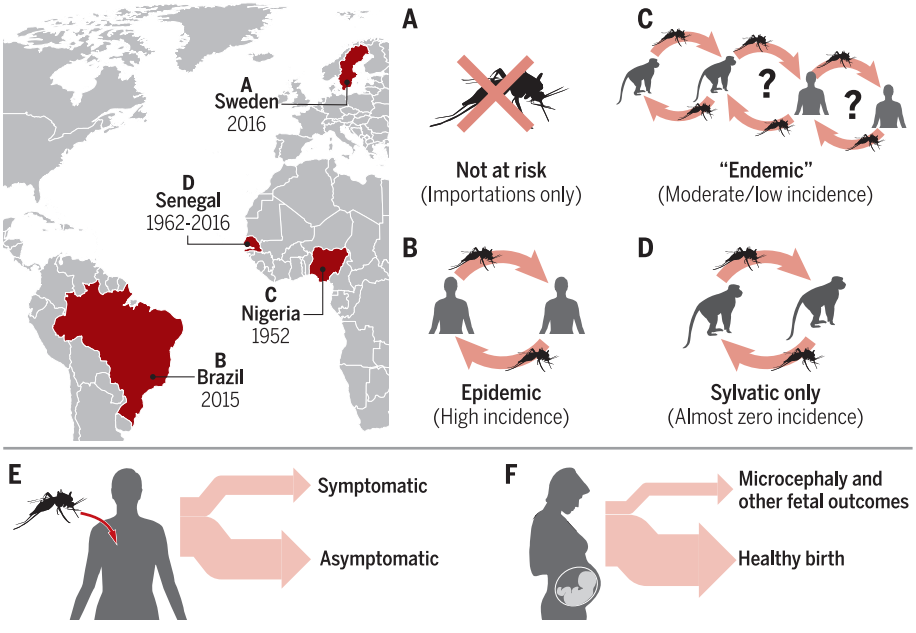
REVIEW SUMMARY

ZIKA

Assessing the global threat from Zika virus

Justin Lessler,*† Lelia H. Chaisson,† Lauren M. Kucirka, Qifang Bi, Kyra Grantz, Henrik Salje, Andrea C. Carcelen, Cassandra T. Ott, Jeanne S. Sheffield, Neil M. Ferguson, Derek A. T. Cummings, C. Jessica E. Metcalf, Isabel Rodriguez-Barraquer

BACKGROUND: First discovered in 1947, Zika virus (ZIKV) received little attention until a surge in microcephaly cases was reported after a 2015 outbreak in Brazil. The size of the outbreak and the severity of associated birth defects prompted the World Health Organization (WHO) to declare a Public Health Emergency of International Concern on 1 February 2016. In response, there has been an explosion in research and planning as the global health community has turned its attention to understanding and controlling ZIKV. Still, much of the information needed to evaluate the global health threat from ZIKV is lacking. The global threat posed by any emerging pathogen depends on its epidemiology, its clinical features, and our ability to implement effective control measures. Whether introductions of ZIKV result in epidemics depends on local ecology, population immunity, regional demographics, and, to no small degree, random chance. The same factors determine whether the virus will establish itself as an endemic disease. The burden of ZIKV spread on human health is mediated by its natural history and pathogenesis, particularly during pregnancy, and our ability to control the virus's spread. In this Review, we examine the empirical evidence for a global threat from ZIKV through the lens of these processes, examining historic and current evidence, as well as parallel processes in closely related viruses.



The effect of ZIKV is a function of the local transmission regime and viral pathogenesis. (**A**) Many countries cannot maintain ongoing vector-mediated ZIKV transmission and are only at risk from importation by travelers and limited onward transmission (e.g., through sex). (**B**) If conditions are appropriate, importations can lead to postinvasion epidemics with high incidence across age ranges, after which the virus may go locally extinct or remain endemic. (**C**) There is evidence of ongoing ZIKV incidence in humans over years (e.g., a 1952 serosurvey in Nigeria), but it is unknown whether this is the result of ongoing circulation in humans or frequent spillover infections from a sylvatic cycle. (**D**) In other areas, ZIKV appears to have been maintained in animals with few human infections. (**E**) The majority of infections are asymptomatic, and severe outcomes, such as Guillain-Barré syndrome, are rare. (**F**) However, there is considerable risk of microcephaly and other fetal sequelae when infection occurs during pregnancy.

ADVANCES: Because ZIKV was not recognized as an important disease in humans until recently, it was little studied before the recent crisis. Nevertheless, the limited data from the decades following its discovery provide important clues into ZIKV's epidemiology and suggest that some populations were at risk for the virus for years in the mid-20th century, although this risk may predominantly have been the result of spillover infections from a sylvatic reservoir. Recent outbreaks on Yap Island (2007) and in French Polynesia (2014) provide the only previous observations of large epidemics and are the basis for the little that we do know about ZIKV's acute symptoms (e.g., rash, fever, conjunctivitis, and arthralgia), the risk of birth defects, such as microcephaly (estimated to be 1 per 100 in French Polynesia), and the incidence of severe neurological outcomes (e.g., Guillain-Barré is estimated to occur in approximately 2 out of every 10,000 cases). The observation of an association between ZIKV and a surge in microcephaly cases in Brazil and the subsequent declaration of a Public Health Emergency of International Concern by the WHO have rapidly accelerated research into the virus. Small, but very important, studies have begun to identify the substantial risk the virus can pose throughout a pregnancy, and careful surveillance has established that ZIKV can be transmitted sexually. Numerous modeling studies have helped to estimate the potential range of ZIKV and measured its reproductive number R_0 (estimates range from 1.4 to 6.6), a key measure of transmissibility in a number of settings. Still, it remains unclear whether the recent epidemic in the Americas is the result of fundamental changes in the virus or merely a chance event.

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OUTLOOK: ZIKV research is progressing rapidly, and over the coming months and years our understanding of the virus will undoubtedly deepen considerably. Key questions about the virus's range, its ability to persist, and its clinical severity will be answered as the current epidemic in the Americas runs its course. Moving forward, it is important that information on ZIKV be placed within the context of its effect on human health and that we remain cognizant of the structure of postinvasion epidemic dynamics as we respond to this emerging threat. ■

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REVIEW

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Assessing the global threat from Zika virus

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First discovered in 1947, Zika virus (ZIKV) infection remained a little-known tropical disease until 2015, when its apparent association with a considerable increase in the incidence of microcephaly in Brazil raised alarms worldwide. There is limited information on the key factors that determine the extent of the global threat from ZIKV infection and resulting complications. Here, we review what is known about the epidemiology, natural history, and public health effects of ZIKV infection, the empirical basis for this knowledge, and the critical knowledge gaps that need to be filled.

Originally discovered in 1947, Zika virus (ZIKV) received little attention until a surge in microcephaly cases was reported after a 2015 outbreak in Brazil (*1*, *2*). Prompted by the size of the outbreak and the severity of associated birth defects, the World Health Organization (WHO) declared ZIKV to be a Public Health Emergency of International Concern on 1 February 2016 (*3*). In response, there has been an explosion in research and planning as the global health community has turned its attention to understanding and controlling ZIKV. Still, much of the information needed to evaluate the global health threat from ZIKV remains unknown.

The global threat posed by any emerging pathogen depends on its epidemiology, its clinical features, and our ability to implement effective control measures (Fig. 1). In an interconnected world, introductions of ZIKV to areas free of the virus may be inevitable. Whether these introductions result in only a few subsequent cases or a major epidemic depends on the local ecology, population immunity, demographics of the region, and random chance. The ability of the virus to transmit in any area can be characterized by its reproductive number R: the number of people we expect to become infected from each case in that area (*4*). When R is greater than one, an epidemic can occur, and when it is less than one, onward transmission will be limited. When ZIKV successfully invades, the threat may be transient and the virus might become locally extinct, as appears to have been the case in Yap Island and French Polynesia (*5*, *6*), or it may persist endemically, as seems to be the case in parts of Africa (*7*). There are two ways in which ZIKV can persist in a region: through ongoing transmission in animals (i.e., a sylvatic cycle) with occasional spillover into the human population, or through sustained transmission in humans (*8*, *9*). Whichever scenario emerges, the natural history and pathogenesis of ZIKV will determine its effect on human health, with infection in pregnant women being particularly important (*10*). Finally, the extent of the global threat from ZIKV is mediated by our ability to control the virus and treat those cases that do occur.

In this review, we examine the empirical evidence for a global threat from ZIKV through the lens of these processes. We review what is known about the natural history and pathogenesis of ZIKV in humans, outline what we know about the ability of ZIKV and similar viruses to invade and persist in diverse settings, and summarize the challenges we face in studying and controlling ZIKV. Finally, we examine what we know about why ZIKV has emerged as a public health threat in the Americas after being known for decades as a rare and mild tropical disease.

A brief history of ZIKV

ZIKV was discovered in the blood of a rhesus monkey in 1947 at the Yellow Fever Research Institute in Entebbe, Uganda (*1*), and was isolated from *Aedes africanus* mosquitoes the following year (*1*). Soon after, multiple serosurveys found evidence of antibodies to ZIKV in human populations throughout Africa (*11*–*14*), India (*15*), and Southeast Asia (*16*, *17*) (Fig. 2). It was not initially clear that ZIKV caused clinical disease (*13*), although early evidence suggested that it was neurotropic in mice (*18*). Human infection was first confirmed in 1953 in Nigeria (*13*), and ZIKV was definitively established as pathogenic in humans after later experimental (*19*) and natural (*20*) infections led to symptoms of fever and rash.

The globally distributed mosquito *A. aegypti* was identified as a likely vector for ZIKV transmission in the 1950s after successful transmission of the virus to a mosquito from an infected human volunteer (*19*). Later experiments confirmed *A. aegypti*'s ability to transmit ZIKV to mice (*21*), and ZIKV has since been isolated from several *Aedes* species (and, in a few cases, other genera) (*22*), including *A. albopictus* (*23*–*26*).

In the decades after its discovery, intermittent serosurveys continued to find evidence of ZIKV infection in humans in Africa (*27*–*29*), the Indian subcontinent (*30*), and Southeast Asia (*16*, *31*, *32*). Evidence for ZIKV's continued presence was further bolstered by limited viral isolations from mosquitoes (*33*–*38*), humans (*7*, *20*, *29*, *39*, *40*), and nonhuman primates (*9*). However, few clinical cases had been reported in humans before 2007 (*20*, *29*, *31*, *40*), and ZIKV was considered to be of limited public health importance.

In 2007, the first known major outbreak of ZIKV occurred on Yap Island in the Federated States of Micronesia (*6*). Although several patients initially tested positive for dengue, the unusual clinical presentation prompted physicians to send serum to the Centers for Disease Control and Prevention (CDC) Arbovirus Diagnostic and Reference Laboratory, where it tested positive for ZIKV (*6*, *41*). During the outbreak, ~73% of the island's residents were infected with ZIKV, and symptoms were generally mild and short-lived (*6*).

After the Yap Island outbreak, there were sporadic isolations of ZIKV in residents of and travelers to Southeast Asia (*42*–*44*), but no other major ZIKV outbreaks were observed until late 2013. From October 2013 to April 2014, French Polynesia experienced a large outbreak of ZIKV, estimated to have infected 66% of the general population (*5*, *45*). A contemporaneous surge in the number of cases of Guillain-Barré syndrome raised concerns of an association with ZIKV (*5*, *45*): A total of 42 cases of Guillain-Barré syndrome were reported from November 2013 to February 2014, compared with three cases in all of 2012. These are the first known instances of neurologic sequelae associated with ZIKV infection. Although not noted at the time, retrospective analyses suggest that there may also have been an increase in microcephaly cases (*46*). After the French Polynesia outbreak, ZIKV spread throughout the South Pacific, including outbreaks in New Caledonia, the Cook Islands, and Easter Island in 2014 (*47*).

The earliest confirmed cases of ZIKV infection in the Americas occurred in late 2014 in northeastern Brazil (*48*). Recent work suggests that the virus may also have been present simultaneously in Haiti (*49*). Over the following months, the virus spread rapidly throughout Brazil (*50*), followed by a substantial rise in cases of Guillain-Barré syndrome and microcephaly in affected regions (*51*), prompting

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the WHO to declare a Public Health Emergency of International Concern on 1 February 2016 (*3*). Phylogenetic evidence suggests that the strains that seeded this outbreak are descendants of those that caused outbreaks in the South Pacific, which in turn descended from the Asian lineage of the virus (*52*).

Since late 2014, ZIKV has spread widely throughout South and Central America and the Caribbean (*2*). As of June 2016, more than 35 countries throughout the Americas have reported locally circulating ZIKV (*53*). This includes a large outbreak in Colombia, with more than 65,000 reported cases, numerous reports of potentially associated neurological syndromes, and ZIKV-associated microcephaly cases (*54*–*56*). As of June 2016, the ZIKV situation continues to evolve, and the global threat ultimately posed by ZIKV remains uncertain.

The natural history and pathogenesis of ZIKV

Transmission and natural history of ZIKV

The primary source of ZIKV infection in humans is from bites of infected mosquitoes (*57*), although there have also been cases of sexual (*58*–*60*), perinatal (*61*), and suspected blood-transfusion transmission (*62*). Evidence from outbreaks in the South Pacific indicates that a minority of those infected with ZIKV develop clinical illness: During the Yap Island outbreak, 19% of people with serological evidence of recent infection [immunoglobulin M (IgM)–positive] reported ZIKV symptoms (*6*); in French Polynesia, 26% of ZIKV-positive blood donors who were asymptomatic at the time of donation later reported symptoms (*63*).

On average, those who do develop ZIKV symptoms will do so 6 days after infection (*64*), and 95% will do so within 11 days (Fig. 3). Virus has been isolated from blood (*13*), urine (*65*, *66*), saliva (*67*), semen (*68*), amniotic fluid (*69*), and neurologic tissue (*70*). Virus can be isolated in blood for an average of 10 days after infection (99% will clear the virus by 24 days) (*64*), and case reports indicate that virus may remain in urine for 12 or more days after infection (*65*) and in semen for more than 60 days (*59*). Pregnancy may affect the length of viral shedding: In one case, a woman remained viremic for at least 10 weeks during pregnancy but cleared the virus within 11 days of termination (*71*). Antibodies to ZIKV become detectable, on average, 9 days after infection (*64*). Although the duration of immunity against ZIKV remains unknown, evidence from other flaviviruses suggests that it should be lifelong (*72*). Mosquitoes become infectious about 10 days after biting an infectious human and likely remain so until death (*19*).

Unfortunately, many of these distributions are estimated based on fewer than 30 cases. Expansion of this pool of evidence is critical for accurate assessment of surveillance activities and modeling of ZIKV risk.

Clinical illness

ZIKV symptoms are typically nonspecific and mild. Consistent with other reports (*73*), symptoms reported from 31 confirmed cases on Yap Island included maculopapular rash (90%), subjective fever (65%), arthralgia or arthritis (65%), nonpurulent conjunctivitis (55%), myalgia (48%), headache (45%), retro-orbital pain (39%), edema (19%), and vomiting (10%) (*6*, *10*). Case reports suggest that acute symptoms of ZIKV will typically fully resolve within 1 to 2 weeks of onset (*44*, *60*, *74*–*80*). Deaths are rare and have primarily occurred in patients with preexisting comorbidities or who are immunocompromised (*81*, *82*).

Persons infected with ZIKV may be at increased risk for severe neurologic sequelae, notably Guillain-Barré syndrome. Data from French Polynesia suggest a risk of Guillain-Barré of 24 per 100,000 ZIKV infections (*5*, *45*), more than 10 times the annual rate in the United States (1.8 per 100,000) (*83*). Regardless of cause, Guillain-Barré is associated with considerable morbidity and 3 to 10% mortality (*84*). Guillain-Barré may be more common in symptomatic ZIKV cases; during the French Polynesia outbreak, 88% of Guillain-Barré cases reported symptoms a median of 6 days before Guillain-Barré onset (*5*, *45*). There have been reports of other neurological sequelae, including meningoencephalitis (*85*) and acute myelitis (*86*), although no causal link has been established.

ZIKV in pregnancy

Much of the concern surrounding ZIKV has focused on the link between infection in pregnancy and fetal microcephaly. As of 7 May 2016, 7438 suspected microcephaly cases have been reported in Brazil since ZIKV's emergence (1326 confirmed out of 4005 investigated), versus fewer than 200 per year before the outbreak (*87*, *88*). Quantifying the risk of microcephaly has been complicated by uncertainty in the number of ZIKV-affected pregnancies, owing to the large fraction of cases that are asymptomatic, a lack of consensus on the definition of microcephaly, and other infectious causes of microcephaly, such as cytomegalovirus and rubella (*89*). However, in light of multiple epidemiologic studies and the isolation of ZIKV in amniotic fluid and fetal brain tissue, the CDC confirmed a causal link between ZIKV infection during pregnancy and severe birth defects, including microcephaly in April 2016 (*90*). This

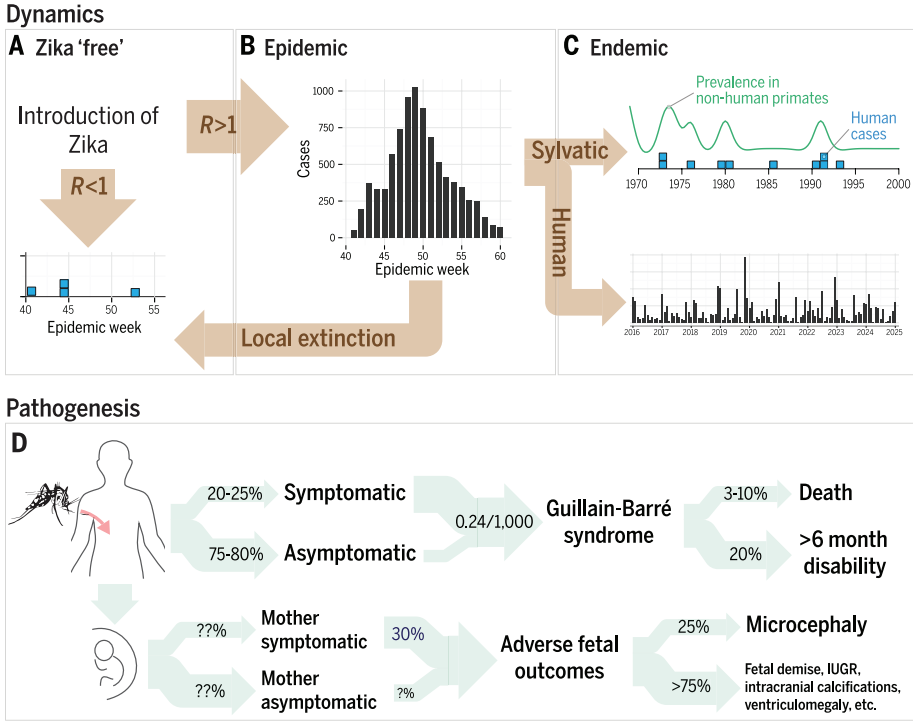

Fig. 1. Factors determining the global risk from ZIKV. (**A**) As long as ZIKV circulates anywhere, periodic introductions into ZIKV-free regions will occur. Whether these lead to an epidemic depends on the reproductive number *R*, a measure of transmission efficiency determined by local ecology and population susceptibility to ZIKV. (**B**) When $R > 1$, introductions can result in major epidemics, after which the virus may go locally extinct or become endemic. (**C**) ZIKV could be maintained endemically either in local nonhuman primates (the sylvatic cycle) or through ongoing human transmission. (**D**) Most ZIKV infections (75 to 80%) are asymptomatic, and those with symptoms are likely at highest risk for rare neurological complications (*6*, *63*, *92*), particularly Guillain-Barré (*45*). Adverse fetal outcomes, notably microcephaly, may also be more common when the mother is symptomatic. Owing to its association with pregnancy, ZIKV's health effects depend on the fertility rate and the age distribution of infections. The age distribution mirrors the general population in ZIKV-free (A) and epidemic (B) settings but is a function of the force of infection in endemic settings (C) (*4*, *45*). Appropriate control measures can reduce *R*, decreasing the probability of successful ZIKV invasion (A) and its subsequent effect [(B) and (C)] [see (*116*)].

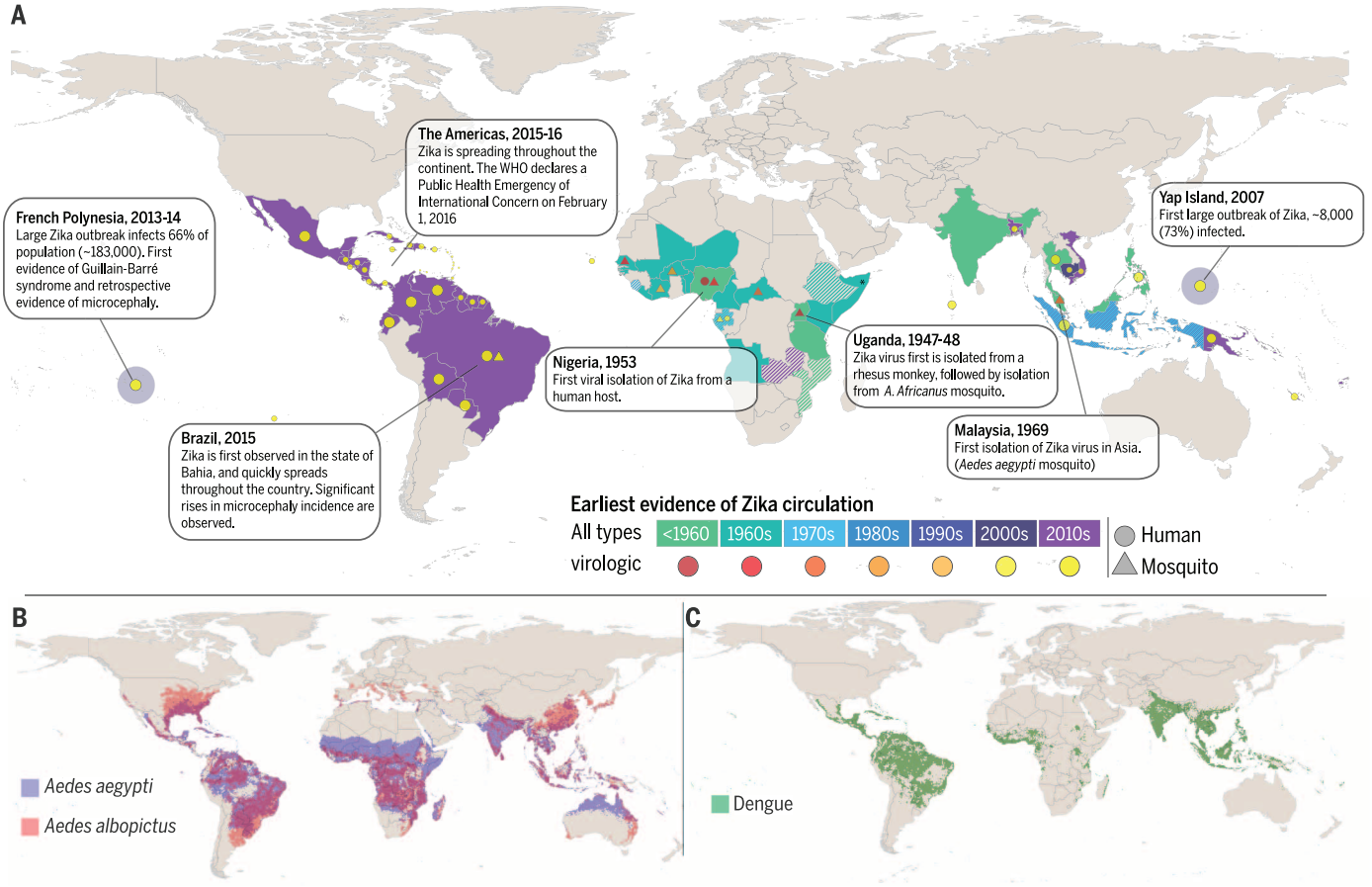

Fig. 2. Current and potential distribution of ZIKV. (**A**) Spread of ZIKV across the globe to date. Countries are colored by the timing of the first indication of local ZIKV transmission by serologic evidence or confirmation of human cases. Solid shading indicates clusters of confirmed cases or seropositivity to ZIKV of >10% in some subpopulations, whereas hatched colors indicate 5 to 10% seropositivity (serosurveys showing <5% seropositivity are not shown). Symbols indicate locations and timings of viral isolations from mosquitoes (triangles) and humans (circles). (**B**) Map of the global occurrence of the widely distributed ZIKV vectors *A. aegypti* and *A. albopictus*. Adapted from (*100*). (**C**) Map of the occurrence of dengue, a closely related *Aedes*-transmitted flavivirus. Adapted from (*103*). Shaded regions correspond to areas with predicted probability of vector or dengue occurrence of >30%. *Somalia did not report the total percentage of those who were ZIKV seropositive, but there was a small percentage of subjects seropositive to ZIKV and no other flavivirus and a large percentage seropositive to two or more flaviviruses, so Somalia's data are included.

conclusion is further supported by the presence of microcephaly and other brain abnormalities in the pups of mice experimentally infected with ZIKV (*91*).

ZIKV symptoms in pregnant women are similar to the general population (*92*), but it is unknown if immunosuppression during pregnancy changes the rate at which they occur. Among those who are symptomatic, adverse fetal outcomes appear to be frequent, occurring in 29% (12 out of 42) of symptomatic ZIKV-infected pregnant women in a prospective study in Brazil (*92*). A second Brazilian study found that 74% (26 out of 35) of mothers of infants with microcephaly reported a rash in the first or second trimester (*51*). The rate of birth defects in asymptomatic pregnant women is likely lower, but not zero. For example, a Colombian study identified four microcephaly cases with virologic evidence of ZIKV infection, all of which were born to women who did not report symptoms of ZIKV (*54*). Modeling studies suggest that the overall risk of ZIKV-associated microcephaly in the first trimester is around 1 per 100, regardless of symptoms, and low to negligible thereafter (*46*, *93*).

Although microcephaly was the first fetal abnormality to be recognized, there is increasing evidence that ZIKV may be responsible for other fetal sequelae, such as intracranial calcifications, ventriculomegaly, ocular impairment, brainstem hypoplasia, intrauterine growth restriction (IUGR), and fetal demise (*92*, *94*). Placental pathology has also been reported. Although microcephaly is detectable at birth, other findings may require additional, less routine procedures, such as imaging or autopsy, and thus may be underreported. Brasil *et al.* found that only one in four fetuses with abnormalities in ZIKV-infected women met the criteria for microcephaly (*92*), indicating that the total number of ZIKV-affected pregnancies may be four times the number of reported microcephaly cases.

Beyond an association with symptoms, it is unclear what factors increase the risk of adverse pregnancy outcomes after maternal ZIKV infection. For other infections that cause fetal abnormalities, risk is often associated with gestational age at infection. For instance, the risk of birth defects from cytomegalovirus and rubella is highest if infection occurs in the first or early in the second trimester (*89*). Epidemiologic evidence suggests a similar association with first-trimester ZIKV infection (*46*, *95*). In a prospective study of 88 women, microcephaly and brain abnormalities occurred only in first- and second-trimester infections (*92*). However, 8 of 12 cases of fetal abnormalities overall occurred in second- and third-trimester infections, and women infected as late as 35 weeks experienced fetal death, IUGR, or anhydramnios [although these outcomes commonly occur in the absence of ZIKV; e.g., in Brazil, 11 fetal deaths occur per 1000 births (*96*), and IUGR rates range from 5 to 7% in developed countries (*97*)]. A recent Colombian study suggests little to no risk from infection in the third trimester; among 616 Colombian women with clinical symptoms of ZIKV during the third trimester, none gave birth to infants with microcephaly or other brain abnormalities (7% were still pregnant at the time of reporting) (*54*).

Adverse outcomes in pregnancy are the most worrisome side effects of ZIKV infection, and research into this association is progressing rapidly.

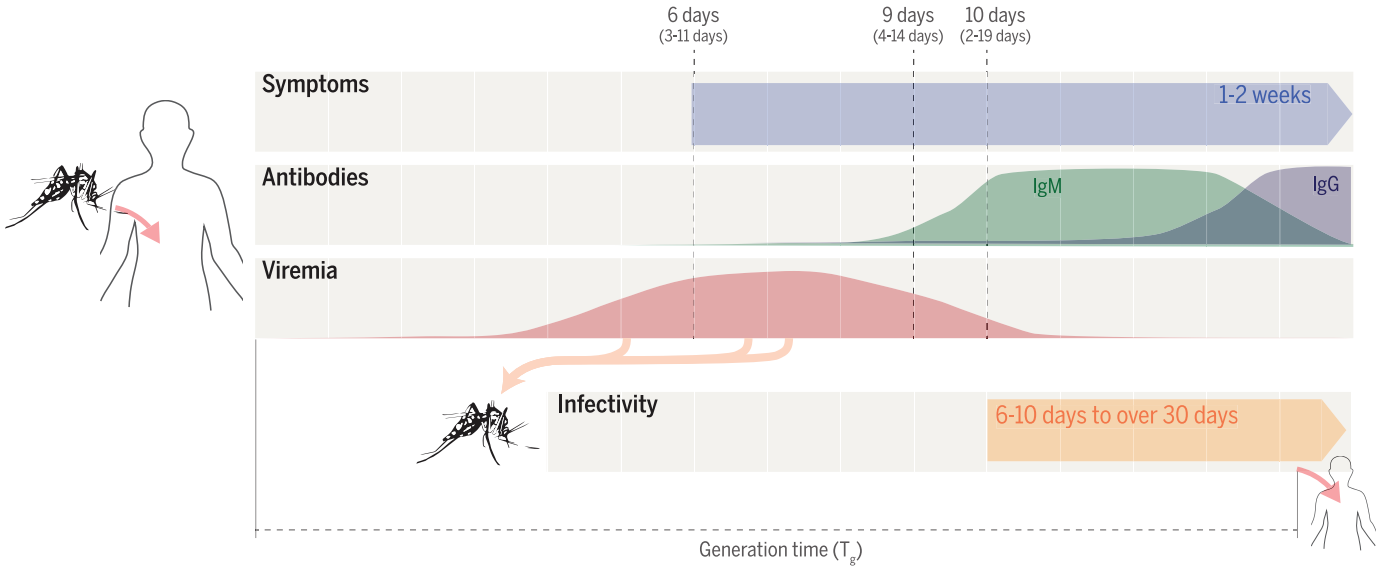

Fig. 3. Schematic of the course of human and mosquito infection. Symptoms develop, on average, 6 days (95% range, 3 to 11 days) after ZIKV infection (*64*). Approximately 9 days (95% range, 4 to 14 days) after infection, antibodies start increasing: The first antibodies detectable will be IgM, which will later decline as IgG antibodies increase, then persist indefinitely (the timing of the IgM/IgG switch is for illustrative purposes only and is not meant to indicate the actual length of IgM persistence). Viremia likely starts to increase before symptoms appear, and the magnitude and length of viremia will shape the risk of infection of susceptible mosquitoes that bite this host. After an incubation period, this infected mosquito will be able to transmit infection to susceptible humans (*19*). The interval from the initial to the subsequent human infection is the generation time of ZIKV, T_g [for estimates, see (*116*)].

Still, much remains to be learned, particularly about the frequency and spectrum of ZIKV sequelae in pregnancy and how we can assess and reduce risk. ZIKV-related birth defects can have long-standing financial, social, and health effects on affected families and communities (*98*). Hence, the threat from ZIKV cannot purely be assessed based on immediate clinical outcomes but also must account for its lifelong effects.

The potential range and effect of ZIKV

Transmissibility and potential range of ZIKV

Transmission of ZIKV in a population is a function of local ecology, the natural history of ZIKV, and the population's susceptibility to infection. The suitability of the local environment for ZIKV transmission and the effect of ZIKV's natural history are captured by the basic reproductive number R_0, the number of secondary infections expected from a single case in a population with no preexisting immunity (e.g., French Polynesia before 2013). R_0 is a function of both disease and setting and will vary between locales based on the local environment, human behavior, vector abundance, and, potentially, interactions with other viruses. The combined effect of these factors and susceptibility will be captured by the reproductive number R, which is related to R_0 by the equation $R = R_0 \times S$, where S is the proportion of the population susceptible to ZIKV. This value, combined with the generation time (the time separating two consecutive infections in a chain of transmission), tells us the speed at which ZIKV will spread in a population. As we consider how to assess the range and effects of ZIKV, we rely both on previous experience with ZIKV and related viruses and on an assessment of factors likely to influence R and R_0.

The size of an outbreak after an introduction will depend on R (R_0 in a ZIKV-naive population) (*99*), with small, self-limiting outbreaks becoming more likely as R approaches one, and increasing epidemics with larger Rs. Hence, ZIKV can successfully spread to a new region if $R > 1$, which requires, among other factors, sufficient density of the vector population. ZIKV has been isolated from multiple *Aedes* genus mosquitoes (*23*–*26*, *38*), including *A. albopictus* and *A. aegypti*, which have a large global range (Fig. 2B) (*100*). Although ZIKV has been occasionally isolated from or experimentally passed to other genera, including *Culex* species, there is no current evidence that they contribute substantially to its spread (*22*, *23*, *101*). It is unclear whether all areas across the range of these mosquitoes are at risk for ZIKV epidemics. Dengue, a virus that is also transmitted by *Aedes* mosquitoes, has caused epidemics throughout the Americas (Fig. 2C) but has not achieved sustained transmission in the continental United States, despite widespread vector presence (*100*, *102*, *103*). The reasons for this may include not only climate but also differences in built environments and social factors (*104*), all of which are likely to affect ZIKV transmission.

Several groups have attempted to map ZIKV's potential global range based on currently available data. These maps have been constructed around combinations of environmental, vector abundance, and socioeconomic factors (*105*–*109*). There is wide agreement that much of the world's tropical and subtropical regions are at risk for ZIKV spread, including major portions of the Americas, Africa, Southeast Asia, and the Indian subcontinent, as well as many Pacific islands and Northern Australia. These maps differ notably in the extent of risk projected in the southeastern United States and inland areas of South America and Africa, with Carlson and colleagues suggesting a more limited range (*107*), particularly in the continental United States, than Messina *et al.* and Samy *et al.* (*108*, *109*). These maps are important attempts to refine estimates of ZIKV's global range beyond those based solely on the distribution of dengue or *Aedes* mosquitoes but, as noted by the authors, are based on limited evidence and should be refined as we learn more about ZIKV. These analyses are, arguably, best interpreted as an assessment of the risk of initial postinvasion ZIKV epidemics, not its long-term persistence. Whether ZIKV will in fact spread throughout these areas is uncertain; similar viruses have failed to spread to or take hold in areas theoretically at risk (e.g., yellow fever in Southeast Asia) (*110*).

R_0 in ZIKV outbreaks in Yap Island and French Polynesia was estimated to be between 1.8 and 5.8 (*111*–*113*), corresponding to 73.2 to 99.9% of the at-risk population becoming infected in an uncontrolled outbreak, based on classic epidemic theory (*4*) [although the true relationship between R_0 and final attack rates for ZIKV will be somewhat more complex (*99*)]. Serosurveys in French Polynesia suggest that 66% of the population was infected (*46*), which is somewhat lower but not inconsistent with these projections. Preliminary estimates of R_0 from Colombia vary by location and range from 1.4 to 6.6 (*114*, *115*). These are similar to R_0 estimates presented by Ferguson *et al.* for 13 countries in the Americas (*116*) and recent estimates of R_0 for Rio de Janeiro (*117*).

These values are consistent with R_0 estimates for dengue in similar settings. Of note, all of these are from settings with recently observed endogenous transmission of ZIKV, and R_0 will vary widely across settings and is likely to be far lower near the limits and outside of ZIKV's range.

ZIKV's potential for endemic circulation

After the initial, postinvasion epidemic of ZIKV, the virus may either go extinct locally or be maintained through endemic human spread or sylvatic transmission (Fig. 1). Early age-stratified serosurveys in Africa and Asia offer some insight into past transmission patterns of ZIKV in these regions and ZIKV's past dynamics (Fig. 4). Serosurveys in Nigeria, the Central African Republic, and Malaysia are consistent with ongoing ZIKV transmission, common spillover infections from a sylvatic reservoir, or frequent reintroductions from other regions over multiple decades (*13*, *16*, *118*). However, these results must be interpreted with caution owing to cross-reactivity with other flaviviruses in serologic tests (*22*). Up-to-date, age-stratified serosurveys, broadly covering regions where ZIKV has previously been detected, would tell us much about the virus's ability to persist.

More recent evidence of sustained transmission comes from Thailand, where seven samples collected in independent outbreak investigations tested positive for ZIKV infection (*43*). The broad geographic spread of these cases is consistent with endemic transmission throughout Thailand. Furthermore, occasional but consistent serologic and virologic evidence of ZIKV transmission in humans and mosquitoes from across Africa, India, and Southeast Asia spanning more than 60 years suggests that ZIKV has been persistently present throughout these regions (*22*) (Fig. 1A). Phylogenetic evidence further supports this supposition, because the African and Asian lineages divided in the 1940s and remain distinct up until the present day (*22*, *26*) (Fig. 5).

The evidence supports ZIKV's ability to persist regionally, but it is unclear whether the human population alone can maintain ZIKV endemically. After an initial postinvasion epidemic, the time until there is a risk of additional epidemics will be driven by the replenishment of susceptibles through births and waning immunity [the latter seems unlikely based on evidence that other flaviviruses provide lifelong immunity to the infecting strain (*22*)]. For ZIKV to persist in the human population over this period, the population must be large enough to support low levels of transmission between epidemics (*4*).

However, all countries with evidence of persistent ZIKV transmission have a plausible sylvatic cycle. Patterns of ZIKV isolations in a study of samples from multiple hosts in Senegal spanning 50 years support episodic transmission across species (*9*); phylogenetic evidence indicates ZIKV passes frequently between nonhuman primates and humans in Africa (*26*); and numerous studies in Africa and Asia show serologic evidence for ZIKV infection in nonhuman primates (*1*, *18*, *22*, *33*, *119*). Some areas, where there has been serological evidence of long periods of consistent risk of ZIKV infection, are near areas where serological evidence suggests that human populations are largely ZIKV free (e.g., Nigeria versus Kenya) (*120*, *121*)—a pattern more consistent with spillover infections from a sylvatic reservoir than of endemic transmission in humans.

In light of this evidence, it is plausible that the persistence of ZIKV in Africa and Asia may depend on the presence of a sustainable sylvatic cycle. However, it is unclear if the primate population in the Americas could support sylvatic transmission (*122*) or if such a cycle is necessary for ZIKV to remain endemic. Nonhuman primates are present throughout South and Central America, and ZIKV has recently been isolated from two species in the Ceará State of Brazil (*123*), suggesting at least the possibility for sustained sylvatic transmission in the region. Further characterization of ZIKV ecology in Asia and Africa and monitoring of the developing situation in the Americas is needed to assess the long-term risk from ZIKV in newly affected regions.

Because the most severe outcomes of ZIKV infection are associated with pregnancy, the risk from endemic ZIKV will depend on the age distribution of those infected. Serosurveys indicating ongoing ZIKV circulation (Fig. 4, A to C) support average ages of infection of 17 (Nigeria, 1952), 29 (Central African Republic, 1979) and 30 years (Malaysia 1953 to 1954) (*13*, *16*, *118*). Likewise, R_0 estimates from the literature are consistent with average ages of infection ranging between 10 and 38 years in the setting of endemic human-to-human transmission (although human-to-human transmission should not be necessarily assumed in the settings covered in Fig. 4, A to C). These ages suggest that in endemic settings, risk of ZIKV infection may be considerable during childbearing years. Importantly, this information could potentially be used to estimate the expected rate of microcephaly and other birth defects in regions where ZIKV becomes endemic.

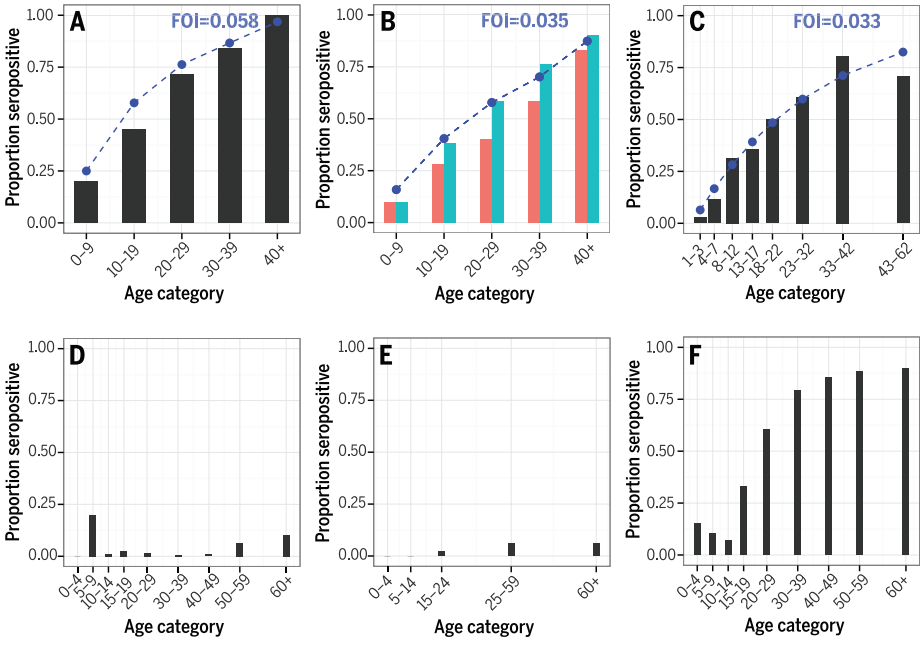

Fig. 4. Age-stratified serosurveys provide important clues to local ZIKV epidemiology. Results must be interpreted with caution because of the possibility of cross-reactivity with other flavivirus antibodies. (**A** to **C**) Ongoing ZIKV transmission, whether from endemic human transmission or a constant risk of zoonotic infection, manifests as a smooth increase in the proportion of the population seropositive with increasing age. This pattern is also consistent with frequent reintroductions leading to periodic outbreaks. If we assume that the risk of ZIKV infection is constant over a lifetime, we can estimate the force of infection (FOI), the proportion of the susceptible population infected each year. Serosurvey results consistent with ongoing transmission include (A) Uburu, Nigeria, 1952 (*13*); (B) Central African Republic, 1979 (pink, female; cyan, male) (*118*); and (C) Malaysia, 1953 to 1954 (*16*). Blue dashed lines and text represent the expected distribution from the estimated FOI. (**D** and **E**) In areas without substantial ZIKV transmission, there will be very low levels of seropositivity across age groups and no clear age pattern. Some individuals may still be seropositive due to cross-reactivity in serological assays, infection of travelers, and limited imported cases. Examples include (D) Central Nyanza, Kenya, 1966 to 1968 (*121*) and (E) Mid-Western Region, Nigeria, 1966 to 1967 (*120*). (**F**) Substantial shifts in seropositivity between age groups inconsistent with ongoing transmission suggest past epidemics—e.g., results from a 1966 to 1968 serosurvey in the Malindi district of Kenya are consistent with one or more epidemics of ZIKV occurring 15 to 30 years previously (*121*). Similar patterns could also occur due to differences in infection risk by age or a sharp reduction in transmission intensity at some point in the past.

Why has ZIKV invaded the Americas now?

Little is known about ZIKV's introduction into the Americas. Phylogenetic analyses indicate

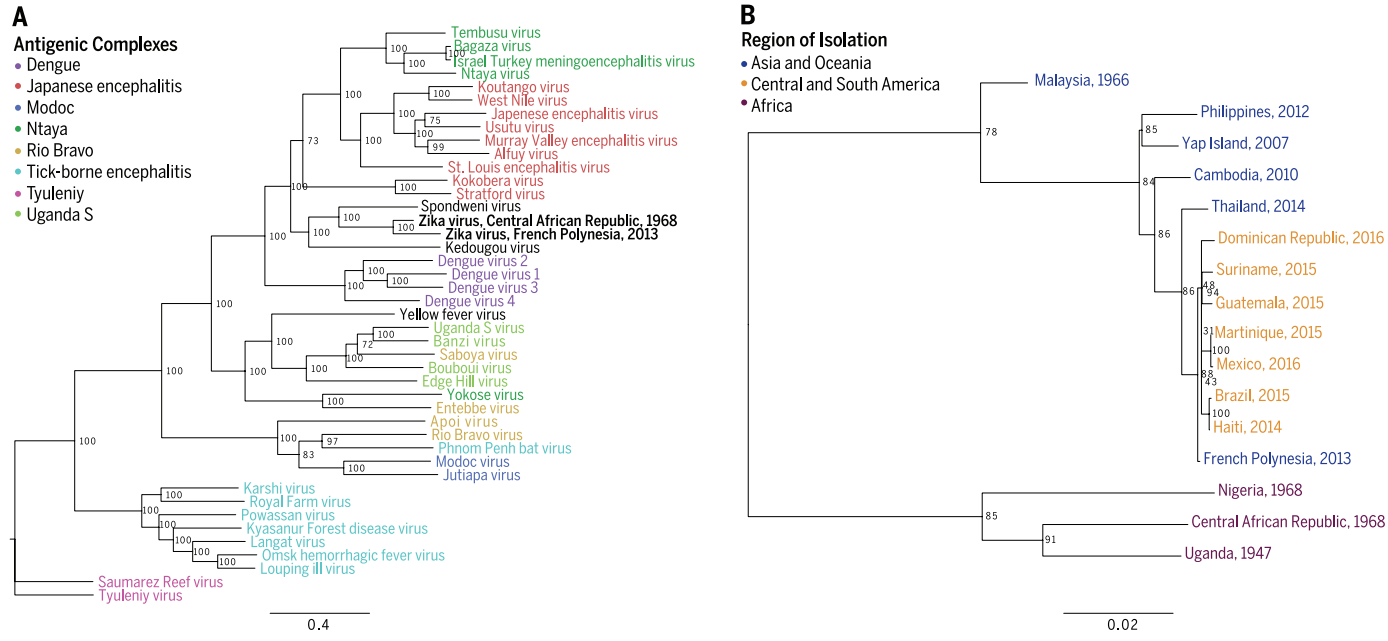

Fig. 5. ZIKV phylogenetics. (**A**) Maximum likelihood tree of phylogenetic relationships between 43 flaviviruses (numbers indicate support from 1000 ultrafast bootstrap replicates), with antigenic clusters from Calisher *et al*. indicated by color (*162*). (**B**) The phylogenetic relationship between ZIKV strains isolated from throughout the globe. Whole-genome nucleotide sequences were aligned using Clustal Omega (*163*), and trees were constructed using IQ-TREE (*164*) under a GTR+G+I evolutionary model.

that a virus descended from the French Polynesian ZIKV strain entered Brazil between May and December 2013 (*52*). Although there has been speculation about introduction during specific sporting events (*52*, *124*), Brazil has more than 6 million visitors per year, providing numerous opportunities for ZIKV introduction. Regardless of how and when ZIKV entered the Americas, the reasons for the size and severity of this outbreak are unclear.

The unprecedented size and effect of the ZIKV epidemic in the Americas may be the natural result of a random introduction into a large population without preexisting immunity. Like the Americas, the populations of Yap Island and French Polynesia were fully susceptible when ZIKV was introduced, and both had large outbreaks infecting more than 65% of their populations (*6*, *45*). However, on these small islands the absolute number of adverse outcomes may have been too low to be noticed initially. Likewise, it is possible that small ZIKV epidemics, and even invasion into Southeast Asia in the mid-1900s, resulted in effects that were unnoticed against the backdrop of other infectious diseases, particularly because small population sizes (compared to Brazil) mean that excess microcephaly cases would likely be in the hundreds (or less) in any given country. Endemic transmission would be even less likely to be noticed, because yearly attack rates would be a tenth again lower (Fig. 4) (*116*). Still, given the magnitude and severity of the outbreak in the Americas, it seems implausible that, if such outbreaks were occurring, none were observed for over 60 years. Hypothesized changes in the biological and ecological drivers of ZIKV transmission must be carefully assessed, because they will influence how we quantify the risk from ZIKV globally.

Warmer temperatures and rainfall resulting from the 2015–2016 El Niño may have facilitated ZIKV transmission throughout the region (*125*) and increased the geographic range of *Aedes* mosquitoes. Warmer temperatures have been associated with more efficient transmission of related flaviviruses (*126*) and greater production of adult mosquitoes (*127*, *128*). El Niño–associated periods of flooding (which increases mosquito breeding sites) and of droughts (which can increase human-mosquito interactions) may facilitate ZIKV transmission (*129*, *130*). However, it should not be assumed that increased temperature or rainfall will universally promote ZIKV transmission, because climatic changes have complex repercussions across food webs (from plant growth to bird behavior) and the thermal effects on the virus itself are likely to be nonlinear (*131*). Over a longer time scale, development and urbanization has led to a proliferation of *A. aegypti* and *A. albopictus* in densely populated areas, which may have facilitated the rise of dengue in the region and may also have provided conditions that favored ZIKV spread (*132*).

There is some possibility that immunological interactions with other flaviviruses may be facilitating the spread or pathogenesis of ZIKV in the Americas. In dengue, preexisting antibodies to one serotype are hypothesized to enhance subsequent infections with another serotype through a mechanism known as antibody-dependent enhancement (ADE) (*133*). ADE may result in increased susceptibility to infection, the likelihood of developing severe disease, and the chances of transmission (*134*, *135*). Evidence from some in vitro experiments and epidemiological studies show both protective and enhancing effects between immunity to Japanese encephalitis and dengue (*136*, *137*), and several in vitro studies have shown enhancement of ZIKV replication in the presence of antibodies to other flaviviruses (*138*, *139*). Dengue has circulated throughout much of Central and South America since it reemerged 30 years ago; hence, it is possible that such interactions are contributing to the current outbreak of severe disease. However, this would raise questions as to why similar interactions have not been seen in the dengue endemic regions of Southeast Asia that also show evidence of ZIKV circulation. Studies that measure preexisting dengue and ZIKV antibodies and track clinical outcomes may help illuminate the issue.

The severity of outcomes in recent outbreaks, compared with past observations of mild disease, has led some to hypothesize that the virus has mutated to be more pathogenic (*140*). Recent evidence suggests distinct codon preferences between African and Asian ZIKV lineages, although adaptive genetic changes may have an effect on viral replication and titers (*141*), whereas the genetic diversity of viruses isolated in ZIKV-associated microcephaly cases suggest that recent mutations may not be involved (*142*). Epidemiologic and laboratory studies are needed to determine whether these changes have had a substantive effect on viral pathogenesis. Until the effect of ZIKV evolution is better understood, we should be careful to balance the need to learn from previous research with the possibility that the virus has fundamentally changed.

Human genetics is known to have a profound effect on the pathogenesis of many infectious

diseases (143), and there is some indication that the same could be true for flaviviruses (144, 145). While there is evidence of ancient intermixing between Polynesian and American populations (146), there are no indications of a link between ancestry and severe outcomes from ZIKV at this point. Likewise, genetic variation in *A. aegypti* is known to affect vector competence to transmit flaviviruses (147); hence, it is possible that changes in the makeup of the vector population also influence ZIKV transmission and account for regional differences in ZIKV effects.

Challenges and research priorities for responding to the ZIKV threat

Surveillance and clinical outcomes

The key challenge in ZIKV surveillance is the proportion of cases that remain asymptomatic and the nonspecificity of ZIKV symptoms (148). Dengue and chikungunya are also transmitted by *Aedes* mosquitoes, cocirculate with ZIKV, and can have a similar presentation, further complicating surveillance efforts.

Laboratory testing is needed to confirm ZIKV infection. Molecular (reverse transcription polymerase chain reaction) techniques can be used to detect ZIKV in serum, saliva, and urine (67, 149). However, there are frequent cases in which testing of different fluids gives discrepant results, and additional studies are needed to assess diagnostic accuracy (67). The timing of sample collection is crucial; viral RNA is only detectable in serum for 3 to 5 days after symptom onset (~10 days after infection) but may persist longer in other fluids (59, 64, 66).

A highly specific, easily administered antibody test would be a boon to surveillance and patient care. Such a test could be used to estimate underlying ZIKV incidence and thus rates of severe outcomes, confirm infection in studies of ZIKV pathogenesis, and test for immunity to ZIKV early in pregnancy so women can know whether they are at risk. However, serological testing is complicated by potential cross-reactivity with other flaviviruses (22). Newer enzyme-linked immunosorbent assay (ELISA) tests show promise, such as an IgG-ELISA test used in French Polynesia that, despite endemic dengue circulation, found <1% ZIKV seropositivity in blood donors before the outbreak (150).

To assess the risk and determinants of ZIKV-related clinical outcomes, we need studies aimed at measuring the underlying incidence of ZIKV infection, regardless of clinical presentation (e.g., serosurveys), the spectrum of illness and risk factors for severe outcomes (e.g., cohort and case-control studies), and the effect of ZIKV over longer time scales, including the length of immunity.

Ecology and evolution

There has been a high level of global concern surrounding the threat from ZIKV. One reason the concern is so great is that we are unable to accurately assess the global threat from the virus, and differing lines of evidence point to conflicting conclusions. For instance, the range of *Aedes* mosquitoes and ecological analyses would suggest that much of the continental United States is at risk from ZIKV, whereas recent experience with dengue and chikungunya would suggest that ZIKV is unlikely to persist in this region. To assess the epidemiologic and ecologic factors that drive global risk, there is a need for studies that more accurately assess where ZIKV circulation persists over long periods (e.g., global age-stratified serosurveys) and the ecological determinants of persistence (e.g., reservoirs, critical population size, and vector competence), as well as studies characterizing interactions between ZIKV and other flaviviruses. Across both clinical and ecological studies, it is important to evaluate the effect of host, viral, and mosquito genetics.

Interventions and control

A ZIKV vaccine may be the best way to protect at-risk populations over the long term. Vaccine development has been prioritized by the WHO and other public health agencies, and there are at least 18 active manufacturers and research institutions pursuing early stages of ZIKV vaccine development (151). However, phase 1 clinical studies are not expected to begin until the end of 2016 (151); hence, a vaccine is unlikely to become available in time to change the course of the current outbreak in the Americas.

Without a vaccine or antiviral drugs, the tools at our disposal for reducing ZIKV incidence are based on vector control and limiting ZIKV exposure. We have little direct evidence of the effectiveness of these approaches in controlling ZIKV transmission, but there are decades of experience in controlling dengue and other flaviviruses (152–154). Effective vector control is possible: Gorgas virtually eliminated yellow fever from Havana and the Panama Canal region in the early 1900s using crude and draconian methods of vector control (155). Intensive vector control in the 1950s and 1960s, including mass DDT spraying, successfully eliminated *A. aegypti* from 18 countries in the Americas, substantially reducing dengue incidence (154, 156, 157). Later, Singapore and Cuba implemented successful vector-control programs lasting decades (154, 158, 159). However, all of these efforts ultimately proved to be unsustainable, and *A. aegypti* and dengue reemerged after their discontinuation (154, 158, 159). Nevertheless, there could be benefits from even short-term elimination, but research is needed to identify sustainable policies that can protect areas from ZIKV and/or other *Aedes*-borne diseases in the long term.

There is limited evidence for the effectiveness of measures aimed at reducing individual exposure to mosquitoes for dengue control. A meta-analysis suggests that use of screens in houses reduces the odds of dengue incidence by 78%, as does combined community environmental management and use of water-container covers (152). Other interventions—such as indoor residual spraying, repellents, bed nets, and traps—showed no statistically significant effect or a negative effect (insecticide aerosols) (152). However, these results are predominantly based on observational studies, limiting the strength of the evidence they provide. Topical insect repellents and other personal protective measures do reduce mosquito biting (160) and should decrease the risk of ZIKV infection. Some randomized trials have assessed the effect of interventions on mosquito populations with inconsistent results (152, 161), and there have been no well-designed trials assessing the effect of the common, WHO-recommended practice of space spraying or fogging to control dengue transmission (152). Well-designed experimental studies with end points of transmission and disease in humans are needed to better evaluate the effectiveness of interventions aimed at vector control and personal risk reduction.

Conclusion

The rise of ZIKV after its long persistence as a disease of apparently little importance highlights how little we truly understand about the global spread of flaviviruses and other vector-borne diseases. Over the past decades, dengue, chikungunya, West Nile virus, and now ZIKV have emerged or reemerged throughout the globe (2, 145). However, why these viruses have expanded their range, while others (e.g., yellow fever) have failed to invade areas potentially ripe for their spread, remains a mystery. New analytic and molecular tools have greatly expanded our ability to forecast risk and track the spread of these viruses, but a deep understanding of what makes one virus a global threat while another is not remains elusive. Although the important role of random chance and the continuing evolution of viral species may make precise forecasting of emerging pandemics impossible, we can continue to improve the speed with which we assess and respond to emerging threats.

The evidence highlighted in this review is both encouraging and disheartening. On the one hand, the speed with which the global community has collected and disseminated clinical, epidemiologic, and laboratory information on ZIKV after identification of the threat is impressive. But the development of therapeutics and diagnostics is hampered by our ignorance, despite knowing of ZIKV's existence for more than half a century. Consequently, we have been able to do little to contain the virus's rapid spread across the Americas. New threats from infectious diseases may emerge from unexpected places, and we need strategies in place that we can roll out to rapidly gain an understanding of the transmission, pathogenesis, and control of previously little-known pathogens to protect global public health.

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Editor's Summary

Global spread of Zika virus

Zika virus was identified in Uganda in 1947; since then, it has enveloped the tropics, causing disease of varying severity. Lessler et al. review the historical literature to remind us that Zika's neurotropism was observed in mice even before clinical case reports in Nigeria in 1953. What determines the clinical manifestations; how local conditions, vectors, genetics, and wild hosts affect transmission and geographical spread; what the best control strategy is; and how to develop effective drugs, vaccines, and diagnostics are all critical questions that are begging for data.

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