SUPPLEMENT ARTICLE

History and Emergence of Zika Virus

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Zika virus was discovered in East Africa in 1947 by the Rockefeller Foundation during investigations on the ecology of yellow fever. Although it was subsequently shown to have widespread distribution in Africa and Asia, it was not known to cause epidemics until 2007. This paper describes the history of the virus discovery, emergence and evolution as an epidemic virus, and the its evolving clinical spectrum.

Key words. *Aedes aegypti*; GBS; microcephaly; mosquito; Zika.

DISCOVERY AND EMERGENCE

The confirmation that yellow fever (YF) was caused by a virus and was transmitted to humans by a mosquito resulted indirectly in the discovery of Zika and many other arboviruses by the Rockefeller Foundation YF program (reviewed in detail by Schwartz [1]). In brief, Zika virus (ZIKV) was first isolated in 1947 from a febrile sentinel rhesus monkey (no. 766) held in a cage on a platform in the canopy of the Zika Forest in Uganda during studies to identify the vector of sylvatic YF [2]. A blood sample from this monkey was collected on day 3 of fever and was inoculated intracerebrally into Swiss mice and into another rhesus monkey (no. 771). All mice showed signs of illness on day 10 postinoculation, and a filterable transmissible agent was isolated from the brains of these sick mice. Monkey 766 showed no other clinical signs or symptoms, and monkey 771 remained asymptomatic. The convalescent serum from both monkeys (766 and 771) neutralized the virus isolated from monkey 766 in mice, which was designated ZIKV 766. Preinfection sera from these monkeys did not neutralize ZIKV 766.

A few months later, another strain of ZIKV was isolated by inoculating mice with the homogenate from a pool of *Aedes africanus* mosquitoes collected in the same area of the Zika Forest [2, 3]. That virus strain was designated ZIKV E/1. The E/1 virus was also inoculated into a rhesus monkey (no. 758), which remained asymptomatic, but convalescent serum from this monkey neutralized ZIKV E/1. Both ZIKV 766 and ZIKV E/1 were neutralized by the convalescent serum from monkeys 766 and 758 showing that the 2 viruses were the same.

There is some controversy surrounding the first ZIKV isolate from humans. The first report was from serum of a 10-year-old Nigerian female in 1954 [4]. The patient was clearly jaundiced, but interpretation of the clinical presentation was complicated by coinfection with malaria. In cross-neutralization tests with convalescent sera from monkeys infected with Bunyamwera, Bwamba, Mengo, Ntaya, Semliki Forest, Uganda S, West Nile, YF, and Zika viruses, only the serum from the monkey infected with ZIKV neutralized the virus isolated from the patient, strongly suggesting the girl was infected with ZIKV. It was subsequently reported that the Nigerian isolate was more closely related to Spondweni virus (also called CHUKU) [5–7]. These events were recently summarized by Wikan and Smith [8] who suggest that the first case of confirmed human ZIKV infection occurred in Uganda in 1962–1963 [9]. Whether the Nigerian virus was Zika or Spondweni will have to await further study using new molecular technology. However, subsequent studies have documented that ZIKV does occur in humans and mosquitoes widely in West Africa [10–12].

Outside of Africa, ZIKV was isolated for the first time from mosquitoes (*Aedes aegypti*) in 1966 in Malaysia [13], but human infections in Asia were not reported until 1977 in Central Java, Indonesia [14]. However, serosurveys conducted in the 1950s, 1960s, and 1970s strongly suggested that ZIKV had a widespread geographic distribution in both tropical Africa and Asia [3]. Unfortunately, the extensive cross-reactivity among the antibodies produced by infection with closely related flaviviruses [3, 15–18] makes interpretation of serological results difficult, but more specific neutralization tests and virologic studies on humans, nonhuman primates, and mosquitoes have confirmed widespread circulation of ZIKV in these regions [3, 19–22]. Collectively, the data suggest that silent ZIKV transmission among humans, animals, and mosquitoes has occurred throughout tropical Africa and Asia for more than 70 years. Significant events in ZIKV history are summarized in Figure 1.

During the first 60 years of its known existence, epidemic ZIKV was never reported, and fewer than 20 human infections were recorded during this extended period of silent transmission [3]. Assuming the earlier serological data were correct,
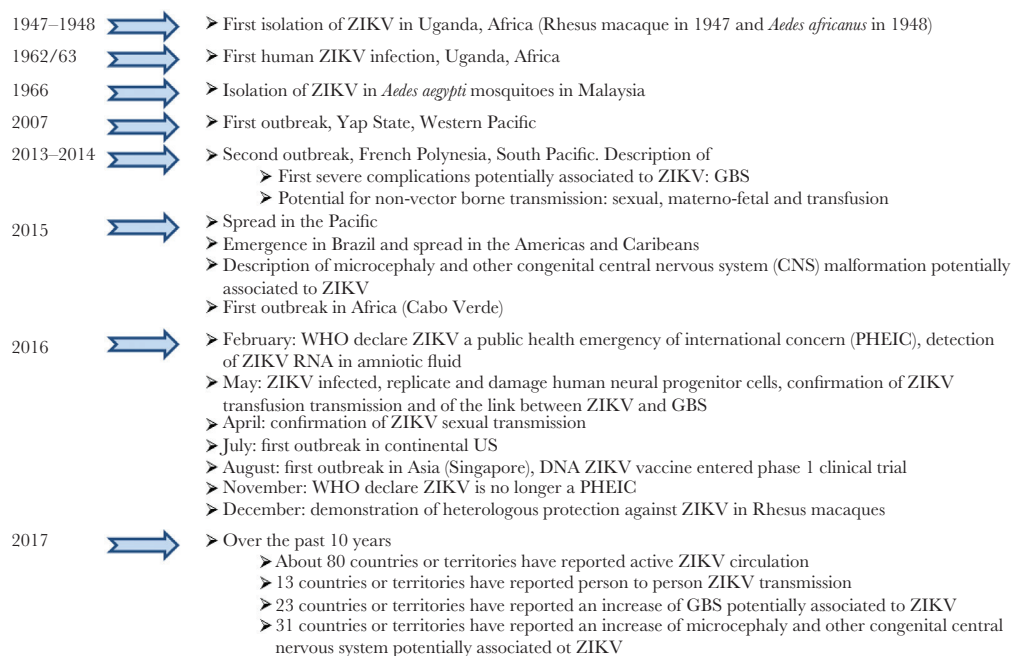
Figure 1. Significant events in the history of Zika virus (ZIKV). Abbreviations: DNA, deoxyribonucleic acid; GBS, Guillain-Barré syndrome; RNA, ribonucleic acid; WHO, World Health Organization.

it is likely that sporadic human cases of ZIKV infection have occurred for decades but were unrecognized or misdiagnosed as dengue, Japanese encephalitis, West Nile, or one of the many other flaviviruses, other viruses, bacteria, and parasites that are enzootic or endemic in these regions. That being the case, then why has epidemic ZIKV emerged in recent years? The definitive answer to that question will have to await more detailed epidemiologic, ecologic, and virologic studies, but current understanding of factors responsible for emergence of other *Aedes*-transmitted viral diseases that have similar epidemiology or ecology suggests that, similar to dengue and chikungunya, genetic changes in the virus likely resulted in emergence of a virus strain with increased transmissibility leading to greater epidemic potential and perhaps virulence [23–31]. As with dengue and chikungunya, emergence and spread of ZIKV was probably facilitated by the global demographic, social and technological trends of population growth, unprecedented urbanization and globalization, combined with lack of effective mosquito control in urban areas, which provided conditions for the "perfect storm", leading to increased transmission and spread of the viruses and their mosquito vectors [32, 33].

The first known ZIKV epidemic occurred in the isolated islands of Yap, Federated States of Micronesia, located in the Western Pacific [34] (Figure 2), when an epidemic of dengue-like illness was reported in April–May 2007. Although dengue had occurred there earlier [35, 36], local physicians suspected a different etiology because of atypical clinical presentation in some

patients. Ross River virus was suspected, but this was ruled out at the University of Hawaii (D. J. G., unpublished data, 2007). Samples were sent to the Centers for Disease Control and Prevention (CDC) Arbovirus Diagnosis and Reference Laboratory (Fort Collins, CO) where ZIKV infection was confirmed [37]. The outbreak was relatively small (approximately 5000 infections, approximately 75% of the population), and all reported illness was mild [34].

No further epidemic ZIKV transmission was reported until October 2013 when cases of ZIKV were reported in French Polynesia, a South Pacific territory [38], while in Southeast Asia only sporadic transmission was occurring [39]. A major epidemic occurred in 2013/2014 involving all French Polynesian islands with more than 30 000 cases, some with neurologic complications [40–42] (see below). The virus spread to New Caledonia, the Cook Islands, Easter Island, and to the rest of the South Pacific [43]. Zika virus is still circulating in the Pacific in 2017 (CDC web site: https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika). The latest data suggest the virus was introduced into Brazil as early as 2013 or 2014 [44, 45] from the Pacific, but the disease was not recognized until November 2015, when a major epidemic of neurologic disease in new born babies occurred, with a second peak in April 2016 [3, 46–49]. From Brazil, ZIKV spread rapidly throughout the American region [49].

In Asia, 2 outbreaks have been reported in Singapore [49, 50] and Vietnam [51], but widespread transmission has occurred in
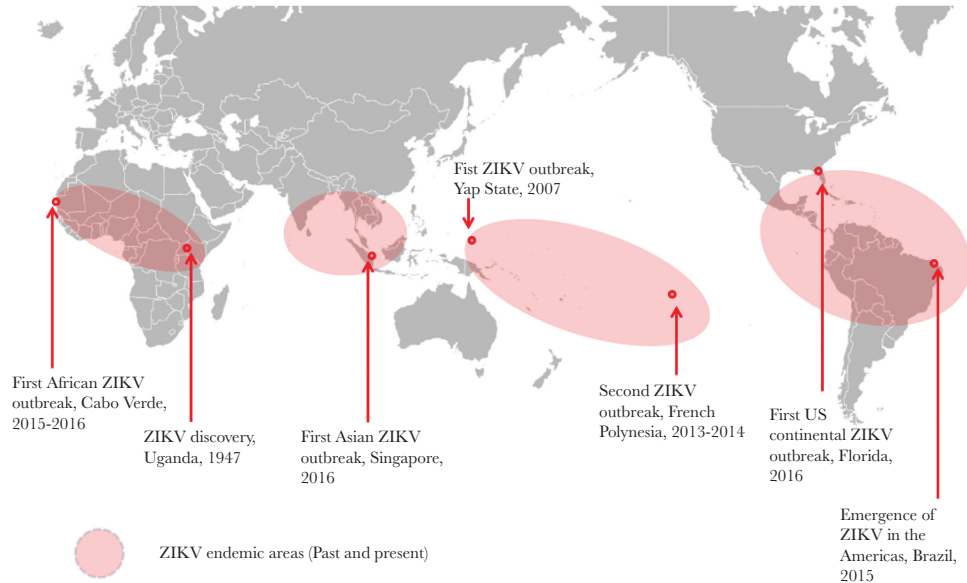
Figure 2. Geographic regions where Zika virus (ZIKV) is enzootic/endemic and has caused epidemics.

Thailand as well (Thailand Ministry of Public Health, unpublished data, 2017), and sporadic cases of ZIKV infection have occurred in 10 countries since 2007 [50, 51]. The first epidemic in Africa occurred in Cabo Verde in 2015–16, apparently the result of introduction from Brazil [52]; from 2007, over 80 countries have reported active transmission of ZIKV [49, 52].

EVOLUTION OF ZIKA VIRUS

The rapid geographic radiation of ZIKV in the past 3 years is consistent with a pattern of intense diversification ("boom and bust" period) (Figure 3), fueled, as noted above, by the explosive and rapid human movement by modern transportation, urbanization, poor water management, and vector control, and facilitated by large immunologically naive human populations and the global spread of the anthropophilic mosquito vector, *Ae aegypti*. The fundamental basis of ZIKV genetic diversity can be attributed to its error-prone ribonucleic acid (RNA)-dependent RNA polymerase, which does not have proof-reading capacity and is thought to produce approximately 1 mutation per round of genome replication. Analyses based on selective pressures, represented as the ratio of nonsynonymous to synonymous substitutions (d_N/d_S) per site, suggest that the majority of DENV mutations are deleterious and subject to strong purifying selection ($d_N/d_S << 1$) [53]. However, genetic variation and population diversity probably played a role for ZIKV to occupy and adapt to new and changing ecological niches and selective pressures.

Current analyses based on 93 complete genome sequences reinforce the hypothesis that ZIKV originated in Africa and diverged into 3 major lineages: African, Asian, and American

(Figure 3). The African strains fall into 2 distinct groups: (1) the Uganda cluster, which is anchored by the prototype strain MR766 and includes isolates from Senegal and Central African Republic sampled from 1947 to 2001; and (2) the Nigeria cluster, which includes strains isolated in Nigeria and Senegal from 1968 to 1997. It is interesting to note that at least 2 distinct lineages are circulating in Senegal (blue and green lines, Figure 3), suggesting multiple introductions, likely fueled by trade routes [54]. It is worth mentioning that most of the known African lineage strains to date were isolated from enzootic vectors, reflecting continuous surveillance efforts in Senegal [54]. The Asian cluster is anchored by the P6-740 strain isolated in Malaysia in 1966 from *Ae aegypti* and includes strains isolated in Cambodia, Thailand, Micronesia, French Polynesia, and the recent introductions in Japan, China, Australia, and Singapore, supporting the presence of the Asian lineage throughout Southeast Asia. Within this cluster, a new American lineage has emerged and includes strains from Brazil, Colombia, Ecuador, Panama, Mexico, Honduras, Venezuela, the Dominican Republic, Puerto Rico, Haiti, Guatemala, United States, and Suriname, as well as Italy and China, reinforcing the role of modern transportation in the rapid spread of these viruses on a global scale.

Recent reports have suggested ZIKV recombination between field isolates [55] or with Spondweni virus [56]. Evidence for recombination among members of the genus *Flavivirus* has been reported mainly in dengue virus ([DENV] reviewed in reference [56]). Despite concerted efforts, however, recombination has not been achieved experimentally, and thus caution should be exercised when inferring conclusions about these putative
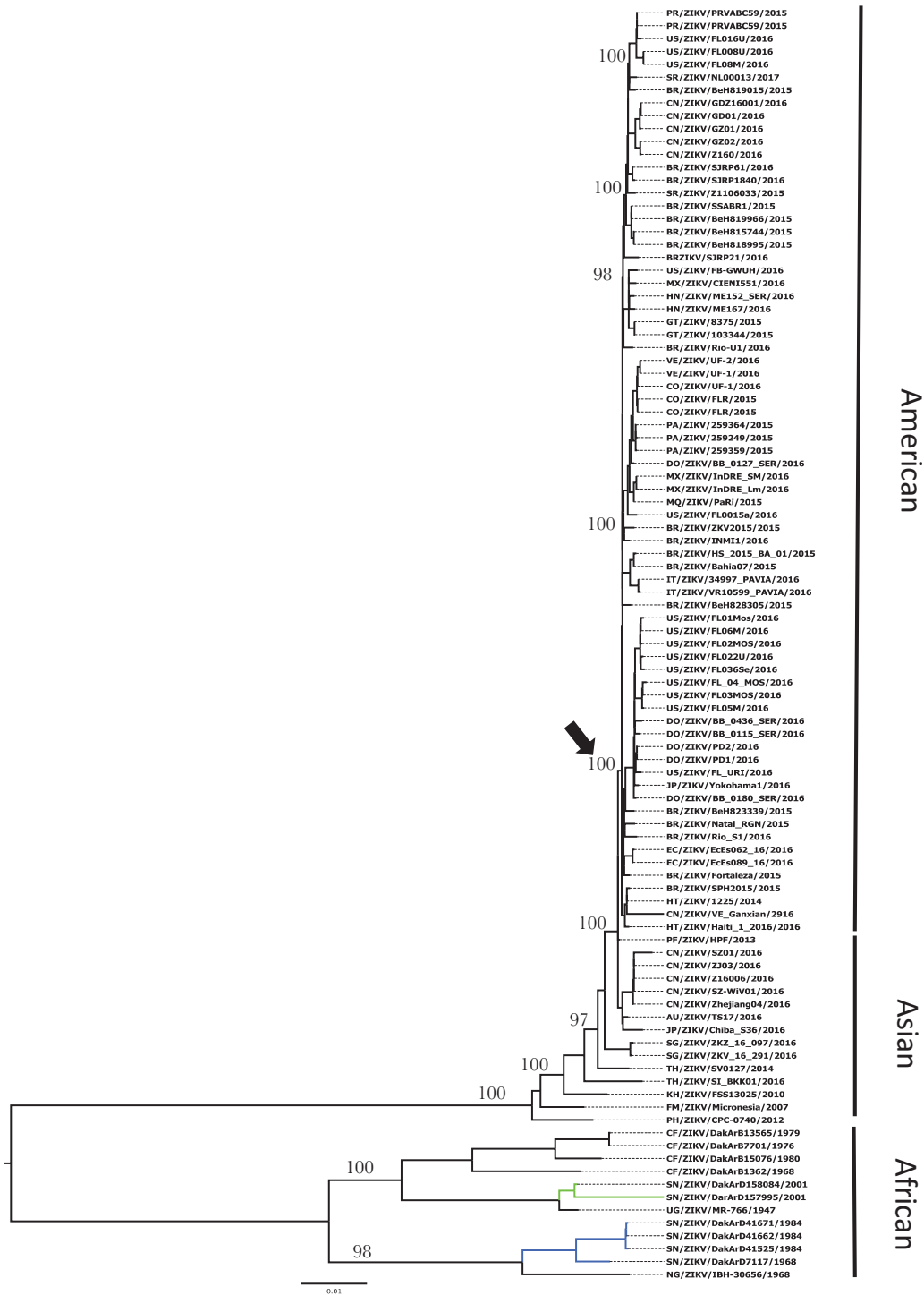
Figure 3. Phylogenetic tree of Zika virus based on 93 complete open reading frame sequences inferred using maximum likelihood methods.

recombination events based solely on coalescent bioinformatic tools. For natural recombination to be definitive, the following prerequisites should be met: (1) the recombinant crossover should be demonstrated in a single polymerase chain reaction amplicon after cloning to ensure it occurs in a single deoxyribonucleic acid molecule, (2) the recombination should be demonstrated repeatedly in clonal populations of viable virus

(eg, a plaque harvest or limited endpoint dilution), and (3) the recombinant should maintain adequate sequence conservation during post-recombination evolution [56].

To explain the rapid global spread of ZIKV, 3 hypotheses have been put forward: (1) ZIKV underwent adaptive evolution facilitating more efficient urban transmission in *Ae aegypti* mosquitoes or in humans, (2) stochastic factors, and (3) a combination

of genetic change and stochastic factors [3, 57]. Although a number of phylogenetic studies [57–59] may support the hypothesis that adaptive evolution may have occurred in southeast Asia where the virus has been circulating since at least the 1960s, to date experimental studies with laboratory colonies or feral populations of mosquitoes (reviewed in [58] and [59–63]) have failed to support this hypothesis, suggesting that the intense ZIKV transmission in the Americas was also influenced by other factors, including immunologically naive human populations. It is possible that the Asian ZIKV lineage may have adapted to generate higher viremia levels in humans, which would lead to more efficient mosquito infection, transmission, and spread. Higher viremia was also suggested to enhance transplacental transmission in humans, which could explain the dramatic emergence of microcephaly in the Americas and remains to be experimentally confirmed. Some studies based on bioinformatic analyses of ZIKV sequences suggested an increase in the use of human codons by the virus, which may support this hypothesis [54, 64, 65]. Nonetheless, the potential link between adaptive evolution and enhanced human infection will require comprehensive longitudinal studies in humans and/or animal models. Ultimately, this hypothesis will be difficult to test because various animal models may not respond to ZIKV infection in the same manner as humans. To date, however, evidence suggests that a combination of stochastic factors and selective evolution may have fueled the spectacular emergence and spread of ZIKV. The initial chance introduction of the virus into naive populations in the South Pacific likely facilitated sufficient amplification by competent mosquito vectors and raised the risk of transport to the Americas. Similar to the spread of dengue in the aftermath of World War II, increased air travel undoubtedly increased the risk of spreading other viruses with increased epidemic potential in recent decades [23–26]. In the case of ZIKV, the origin of introduction in Brazil is unknown, but athletic competitions in Brazil (Soccer Confederation Cup in June 2013, soccer World Cup in June 2014, Va'a World Sprint Championship canoe race in August 2014) are believed to have brought travelers from the South Pacific around the time that ZIKV circulation was discovered there [66–69]; however, molecular clock analyses suggested that introduction may have occurred between May and November 2013 [44, 45, 70]. One hypothesis cannot be favored over another, because introduction by a single traveler coming from the Pacific is also possible. The area of first introduction of ZIKV in Brazil is also a matter of debate The recent epidemics in Singapore and widespread introduced cases and/or sporadic transmission in other Asian countries support the notion that stochastic events have played a role in the global spread of ZIKV. Unanswered is the question of whether emergence and spread were facilitated by new strains of virus with greater epidemic potential that took advantage of the global trends of the 21st century [3, 49].

EVOLUTION OF THE CLINICAL PRESENTATION AND NONVECTOR-BORNE TRANSMISSION

Because of the small number of human cases reported before 2007, the clinical presentation associated with ZIKV infection was ill defined. When the virus emerged in Yap State in 2007, the majority of patients presented with rash, low-grade fever, conjunctivitis, arthralgia, and myalgia [3, 34]. The same clinical presentation was observed when ZIKV emerged in French Polynesia in 2013/2014 and in Brazil in 2015 [3, 38, 47, 71]. Serosurvey studies conducted after the outbreaks in Yap State and French Polynesia suggested that most of the infections were asymptomatic [34, 72]. The first description of severe neurological complications in adults and the potential for non-vector-borne transmission of ZIKV were reported during the French Polynesia outbreak [3]. These new data were subsequently confirmed with the emergence of ZIKV in the Americas and additionally the first description of severe central nervous system malformation in fetuses/neonates [49].

Neurological complications have been reported for arbovirus infections, especially those caused by the *Flavivirus* [73] and *Alphavirus* genera [74] (Table 1). Although Guillain-Barré syndrome (GBS) had been associated with other flaviviruses, the 20-fold increase in GBS observed during the ZIKV epidemic in French Polynesia was unexpected [3, 41, 75]. The incidence of GBS in French Polynesia was 1 in 6500 inhabitants,

Table 1. Clinical Features of ZIKV Compared With Other Arboviruses

Flavivirus						Alphavirus
	ZIKV	DENV	WNV	YFV	JEV	CHIKV
Nonvector borne transmission						
Materno fetal	Yes	Yes	No	Yes[a]	No	Yes
Sexual	Yes	No	No	No	No	No
Transfusion	Yes	Yes	Yes	Yes[a]	No	No
Main complication in newborn						
Microcephaly	Yes	No	No	No	No	No
Other CNS malformation	Yes	No	No	No	No	No
Main complications in infants and adults						
Bleeding	No	Yes	Yes	Yes	No	Yes
Plasma leakage	No	Yes	No	Yes	No	No
Severe organ involvement	No	Yes	Yes	Yes	No	No
Chronic arthralgia	No	No	No	No	No	Yes
Main complications in adults						
Guillain-Barré syndrome	Yes	Yes	Yes	Yes[a]	Yes	Yes
Meningoencephalitis	Yes	Yes	Yes	Yes[a]	Yes	Yes
Myelitis	Yes	Yes	No	Yes[a]	Yes	Yes
Meningitis	No	No	Yes	Yes[a]	Yes	No
Prevention and treatment						
Vaccine	No	Yes	No	Yes	Yes	No
Specific treatment	No	No	No	No	No	No

Abbreviations: CHIKV, chikungunya virus; CNS, central nervous system; DENV, dengue virus; JEV, Japanese encephalitis virus; WNV, West Nile virus; YVF, yellow virus fever; ZIKV, Zika virus.

[a]With yellow fever vaccine virus.

which is approximately the population of Yap State. Because it is a rare complication, it is not possible to know whether the potential for GBS was present in Yap State. For the same reason, microcephaly in newborns was reported only retrospectively in French Polynesia because of the small number of cases [76]. The link between ZIKV and GBS was demonstrated in a retrospective case-control study [41, 77, 78], and the association was subsequently confirmed in the Americas [79]. Similar findings were observed when West Nile virus (WNV) emerged in the Americas causing increased numbers of meningoencephalitis cases [80]. The potential for maternofetal transmission of ZIKV was suspected in French Polynesia [81]. During the 2015 ZIKV epidemic in Brazil, a 20-fold increase in the incidence of neonates with microcephaly coincided with reports of cases of a febrile rash illness compatible with ZIKV infection in pregnant women [82]. The link between ZIKV and severe central nervous system malformations (especially microcephaly) was confirmed in numerous studies [83–86] in Brazil and retrospectively reported in French Polynesia [87]. Other malformations in fetuses/neonates have been reported, but the "congenital ZIKV syndrome" is not yet fully described [88]. Although maternofetal transmission of arboviruses was reported for DENV [89] and chikungunya virus [90], fetus/neonate malformations were not. On the other hand, severe complications caused by the closely related DENV (plasma leakage, bleeding, and severe organ involvement) [91] have not been reported in ZIKV infections.

Arbovirus transfusion-transmission (TT) has been described for WNV [92] and DENV [93], so the potential for ZIKV TT was suspected in French Polynesia [94] and demonstrated in Brazil [95]. Although predictable, the percentage of positive blood donations was higher than reported for DENV and WNV.

Also new for an arbovirus was sexual transmission, first suspected in a single case in a US citizen returning from Senegal [96]. Infectious ZIKV was then detected in the semen of a French Polynesian patient, and sexual transmission of ZIKV was confirmed after its emergence in the Americas [97, 98]. The duration of infectivity of semen and vaginal fluids, the impact of ZIKV infection on fertility, and the impact of nonvector-borne transmission on the burden of ZIKV disease remain to be determined [49].

As noted above, it is uncertain whether the unusual clinical pattern observed in ZIKV infections from its emergence in French Polynesia was the result of observing larger numbers of patients during the epidemics or whether genetic changes in the virus resulted in greater virulence [31] or, most likely, a combination of both [3, 50]. Zika virus shares common clinical features with other arboviruses, especially flaviviruses, including the high rate of asymptomatic infections and the neurotropism of the virus in adults. However, congenital central nervous system malformations and sexual transmission make ZIKV unique among the arboviruses.

CONCLUSIONS

Zika virus has spread rapidly throughout the Pacific and Americas in the past 10 years, but critical gaps remain in our knowledge of the epidemiology and biology of this virus. In the near term, the following concerns must be of the highest priority: (1) development and application of preventive measures, including use of repellants, insecticide-impregnated clothing, elimination of household breeding habitats, and sustainable vector control at the community, state, and federal level to decrease contact between people and *Ae aegypti* mosquitoes; (2) establishment of outreach and awareness programs targeted especially to sexually active individuals and pregnant women to avoid contact with the vectors and practice safe sex; (3) establishment of prospective cohorts to determine the risk of congenital Zika syndrome, GBS, and human-to-human transmission; and (4) determine whether ZIKV can establish an enzootic transmission cycle in the Americas. This prospect will certainly render future eradication efforts practically impossible, and it also might inhibit our ability to control the ongoing outbreak of congenital Zika syndrome. In the longer term, we need to develop the following: (1) more effective prevention tools, eg, vaccines, therapeutics, and mosquito control measures; (2) better diagnostics that are accurate, inexpensive, and user friendly for use at point-of-care, as well as for sustainable, laboratory-based surveillance—this may be challenging once the current epidemics subside with growing herd immunity and diagnostics that cannot distinguish ZIKV infections from DENV and other flaviviruses; and (3) more effective surveillance for arboviral diseases in general, especially in tropical areas where the potential risk of epidemic emergence is greatest.

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