (*Macaca mulatta*, *Callithrix jacchus*, *Macaca fascicularis*, *Saimiri boliviensis boliviensis* and *Saimiri sciureus sciureus*) infected experimentally (Supplementary Table 3).

The ZIKV sylvatic transmission cycle between non-human hosts and arboreal mosquitoes has been most thoroughly studied in Africa (Fig. 4), and seroprevalence data suggests that nonhuman primates are important enzootic amplification hosts for ZIKV maintenance. The most intensively studied enzootic ZIKV focus is in eastern Senegal, where annual mosquito collections and periodic nonhuman primate sampling have revealed strong

evidence of regular or continuous arboreal circulation. Interestingly, the same area also harbors dengue, chikungunya and yellow fever viruses with no apparent difference in nonhuman primate amplification hosts or mosquito vectors. However, while the latter three viruses are detected in mosquitoes only periodically in asynchronous 7-8-year cycles, ZIKV is detected more frequently (ca. 4-year cycles)⁴³. This suggests that ZIKV may exploit additional, shorter-lived vertebrate hosts with faster turnover than the three monkey species (*Chlorocebus aethiops*, *Erythrocebus patas* and *Papio papio*) typically found in the Senegalese focus. Unfortunately, knowledge of animal reservoirs is lacking in regions outside Africa, since only four studies have been published on this topic, Brazil⁵⁰, Pakistan⁵¹, Indonesia⁵² and Thailand⁵³ (Fig. 4, Supplementary Table 3). Additional research using appropriate diagnostic techniques on potential zoonotic ZIKV hosts could offer important predictive data about the possibility of enzootic establishment outside Africa. Diagnostic methods allowing determination of viral loads in vertebrate hosts should be privileged, as this information is crucial to know which species can generate sufficient viremia to infect mosquitoes and thus contribute to circulation.

ESTABLISHMENT OF A ZIKV ENZOOTIC CYCLE IN THE AMERICAS

The arboviruses yellow fever (YFV), chikungunya (CHIKV) and dengue (DENV) were introduced to the Americas following European discovery in the late 15th Century. An enzootic transmission cycle has established for YFV in the Americas⁵⁴, but has not been documented for CHIKV⁵⁵ and DENV⁵⁶.

The recent introduction and explosive spread of ZIKV in urban and rural settings throughout the Americas begs the question whether spillback and establishment of an enzootic ZIKV transmission cycle could occur in the Americas. Brazil is home to multiple species of primates and mosquitoes potentially capable of ZIKV transmission, although direct assessment of host competence and vector competence of New World species is currently not known. The probability of enzootic establishment is dependent on host and vector population sizes, host birthrates, and the ZIKV force of infection. We urgently need investigations of the host competence of New World monkeys or other mammals to ZIKV, of the vector competence of sylvatic New World *Aedes*, *Sabethes*, and *Haemagogus*

mosquitoes for ZIKV, and of the geographic range of these potential hosts and vectors. Moreover, independent enzootic circulation is difficult to distinguish from temporary spillback from interhuman transmission unless sufficient divergence between enzootic and human strains can be detected, or epizootics in nonhuman primates suggest the presence of an enzootic cycle. Nonetheless, based on the experience acquired with the enzootic transmission cycle of YFV, the establishment of a ZIKV enzootic cycle in the Americas (or in Asia) could have important implications for the ultimate control of future epidemics, as these cycles are not amenable to human intervention and control.

Transmission in neotropical sylvatic mosquito species

Transmission of ZIKV in urban settings occurs mainly via *Aedes* spp. mosquitoes. However, because of the invasive nature and extensive geographic distribution of *Ae. albopictus* in tropical as well as temperate settings, this species has the potential to become a major ZIKV vector globally. Given that it has been implicated in Asia as a bridge vector for sylvatic DENV movement into the urban cycle [reviewed in ^{56,57}], could this vector serve as the bridge to facilitate reverse spillback and establishment of an enzootic ZIKV transmission cycle in the Americas? Subsequently, a number of New World mosquitoes involved in the enzootic transmission of YFV, 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 ⁵⁷] could serve as competent enzootic vectors of ZIKV and should be evaluated experimentally.

A recent mathematical dynamic transmission model to assess the probability of establishment of a sylvatic ZIKV transmission cycle in non-human primates and/or other mammals, via arboreal mosquito vectors in Brazil, demonstrated a high probability of establishment of enzootic ZIKV across a large range of biologically plausible parameters: mean mosquito lifespan, mean ZIKV recovery in non-human primates (NHPs), mosquito vertical transmission and rate of yearly ZIKV introduction ⁴⁹. Whether ZIKV will emulate YFV (neotropical enzootic establishment) or DENV (lack of evidence for neotropical enzootic transmission) is an open and critical question. If ZIKV establishes a sylvatic cycle in the Americas (or in Asia), then mosquito control and even human herd immunity from

vaccination (if a ZIKV vaccine becomes available) or limitation of transmission from demographic turnover will not suffice to eradicate it from the region.

Transmission in neotropical NHPs

There are more than 190 species and subspecies of non-human primates in South America, of which a large number live in the Amazon Basin in proximity in some cases (e.g., Saimiri) to human activities ⁵⁸. This diversity underscores the need for data on their susceptibility to ZIKV infection to predict potential future circulation in an enzootic cycle as well as re-emergence into the human transmission cycle.

In 2015, a serosurvey conducted in diverse ecotypes from Ceará State, Brazil, which at the time was a ZIKV-epidemic area, sampled sera and oral swabs from fifteen marmosets (*Callithrix jacchus*) and nine capuchin monkeys (*Sapajus libidinosus*). Four ZIKV-positive samples from marmosets and three positives from capuchin monkeys were identified ⁵⁰ (Supplementary Table 3). Subsequent sequencing of amplified products indicated that they were identical to ZIKV strains circulating epidemically at the time, suggesting that they could serve as reservoirs for enzootic transmission. In addition, recent experimental ZIKV infections of marmosets reproduced key features of human ZIKV infection and viremia titers were near the necessary threshold for transmission ^{59,60}.

Another study characterized the dynamics of ZIKV infection in neotropical squirrel (*Saimiri* spp.) and owl monkeys (*Aotus* spp.)⁶¹ (Supplementary Table 3). Viremia was observed in both species in the absence of detectible disease and seroconversion occurred by day 28. This experimental study confirms the susceptibility to ZIKV infection of two New World NHP species living in close proximity to humans in South America, suggesting that they could support a neotropical enzootic ZIKV cycle. However, it remains to be experimentally validated whether the observed viremia is sufficient to infect sympatric sylvatic mosquitoes (host competence) and whether the New World arboreal enzootic mosquitoes have the ability to become infected with ZIKV and transmit upon subsequent feedings (vector competence) to susceptible NHPs.

ZIKA VIRUS RECENT EMERGENCE AND EVOLUTION

Evolutionary studies of Recent ZIKV Spread

The first direct phylogenetic studies of ZIKV were reported in 2012, when Haddow et al.²⁸ analyzed the genomic sequences of six ZIKV strains and found that they grouped by geographic origin, suggesting that African and Asian lineages diverged over long periods of isolation. Because the closest relative, Spondweni virus, is found only in Africa, the authors concluded that ZIKV originated on that continent. More extensive analyses of ZIKV strains dating from 1968 to 2002, collected in several locations of Africa, suggested at least two independent introductions into West Africa during the 20th century, and the possibility of recombination there¹⁷. However, the extremely limited ZIKV sampling, especially in East Africa since the 1950s, suggests that sampling bias affects such phylogeographic analyses.

Since the arrival of ZIKV in French Polynesia and the Americas, major phylogenetic analyses using much larger strain numbers have provided detailed understanding of patterns of its spread and evolution. ZIKV was introduced from somewhere in Southeast Asia into French Polynesia, followed by spread both eastward and westward in the South Pacific, presumably by infected air travelers. Introduction into the Americas from French Polynesia is estimated to have occurred in late 2013⁶², followed by a period of undetected circulation in Northeastern Brazil in early 2014. Dissemination to other parts of the Americas occurred subsequently before the first Brazilian outbreak was detected in early 2015⁶³ (Fig. 1). The rapid spread throughout the South American continent seems to have been enhanced by the warm temperatures associated with the 2015 appearance of El Niño, perhaps through stimulation of mosquito biting rates and shortening the ZIKV extrinsic incubation period⁶⁴. The subsequent explosive spread of ZIKV throughout the Americas facilitated its spread eastward, reaching Cape Verde in late 2015⁶⁵. In addition, ZIKV cases have been detected in Guinea Bissau⁶⁶, Angola⁶⁷, Senegal and Nigeria⁶⁸, but the lineage of the concerned strains has not been yet determined. The most detailed study of ZIKV introduction and spread into new territories comes from Florida in the U.S., where an estimated 4-40 introductions (mainly from the Caribbean) seeded local transmission that probably began in the spring of 2016⁶⁹.

Emergence Mechanisms of urban ZIKV transmission

The broad distribution and abundance of *Aedes* spp. vectors (especially domestic *Ae.*

aegypti)²⁴, coupled with the inefficacy of traditional vector control measures, are key elements in ZIKV emergence⁷⁰. Poverty and inadequate or damaged infrastructure, deforestation and urbanization are factors that favor mosquito larval development sites, human-mosquito contacts and thereby ZIKV transmission^{71,72}. In addition, human movement and intercontinental air travel has expedited the spread of vector-borne diseases^{71,73–75}. Nevertheless, the impact of these socio-economic and environmental factors on vector-borne transmission are a common feature for all emerging mosquito-borne viruses and they do not explain the absence of ZIKV urban epidemics before 2007.

An intuitive explanation for the emergence of urban ZIKV transmission and congenital Zika syndrome was a change in ZIKV phenotypes coincident with its spread into the South Pacific and Americas. This hypothesis was suggested following the observed vector-adaptive evolution of the Indian Ocean lineage of chikungunya virus, which allowed it for the first time to exploit *Ae. albopictus* as a major urban vector via a series of envelope glycoprotein substitutions that enhance transmission by this species⁷⁶. Could a similar phenomenon explain the massive urban amplification and spread of ZIKV? Or could the pathogenicity of ZIKV have changed coincident with this spread, for example selected by increased viremia for transmission by peridomestic mosquitoes, which might also enhance fetal infection? Comprehensive sequencing and phylogenetic studies like those above have also been used to identify recent mutations in the ZIKV genome that might be associated with altered pathogenicity or urban vector transmission to explain the explosive nature of recent outbreaks and the lack of evidence for such epidemics in the past. Two approaches have been used to determine if such mutations, several of which were traced to ZIKV spread into the South Pacific and the Americas⁷⁷ could have encoded critical phenotypes responsible for epidemic emergence and congenital disease.

Hypothetical emergence mechanism 1: adaptation for Transmission by Urban Vectors.

Urban vector-adaptive evolution has been identified as a major factor in the emergence of two other viruses with origins in nonhuman primate-arboreal mosquito vector enzootic cycles: dengue and chikungunya viruses. Although no overall increase in urban vector transmission efficiency has been linked to emergence of the human transmission cycle⁷⁸, the Asian lineage of dengue virus-2 (DENV-2) evolved for more efficient transmissibility

by *Ae. aegypti*⁷⁹, and this phenotype has been linked to its replacement of the less transmissible, and also less human-virulent American DENV-2 genotype⁸⁰.

A mechanism for subgenomic flavivirus RNA (sfRNA)-mediated enhancement of flavivirus transmission by mosquitoes has also been suggested⁸¹. Substitutions in the 3'UTR (untranslated region) from DENV genome have led to higher amounts of sfRNA in *Ae. aegypti* salivary glands, which resulted in increased DENV infection rates and loads, as well as in suppression of mosquito immune response in in this latter organ⁸². Similar results have been obtained using the West Nile virus-*Cx. pipiens* model⁸³, suggesting a potential role of sfRNA produced by the host metabolic machinery as a driver for ZIKV transmission.

The most striking example of vector-adaptive evolution by an arbovirus is CHIKV repeated emergence events and spread which since 2004. One explanation for this dramatic spread is the adaptation via a series of mutations⁸⁴ of one CHIKV strain, the Indian Ocean Lineage, for efficient midgut infection and transmission by the highly invasive mosquito, *Ae. albopictus*, never before implicated as an important vector. Surprisingly, these mutations have little or no impact on infection of the primary vector, *Ae. aegypti*, in most locations, and do not affect infection of *Ae. albopictus* in the genetic backbone of CHIKV strains circulating in the Americas⁷⁶.

The first evidence of potential *Ae. aegypti*-adaptive ZIKV evolution came from work examining the flavivirus non-structural glycoprotein NS1 substitution that enhances infection of this species⁸⁵. Starting with natural isolates that differ by an Alanine versus Valine residue at position 188 showed that a strain encoding Valine imported to China from the Americas generated higher levels of NS1 in the blood of infected mice as well as in the supernatant of infected cell lines. The strain encoding V188 also infects the Rockefeller colony of *Ae. aegypti* more efficiently, and NS1 spiked into artificial bloodmeals recapitulates this finding. However, other studies with ZIKV strains differing in these NS1 residues have not revealed comparable differences^{86,87}. Additional studies with wild mosquito populations (the Rockefeller colony is many decades old, and colonization is known to affect the susceptibility of mosquitoes to arboviruses) are needed to further evaluate the importance of NS1 change. Interestingly, the V188 residue

is also present in African ZIKV strains, suggesting it was lost upon the introduction into Asia many decades ago, possibly the result of a founder effect.

Hypothetical Emergence Mechanism 2: ZIKV adaptive evolution in vertebrate hosts

Vertebrate-adaptive evolution has been identified as a possible factor in the emergence of DENV. Southeast Asian genotype of serotype 2 and genotype III of serotype 3 have been associated with higher viremias in humans, leading to severe dengue disease but also to higher transmission rates by susceptible *Aedes* spp. mosquitoes^{80,88–91}. Duplication of an adaptable RNA element has been suggested as a possible mechanism of sustaining high viral fitness for a virus that cycles between hosts⁹². However, when mechanisms of human DENV emergence due to host range expansion of sylvatic strains by adaptation to use humans as reservoirs (via increased magnitude of replication) were evaluated in two surrogate models of human infection, there were no significant differences suggesting that the historical emergence of DENV from the ancestral sylvatic transmission cycle into human cycles may not have required adaptation to replicate in humans as reservoir hosts⁹³. In a similar manner, the rate of evolutionary change and pattern of natural selection are similar among endemic and sylvatic DENV, suggesting that the dynamics of mutation, replication and selection are broadly equivalent for DENV across its host range⁹⁴, and thus the potential for additional zoonotic virus emergence into the human transmission cycle is high.

The explosive global spread of ZIKV has been hypothesized to be attributed to adaptive evolution for efficient urban transmission in humans. A number of phylogenetic studies^{62,95} have suggested that adaptive evolution may have occurred in Southeast Asia. The Asian ZIKV lineage may have adapted to generate higher viremia levels in humans, leading to increased efficiencies in mosquito infection, transmission and spread. Higher viremia could then enhance transplacental transmission in humans, which could explain the dramatic emergence of microcephaly in the Americas. Some bioinformatic studies suggested an increase in the use of human codons by the virus, which may support the notion of adapted evolution in humans^{17,96,97}. In addition, one study⁹⁸ showed that a single serine-to-asparagine substitution [Ser17→Asn17 (S17N)] in the ZIKV structural protein prM increased infectivity in both human and mouse neural progenitor cells, leading to

more severe microcephaly in the mouse fetus. However, this potential link will require comprehensive longitudinal studies in humans and/or animal models, which will be difficult to test, because various animal models may not respond to ZIKV infection in the same manner as humans. To date, the lack of solid evidence of adaptive evolution in humans, suggests that a combination of stochastic factors and selective evolution may have contributed to ZIKV's global emergence and spread.

CONCLUSION

Ae. aegypti is the principal vector in urban ZIKV transmission worldwide, while other broadly distributed *Aedes* species may act as ZIKV vectors in specific environments where their abundance is important. However, information about ZIKV titers in mosquitoes consistent with transmission-competence is still scarce, resulting in difficulty in assessing their specific roles in transmission. Another important knowledge gap that deserves more investigation concerns the contribution of vertical and venereal transmission in mosquito-human transmission.

The NHPs are the most important enzootic amplification hosts for ZIKV maintenance in the sylvatic cycle, although other orders of animal species appear to be susceptible to ZIKV infection. However, there is scarce information on the viremia levels that these potential hosts can develop, which limits a complete comprehension of their contribution to ZIKV transmission. In addition, the knowledge of sylvatic species' competence (both vectors and hosts) to transmit ZIKV in the Americas and Asia is still limited. Despite these gaps, the evidence collected in the wild and the lab suggest a high probability of establishment of enzootic ZIKV in the Americas, which could make impossible its eradication from the region. Finally, the conducted studies regarding ZIKV-adaptive evolution in vectors and vertebrate hosts suggest that a combination of stochastic factors and Darwinian evolution may have contributed to ZIKV's global emergence and spread.

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AUTHOR CONTRIBUTIONS

GGB, LAP, MR, JB, RLO, SW, NV and AVR participated in data acquisition, analysis and interpretation. GGB, AVR, SW and NV wrote the paper. AVR conceived the study. All authors revised and approved the final manuscript.

COMPETING INTERESTS STATEMENT

The authors declare that no competing financial interests.

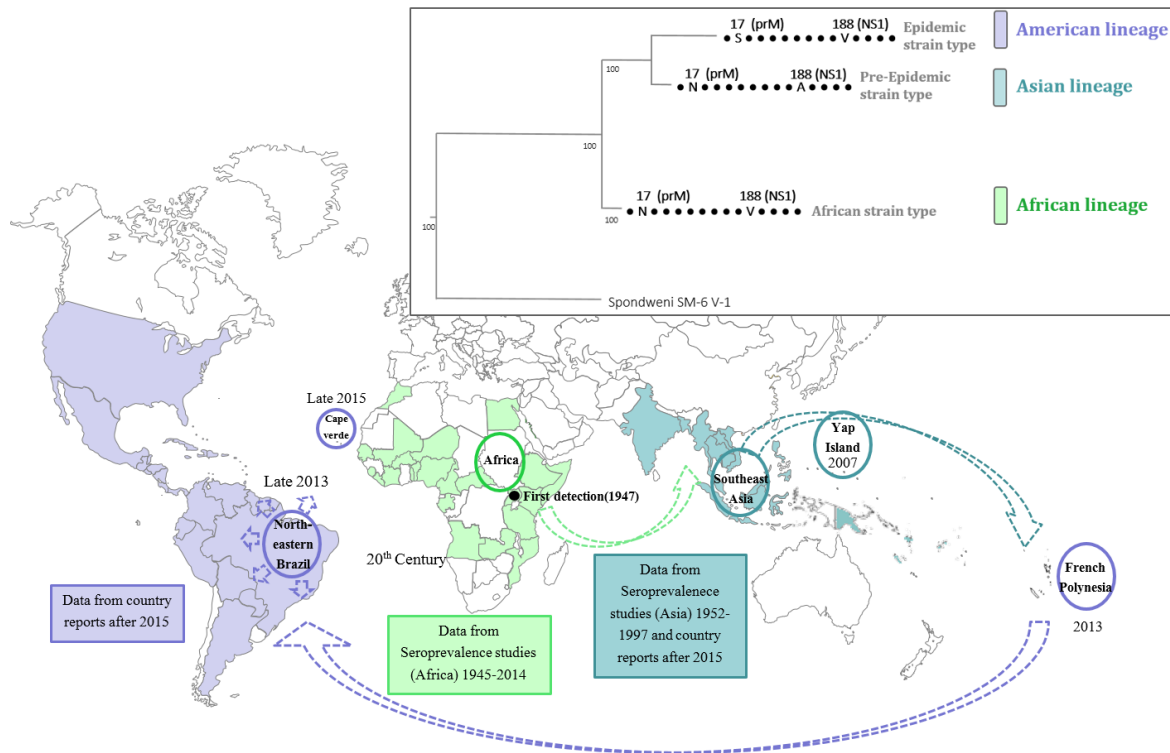


Figure 1. **Emergence and evolution of Zika virus vector-borne transmission.** Zika virus was first detected in Uganda in 1947. Seroprevalence data suggests the virus was present in Africa and Asia from the 1950s, and spread to the Pacific and the Americas from 2013 onwards. There are three recognized lineages of Zika virus (African lineage, green; Asian lineage, blue and American lineage, purple), characterized by key pre-epidemic and post-epidemic mutations, shown on the phylogeny.

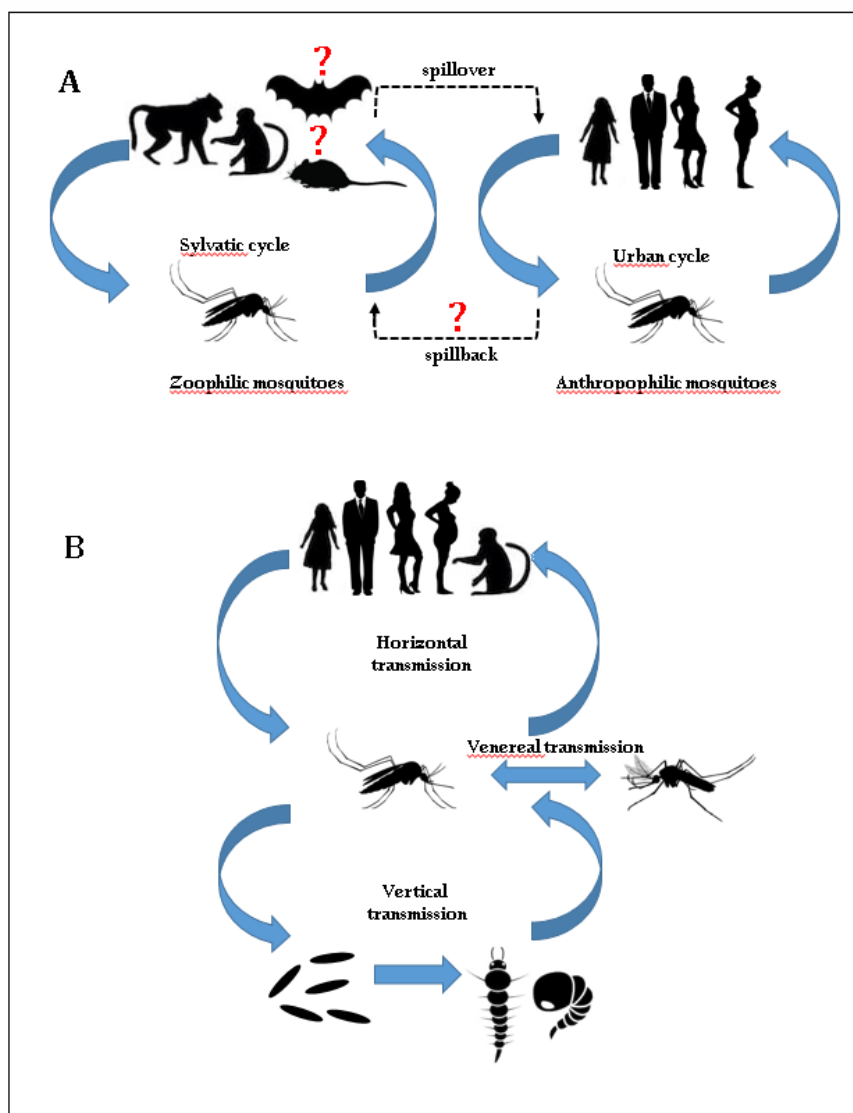


Figure 2. **Zika virus vector-borne transmission.** A: Horizontal transmission of ZIKV occurs in two distinct cycles: a sylvatic cycle where the virus circulates between animal vertebrate hosts (i.e. probably non-human primates) and zoophilic mosquitoes, and an urban cycle where the virus is transmitted to humans by highly anthropophilic mosquitoes (such as *Ae. aegypti*). B: Vector-borne transmission of ZIKV occurs via three main patterns: horizontal transmission between vertebrates and vectors, vertical transmission from and infected mosquito female to its progeny, and venereal transmission from an infected female to a mosquito male and vice versa.

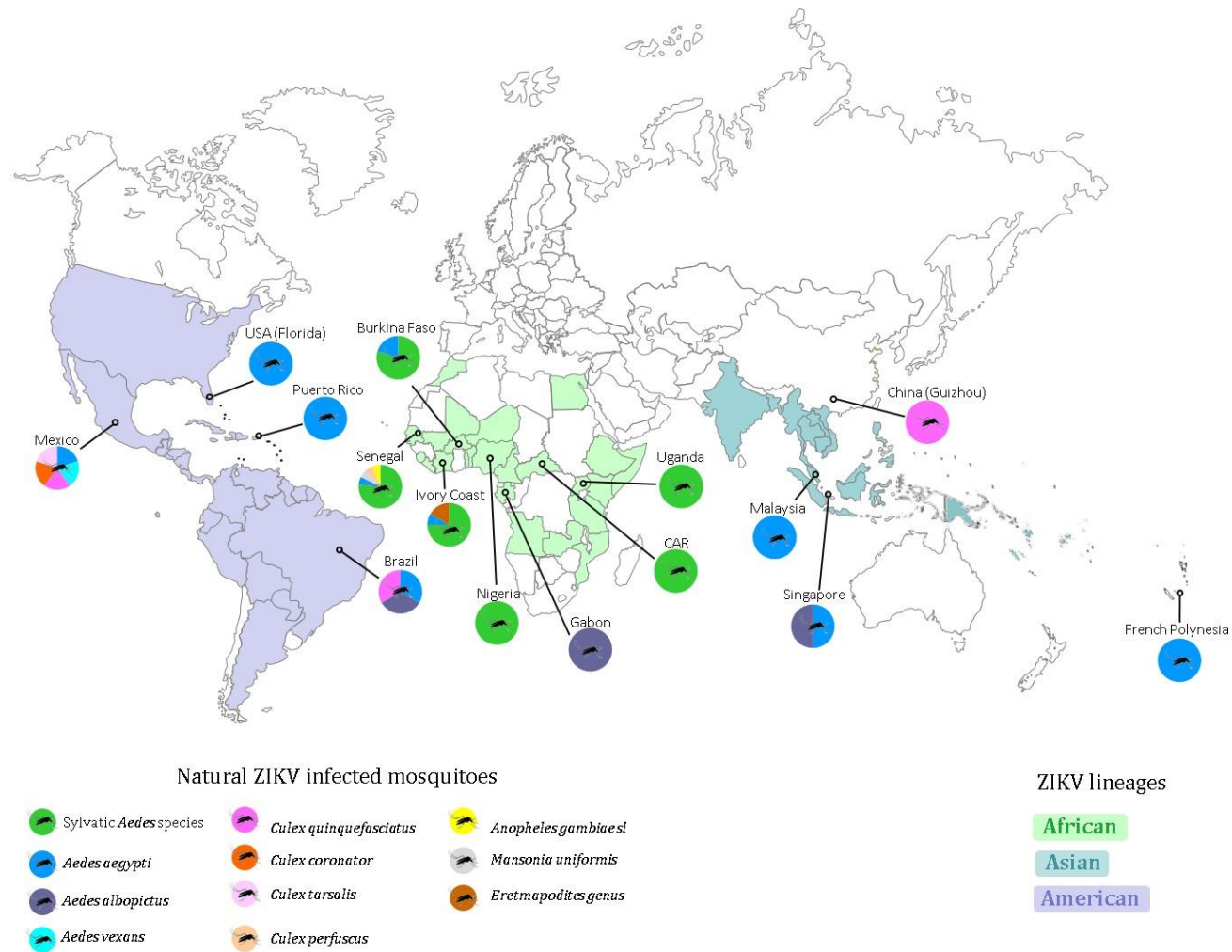


Figure 3. **Distribution of vector species naturally infected with Zika virus.** The color-code used for countries/territories represent the Zika virus lineages that have been epidemiologically associated with human infections in those regions.

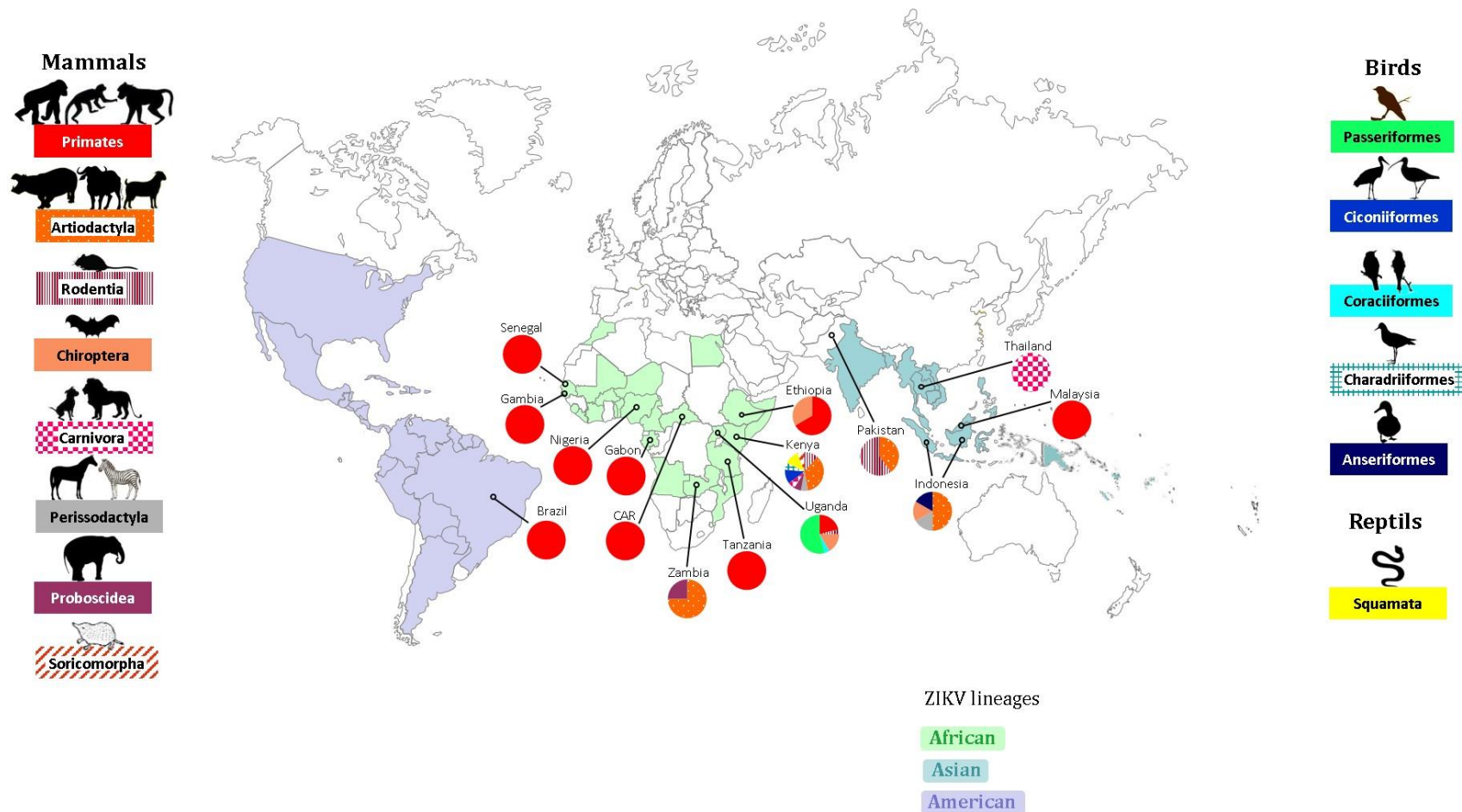


Figure 4. **Distribution of host orders reported as susceptible to Zika virus in natural conditions.** The color-code used for countries/territories represent the Zika virus lineages that have been epidemiologically associated with human infections in those regions (serological assays have been the tests used to assess ZIKV exposure and susceptibility in 87.1% of animals sampled in the field).