REVIEW ARTICLE

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Zika Virus Infection — After the Pandemic

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Zika virus (ZIKV) was discovered in Africa in 1947 and was first detected in Asia in 1966, yet its potential effect on public health was not recognized until the virus caused outbreaks in the Pacific from 2007 to 2015 and began spreading throughout the Americas in 2015.[1,2] The ability of ZIKV to cause congenital defects in fetuses and infants, as exemplified by the microcephaly epidemic in Brazil, is an unprecedented feature in a mosquito-borne viral infection.[2-4] Although transmission of ZIKV has declined in the Americas, outbreaks and infection clusters continue to occur in some regions, such as India and Southeast Asia, where there are large populations of women of childbearing age who are susceptible to the virus.[5] We review the body of information that was acquired during the pandemic and discuss the epidemiologic trends, current knowledge about the transmission and natural history of ZIKV infection and its sequelae, and the principles of diagnosis and clinical management.

Epidemiologic Features

ZIKV is a positive-sense RNA flavivirus in the family Flaviviridae, which also includes dengue (DENV), West Nile, yellow fever, and Japanese encephalitis viruses.[6] ZIKV was first isolated in 1947 in the Zika Forest in Uganda (Fig. 1),[7] where transmission of the ancestral African lineage of ZIKV was limited to enzootic circulation between nonhuman primates and sylvatic aedes mosquitoes, with sporadic spillover infection to humans.[2] As ZIKV migrated to Asia, the Asian lineage of the virus emerged (Fig. 2), which was capable of being transmitted by human-adapted aedes mosquitoes (e.g., *Aedes aegypti*).[1,2] Results of serologic and entomologic investigations suggest that ZIKV had an extensive geographic distribution in Africa and Asia before 2007.[1,9] However, fewer than 20 cases in humans were reported before 2007, and all had mild, self-limiting clinical manifestations.[1,2,10]

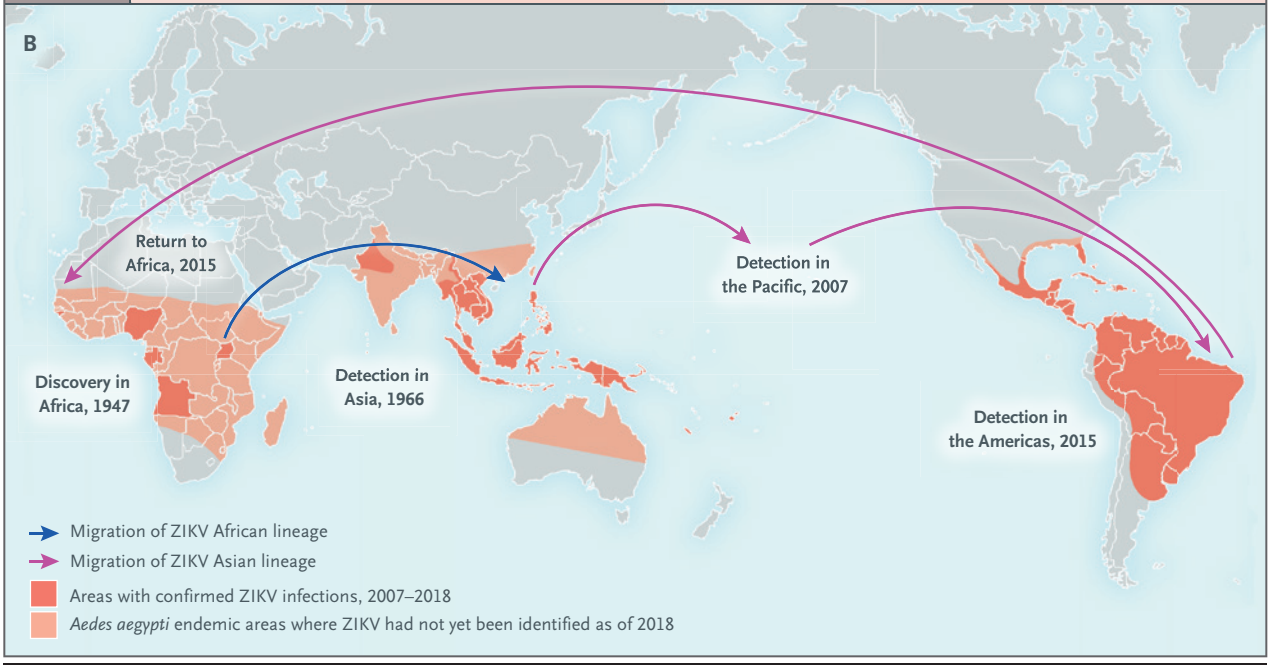
The first indications of a change in the epidemiology of ZIKV were the outbreaks reported in the Pacific in the Yap Islands, Micronesia, in 2007 and French Polynesia in 2013 and 2014, which were followed by pandemic spread of the virus to the

Figure 1 (facing page). Emergence and Spread of ZIKV and Timeline of the Zika Virus Pandemic.
Panel A shows the major epidemiologic events in the emergence and spread of Zika virus (ZIKV) from its discovery in 1947 through 2018, including outbreaks during which cases of ZIKV-associated birth defects were identified in newborns (*). Panel B is a map of regions where confirmed cases of ZIKV infections have occurred from 2007 through 2018 (red) and areas where *Aedes aegypti* is endemic but where ZIKV had not yet been identified (pink) as of 2018. Also shown is the migration of African (blue arrow) and Asian (purple arrows) lineages of ZIKV during its global emergence. The epidemiologic events associated with the spread of ZIKV are described in detail in Figure S1 and Table S1 in the Supplementary Appendix.

A

	1945–1955	1955–1965	1965–1975	1975–2005	2005–2010	2010–2013	2013–2014	2014–2015	2015–2016	2016–2017	2017–2018
Africa	**1947** Discovery of ZIKV in monkeys (Uganda)		**1962–3** First human case (Uganda)					**2015** Cape Verde outbreak*	**2016** Guinea–Bissau outbreak* **2016–2017** Angola outbreak*		
Asia			**1966** Detection of ZIKV in Asia (Malaysia) in mosquitos (*Aedes aegypti*)						**2016** Singapore, Vietnam*, and Thailand* outbreaks		**2018** India outbreak
Pacific				**2007** Yap Islands outbreak			**2013–2014** French Polynesia outbreak* • Cluster of Guillain–Barré syndrome (GBS) • Maternal–fetal transmission identified • Detection of ZIKV in semen and asymptomatic blood donors **2014–2016** Spread in the Pacific		**2016** Link established between ZIKV and GBS		
Americas				**2008** Suspected sexual transmission after exposure to a returning traveler from Senegal				**2015** Detection of ZIKV in Brazil* • Detection occurred in March • Increased numbers of microcephaly cases reported in October • Declaration of public health emergency in November	**2016** • WHO declares ZIKV a Public Health Emergency of International Concern (PHEIC) (February) • Pandemic spread to South America*, Central America*, and North America • Transmission in continental United States • Blood-transfusion–associated transmission confirmed • Link established between ZIKV and severe birth defects • Sexual transmission confirmed	**2017** Declining circulation	**2018** Low-level circulation

B



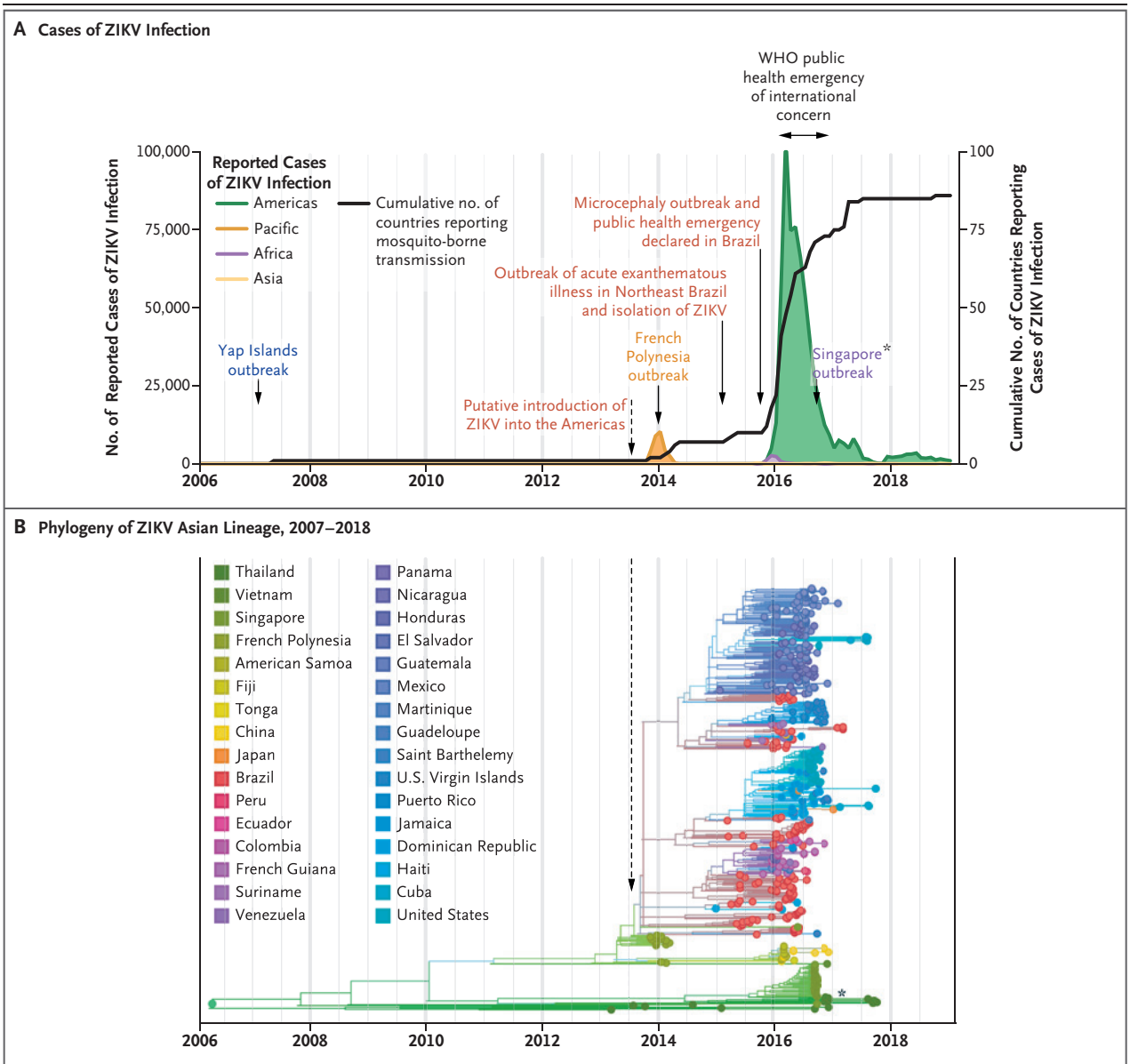


Figure 2. Reported Cases and Spread of the Virus during the Zika Pandemic.

Panel A shows the number of reported cases of ZIKV infection in the Americas, Pacific Islands, Africa, and Asia, as well as the cumulative number of countries or territories worldwide that reported mosquito-borne transmission from January 2007 through December 2018. Panel B shows a ZIKV time-resolved phylogenetic tree that was reconstructed by Nextstrain (https://nextstrain.org/zika, with permission from Trevor Bedford and Richard Neher) with the use of 506 genomes from 32 countries sampled from February 2013 to September 2017. The American subclade emerged from the Asian lineage and caused outbreaks throughout the Pacific Islands and the epidemic in the Americas.[6] The dashed line shows the estimated period (May through November 2013) when ZIKV was introduced into the Americas.[8] The cluster of sequences that were obtained from outbreaks in Singapore in August 2016 and Thailand and Vietnam in 2016 and 2017, which are indicated by an asterisk, are distinct from the sequences of pandemic strains from the Pacific Islands and the Americas.

Americas, the Caribbean, and Africa in 2015 (Fig. 1; and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[1,2,11-13] ZIKV may have been introduced into Brazil as early as late 2013 — more than 1 year before detection of the initial outbreak in the Americas (Fig. 2A and 2B).[8] The ZIKV pandemic was an example of a "perfect

storm," in which a new American subclade (strains isolated in the Americas) emerged from the Asian lineage of the virus (Figs. 1B and 2B) and was introduced into a uniformly susceptible population that had not been previously exposed to ZIKV.[8,14,15] The pandemic underscores the ability of the virus to be efficiently transmitted in aedes-infested settings and to spread across regions through human mobility and travel.[1]

Another striking feature of the pandemic was the emergence of severe complications of ZIKV infection. Clusters of the Guillain–Barré syndrome were first identified during the outbreak in French Polynesia and later in the Americas (Fig. 1A).[16,17] In Brazil, a dramatic increase in microcephaly cases was detected among newborns, which led to a declaration by the World Health Organization (WHO) in February 2016 of a public health emergency of international concern (Figs. 1A and 2A) and to the identification of a causal link between ZIKV and birth defects.[18-20] As of January 2018, more than 3700 cases of congenital birth defects associated with ZIKV infection had been reported in the Americas.[21] However, accurate estimates of the burden of the Guillain–Barré syndrome and birth defects attributable to ZIKV infection have been hampered by a lack of systematic surveillance of these syndromes before and during the pandemic.[22] Initial reports overestimated microcephaly case numbers in Brazil because a sensitive yet nonspecific case definition was used before the INTERGROWTH-21st reference-based standards (https://intergrowth21.tghn.org/standards-tools/) were implemented.[22] Furthermore, accurate ascertainment of microcephaly requires multiple measurements after birth, as shown by an investigation in Paraíba, Brazil, that confirmed microcephaly in only 55% of infants who were initially reported to have the condition.[4] At present, congenital birth defects have been reported only in cases of infection by ZIKV strains belonging to the Asian lineage, including those identified during a 2016 outbreak in Angola.[23]

The high infection rate in affected populations was a major contributing factor to the detection of ZIKV-associated complications and to the disease burden of those complications during the pandemic. In communities at the epicenter of the microcephaly epidemic in northeast Brazil, more than 60% of the exposed population was infected.[15,19] The magnitude of the ZIKV emergence and the risk of severe complications, however, varied over time and with location. For example, an increase in the Guillain–Barré syndrome was observed during the 2015 and 2016 waves of ZIKV circulation in Brazil, whereas the increase in congenital malformations was detected mostly during the 2015 wave.[3,24]

Although the pandemic yielded a large body of information about ZIKV, important knowledge gaps remain (Table S2 in the Supplementary Appendix). Still unknown is whether the ZIKV-associated complications that were identified during the pandemic were new emerging phenomena — perhaps caused by the virus acquiring enhanced fitness, transmissibility, or disease severity phenotype — or had occurred previously but went undetected because of limited surveillance or infrequent transmission.[9,13] Data from in vitro studies and experimental studies in animals suggest that ZIKV mutations may increase the infectiousness of the virus in the *A. aegypti* vector and the risk of fetal microcephaly.[6,14,25,26] However, birth defects have been associated with infections by strains that do not contain these mutations, and pathogen-specific markers that predict the risk of birth defects have not been identified.[5] Therefore, ZIKV strains not harboring these mutations cannot be considered low-risk, as was suggested by health authorities during the 2018 outbreak in India.

ZIKV and DENV share antigenic similarities and have overlapping geographic distributions.[1] The effect of preexisting immunity against flaviviruses on ZIKV infection outcomes — whether the immunity is elicited by infection or by immunization with flavivirus vaccines — is a matter of debate. Laboratory investigations have yielded contradictory findings with respect to whether DENV infection elicits an immune response that protects against ZIKV infection or exacerbates infection by way of antibody-dependent enhancement.[27,28] Prospective studies in humans showed that prior dengue infection and preexisting anti-DENV antibodies reduced rather than enhanced the risk of ZIKV infection and disease.[15,29] Further investigation is needed to determine whether these findings are generalizable across regions in which ZIKV has emerged, whether they apply to severe ZIKV-associated outcomes such as the Guillain–Barré syndrome and birth defects, and whether differing amounts or types of

dengue antibodies influence the balance between protection from and enhancement of ZIKV infection.

Autochthonous transmission of ZIKV has been reported in 87 countries and territories (Fig. 1B, and Table S1 in the Supplementary Appendix) in subtropical as well as tropical climates, as exemplified by the spread of ZIKV to Florida and Texas. ZIKV transmission has declined markedly in the Americas since late 2016; fewer than 30,000 cases were reported in 2018, as compared with more than 500,000 cases reported at the peak of the pandemic in 2016 (Fig. 2A). Cumulative population-level immunity owing to naturally acquired infection appears to have driven ZIKV to extinction in many regions.[15,30] However, spatial heterogeneity in ZIKV infection rates during the pandemic may have created pockets of susceptible populations that can sustain transmission in the future.[15] Indeed, large population centers, such as the city of São Paulo, were unaffected by the pandemic, and cases of ZIKV infection continue to be detected in the Americas (Fig. 2A).[31]

Furthermore, ZIKV transmission may be occurring without an identifiable outbreak, since the majority of infections are asymptomatic.[1,11] The identification of a large and unreported outbreak in Cuba in 2017, with cases still being identified in 2018,[32] suggests that ZIKV may still be spreading silently in the Americas.

At present, there is no evidence of a nonprimate animal reservoir for ZIKV. However, another concern, supported by the detection of ZIKV RNA in Brazilian monkeys living in proximity to humans, is the possibility that ZIKV will establish a zoonotic cycle in the Americas. This would be akin to what occurred with the introduction of yellow fever to the Americas in the 17th century and would serve as a focus for future spillover infection to humans.[33]

The identification of ZIKV outbreaks in Southeast Asia and South Asia is a new and important public health concern (Figs. 1 and 2A). These outbreaks, which are due to transmission of the local Asian subclade rather than the pandemic American subclade (Fig. 2B), have been reported to cause birth defects among newborns and have occurred in large population centers in Singapore, Thailand, Vietnam, and India.[5,34,35]

TRANSMISSION

Mosquito-borne transmission is the primary mechanism for epidemic spread. *A. aegypti* is the major vector for horizontal transmission of ZIKV to humans.[36] *A. albopictus*, which has a greater distribution in temperate climates, is a competent vector but does not appear to play an important role.[36] Predictive models suggest that the geographic distribution of *A. aegypti* will continue to expand as a consequence of population growth and movement, urbanization, and climate change.[37] However, ZIKV can be transmitted to humans by non-vectorborne mechanisms (Fig. 3), such as blood transfusion,[38] and is unique among arboviruses in that it can be transmitted during sexual contact and can cause teratogenic outcomes as a consequence of maternal–fetal transmission.

In humans, male-to-female sexual transmission can occur whether the male partner with ZIKV infection is symptomatic or asymptomatic and has been observed more frequently than female-to-male and male-to-male transmission.[39] Although the effect of sexual transmission in areas in which the virus is endemic is difficult to assess, estimates are that 1% of ZIKV infections reported in Europe and the United States were acquired through sexual transmission.[40] ZIKV RNA has been detected in semen, by reverse-transcriptase–polymerase-chain-reaction assay, up to 370 days after onset of illness, but shedding of infective viral particles is rare after 30 days from the onset of illness.[39,41] Although alterations in semen and sperm quality have been observed in men with ZIKV infection, an adverse effect on male fertility has not been shown.[42]

Maternal–fetal transmission of ZIKV may occur in all trimesters of pregnancy, whether infection in the mother is symptomatic or asymptomatic (Fig. 3).[18,43-46] Vertical transmission has been estimated to occur in 26% of fetuses of ZIKV-infected mothers in French Guiana, a percentage similar to transmission percentages that have been observed for other congenital infections.[46] Among fetuses that were exposed to ZIKV by vertical transmission, fetal loss occurred in 14% and severe complications compatible with congenital Zika syndrome occurred in 21%. In addition, 45% of the fetuses that were exposed

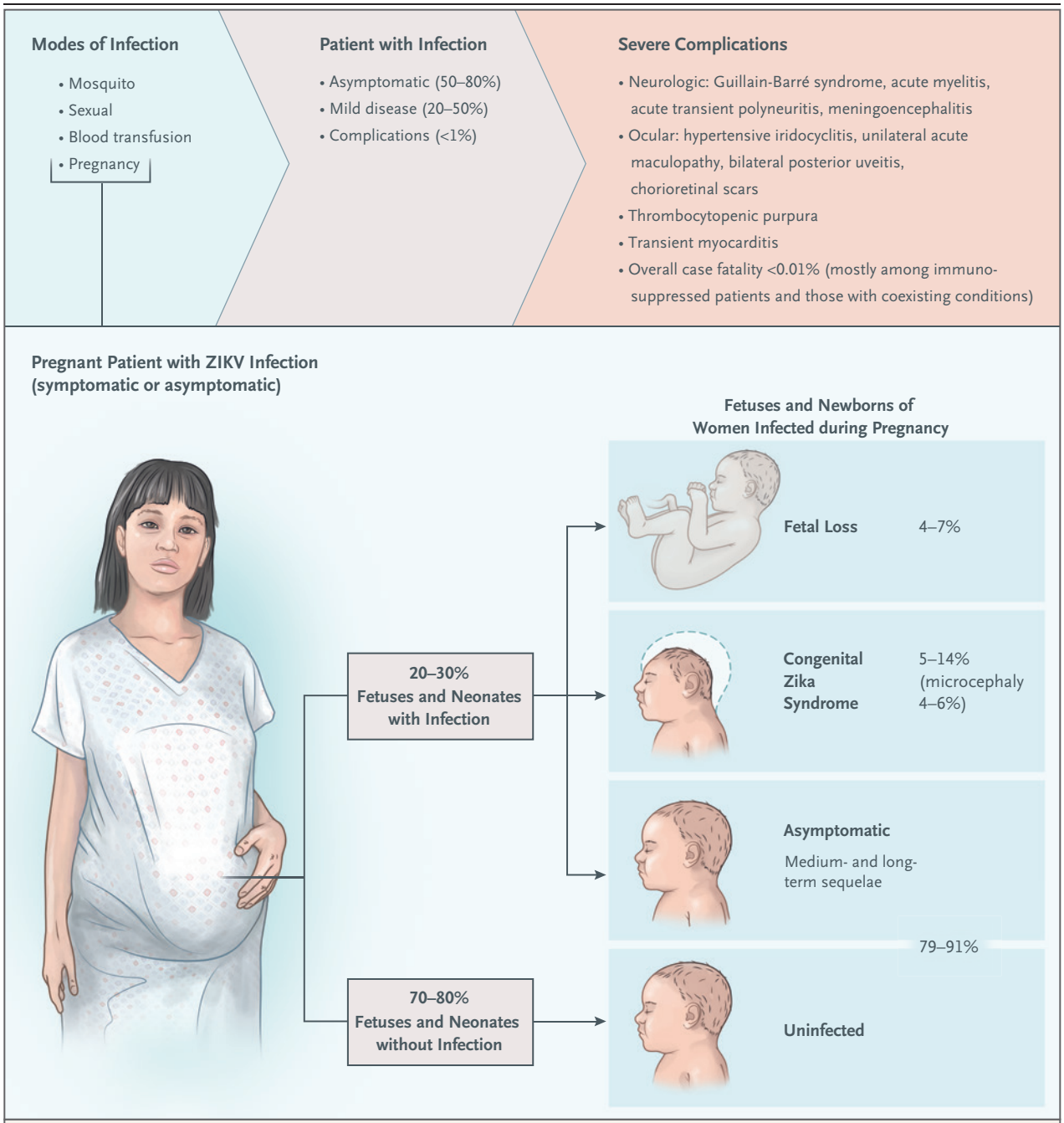


Figure 3. Zika Virus Transmission and Clinical Features.

Shown are the modes of transmission, complications observed in adults and children after infection, and natural history of ZIKV infection during gestation and birth. Percentages of maternal–fetal transmission, fetal loss, acquisition of congenital Zika syndrome, and ZIKV-associated microcephaly among fetuses and infants of women infected with ZIKV during pregnancy were estimated on the basis of the findings of prospective studies and case series (included in the Supplementary Appendix). The estimates do not include data from a prospective study from Rio de Janeiro that showed a high percentage (42%) of adverse outcomes among fetuses and newborns whose mothers were infected with ZIKV.[18] At present, the spectrum and risk of medium- and long-term sequelae, including neurodevelopmental delay, have not been fully delineated.

to ZIKV by vertical transmission had no signs or symptoms of congenital Zika syndrome in the first week of life.[46] The majority of reports of ZIKV-associated fetal and infant outcomes did not ascertain fetal infection due to vertical transmission. Figure 3 therefore summarizes the evidence on the proportions of fetal loss and congenital Zika syndrome that occurred among fetuses of women who were infected with ZIKV during pregnancy (see also Table S3 in the Supplementary Appendix).

Although infective ZIKV particles have been detected in breast milk, milkborne transmission has not been confirmed as a mode of transmission.[47] At present, the WHO recommends that mothers with possible or confirmed ZIKV infection continue to breast-feed their infants.

CLINICAL MANIFESTATIONS

The majority (50 to 80%) of ZIKV infections are asymptomatic.[1,2,9,11-13] Symptomatic ZIKV infection has an incubation period of 3 to 14 days and is a mild illness, with a duration of up to 1 week, that manifests as a rash, low-grade fever, arthralgia and myalgia, and conjunctivitis.[1,11,12] Complications are infrequent, but when they occur, they are severe and may be fatal (Fig. 3).[1] The manifestations of acute ZIKV infection are similar across age groups, in both sexes, and in pregnant women. Although ZIKV shows broad cellular tropism, the striking feature of the clinical manifestation is the neurologic complications that result from postinfectious immune response or direct viral neurotropism.[48]

Figure 4 (facing page). Clinical and Imaging Findings of Congenital Zika Syndrome.

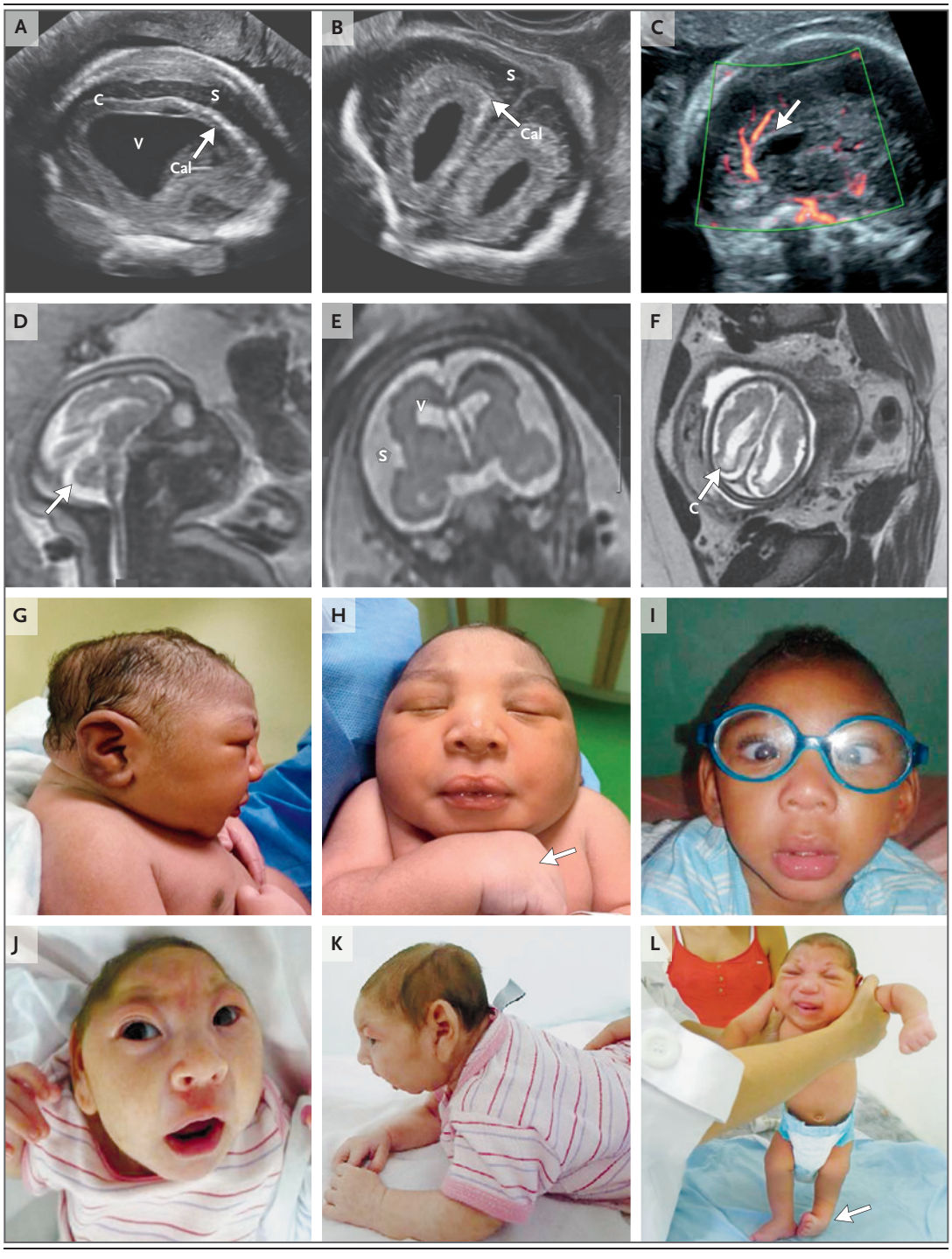
Images illustrate selected features[18,46,54-59] of the manifestation of congenital Zika syndrome in fetuses and newborns. Prenatal neurosonograms of fetuses with ZIKV infection (Panels A, B, and C, at 22, 22, and 26 weeks of gestation, respectively) show linear calcifications (Cal, arrows, Panels A and B), increased pericerebral spaces (S, Panels A and B), ventriculomegaly (V, Panel A), cortical thinning (C, Panel A), and dysgenesis of the corpus callosum (arrow, Panel C). MRIs of a fetus with ZIKV infection at 32 weeks of gestation (Panels D, E, and F) show microcephaly (Panel D), hypoplasia of the cerebellum and vermis (arrow, Panel D), premature closure of the fontanels and partial collapse of the skull (Panel D), increased pericerebral spaces (S, Panel E), ventriculomegaly (V, Panel E), cortical thinning (C, Panel F), and dysgenesis of the corpus callosum and gyral anomalies (Panel E). Photographs of three infants — one at 1 week of age (Panels G and H) and 10 months of age (Panel I); the second at 14 days of age (Panels J and K); and the third at 51 days of age (Panel L) — show findings of severe disproportionate microcephaly and cranial dysmorphism (Panels G through L), arthrogryposis (arrow, Panel H), strabismus (Panel I), neck rigidity caused by axial hypertonicity (Panel K), and talipes equinovarus (arrow, Panel L).

ZIKV-ASSOCIATED GUILLAIN–BARRÉ SYNDROME

The incidence of ZIKV-associated Guillain–Barré syndrome is estimated to be 2 to 3 cases per 10,000 ZIKV infections, which is similar to the risk associated with campylobacter infection.[49,50] The interval between antecedent illness and onset of the Guillain–Barré syndrome is 5 to 10 days, which has led to speculation about a contributory parainfectious process.[51] Acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, and the Miller–Fisher syndrome (a subset of the Guillain–Barré syndrome characterized by ophthalmoplegia, ataxia, and areflexia) have been observed with ZIKV-associated Guillain–Barré syndrome, but the relative proportions of these subtypes vary across studies and regions.[16,17,51] Several case series showed that the prognosis of ZIKV-associated Guillain–Barré syndrome was similar to that of Guillain–Barré syndrome associated with other infectious or noninfectious processes; however, findings from a case–control study suggest that ZIKV-associated Guillain–Barré syndrome results in higher morbidity and more frequent cranial neuropathy.[51,52] Other autoimmune disorders, such as thrombocytopenic purpura, have also been associated with ZIKV infection.

CONGENITAL ZIKA SYNDROME

As became evident early in the microcephaly epidemic, ZIKV causes a spectrum of fetal and birth defects that extends beyond microcephaly and is distinct from other congenital infections in that its pathologic manifestations are restricted primarily to the central nervous system.[53,54] Prominent features of congenital Zika syndrome (Fig. 4 and Table 1) include fetal brain disruption sequence, a condition that arises from partial brain disruption during gestation with subsequent collapse of the fetal skull caused by decreased intracranial hydrostatic pressure; subcortical calcifications; pyramidal and extrapyramidal signs; ocular lesions of chorioretinal atrophy and focal pigmented mottling of the retina; and congenital contractures that appear to be



caused by a neurogenic process.[55] Although these anomalies are seen in other congenital infections, they appear to be more frequently associated with congenital Zika syndrome.[55]

Newborns of women infected with ZIKV during pregnancy have a 5 to 14% risk of congenital Zika syndrome and a 4 to 6% risk of ZIKV-associated microcephaly (Fig. 3, and Table S3 in the Supplementary Appendix).[18,43-46,56,57] A study involving pregnant women from Rio de Janeiro used a broader definition for ZIKV-associated outcomes and identified adverse outcomes in 42% of fetuses and infants exposed to the virus.[18] Although ZIKV infection in any trimester of

Table 1. Key Features of Congenital Zika Syndrome.

Lesion Type	Manifestations
Structural lesions	
Fetal brain disruption sequence*	Severe microcephaly, premature closure of fontanels, collapsed skull, overlapping sutures, redundant scalp skin
Brain abnormalities	Cortical atrophy with decreased myelination, cerebellar hypoplasia Neuronal migration disorder — lissencephaly, agyria, pachygyria, polymicrogyria, heterotopia, dysgenesis of corpus callosum Calcifications, mainly subcortical* Ventriculomegaly, increased posterior fossa and pericerebral spaces
Ocular abnormalities	Pigmented retinal mottling*, chorioretinal atrophy*, macular scarring, glaucoma, optic nerve atrophy and abnormalities, intraocular calcifications Microphthalmia, anophthalmia Iris coloboma, lens subluxation, cataract
Congenital contractures	Arthrogryposis, talipes equinovarus, hip dislocation
Intrauterine growth restriction	
Functional lesions	
Seizures	
Pyramidal or extrapyramidal abnormalities*	Body tone abnormalities (mainly hypertonia), swallowing disorder, movement abnormalities (dyskinesia, dystonia), hyperexcitability, impatient crying, sleep disorders
Neurodevelopmental abnormalities	Visual impairment (strabismus, nystagmus, vision loss) Hearing loss or deafness Developmental delay

* Lesions are rarely observed in other congenital infections.

pregnancy may cause congenital Zika syndrome, the risk is greatest with infections occurring in the first trimester.[18,43,44,56] Exposures to pesticides, toxins, medications, and maternal immunizations have not been found to be risk cofactors.[4,46]

Neonatal mortality in the first week of life among infants with congenital Zika syndrome may be as high as 4 to 7%; better estimates of neonatal mortality past the first week of life are needed.[18,46] The absence of clinical and radiologic abnormalities indicative of congenital Zika syndrome at birth (Fig. 4) does not exclude the risk of abnormalities such as seizures, hearing loss, visual impairment, dysphagia, and developmental delay later in life (Fig. 3). Among U.S. children who were born to mothers infected with ZIKV during pregnancy and who had no identified birth defects, 9% had at least one neurodevelopmental abnormality before they reached 2 years of age, a finding that underscores the need for long-term surveillance of children born to mothers with ZIKV infection.[46,57-59]

The use of varying definitions of cases and complications, in particular microcephaly, as well as inclusion of suspected but unconfirmed cases and bias in case reporting may have contributed to observed differences among studies in transmission and outcomes. Differences may also reflect regional variation in transmission and in the severity of complications. The full spectrum and risk of congenital Zika syndrome therefore remain incompletely delineated.

DIAGNOSIS

Since the clinical manifestation of acute ZIKV infection is nonspecific, a definitive diagnosis relies on nucleic acid testing or serologic testing (Table 2, and Table S4 in the Supplementary Appendix). Nucleic acid testing should be performed on whole blood or serum samples obtained during the first days of illness. However, testing paired blood and urine samples obtained within 2 weeks after the onset of illness is recommended given the potentially prolonged duration of ZIKV RNA in these fluids.[60,63] Although ZIKV RNA detection provides conclusive evidence of an infection, a negative result does not rule out the diagnosis.[60,64] A positive nucleic acid test shows the presence of ZIKV RNA but does not necessarily indicate the presence of infectious virus.

Serodiagnosis is complicated by false positive results owing to cross-reactivity in persons who have been exposed to other flaviviruses.[60] Screen-

ing by detection of ZIKV IgM is performed on serum samples obtained 2 to 12 weeks after the onset of illness. Confirmation of inconclusive and positive IgM results requires further testing with the plaque reduction neutralization test (PRNT), which can be performed only at highly specialized reference laboratories and is also subject to false positive results.[60] It is therefore important when interpreting serologic results to consider past exposure to flaviviruses, including exposure resulting from travel in areas in which those viruses are endemic and from vaccination.

The diagnosis of ZIKV infection in pregnant women and infants poses several challenges. ZIKV RNA is often detected transiently in an infected mother and fetus despite the observation of prolonged viremia during pregnancy.[64] ZIKV RNA can be detected in amniotic fluid, but a negative result does not rule out the diagnosis.[64,65] Thus, amniocentesis is not routinely recommended and should be used primarily to rule out other diagnoses in fetuses with prenatal findings consistent with a congenital ZIKV infection. The diagnostic goal is to determine the timing of asymptomatic as well as symptomatic infections, since both pose a risk for vertical transmission. However, serodiagnosis is hampered by the persistence of ZIKV IgM for up to 12 weeks after the onset of illness and the inability of PRNT to distinguish between recent and past infections.[61]

Established guidelines recommend a complex algorithm of laboratory and clinical testing during pregnancy (Table 2).[60,61] Given the limitations of laboratory diagnosis, serial ultrasound monitoring of the fetus during pregnancy is key, but its effectiveness is dependent on access and on the ultrasonographer's expertise.[66] Magnetic resonance imaging of the fetus may contribute to assessment.[44,57,59] Laboratory confirmation of congenital ZIKV infection in newborns is highly insensitive. When congenital Zika syndrome is suspected, other causes of fetal anomalies (infectious causes, such as TORCHS [toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis], and genetic, toxic, and metabolic disorders) should also be investigated.[61] In regions with active or past ZIKV transmission, close monitoring of infant growth and developmental milestones is essential, since a large proportion of infants may have been exposed to ZIKV in utero without documentation of exposure in the mother.

TREATMENT AND PREVENTION

Several compounds have shown activity against ZIKV in vitro, but none of them have yet been evaluated in clinical trials.[67] Since no antiviral agents have been approved by regulatory agencies for the treatment of ZIKV infection, the clinical management of acute ZIKV infection is supportive care.[67] The therapeutic approach to ZIKV-associated Guillain–Barré syndrome is the same as that for classic Guillain–Barré syndrome and includes the use of therapeutic plasma exchange or intravenous immune globulin.[62] Recommendations regarding the care of infants are stratified according to the clinical and imaging findings in the infant and laboratory evidence of ZIKV infection in the mother during pregnancy (Table 2).[61] Infants with congenital ZIKV infection require care from a multidisciplinary team that monitors complications and, given the risk for developmental delays, includes a developmental specialist and provides early-intervention services.[61] Family and supportive services are key elements in the care of infants with ZIKV infection.[61]

Recommendations for the protection of the general population against mosquito bites and for vector-control strategies to prevent ZIKV infections are similar to those for other aedes-transmitted viruses.[68] Prevention of sexual transmission relies on abstinence or protected sexual intercourse after suspected infection — for 2 months if the partner with suspected infection is female and for 3 months if the partner with suspected infection is male.[39] Prevention of congenital Zika syndrome relies on avoidance of infection during pregnancy or postponement of pregnancy.[69]

More than 10 candidate vaccines have advanced to phase 1 clinical trials and 1 has begun phase 2 clinical trials.[70] However, a major barrier to evaluating vaccine effectiveness is the waning incidence of ZIKV after the pandemic, which in turn has hampered implementation of phase 2 and phase 3 clinical trials.[70,71] Alternative approaches, such as controlled human challenge infection models, are being considered to obtain efficacy data for regulatory approval of a vaccine.[71]

CONCLUSIONS — LESSONS LEARNED FROM THE PANDEMIC

The public health community was unprepared for the emergence of ZIKV and the dramatic and

Table 2. Diagnostic and Clinical Evaluation According to Patient Population and Zika Virus Exposure.*

Patient Population and ZIKV Exposure	ZIKV Laboratory Investigations (Schedule)		Other Evaluations (Schedule)
	Nucleic Acid Testing	IgM Serologic Testing	
General population			
Uncomplicated ZIKV infection	Not recommended	Not recommended	Not recommended
Possible associated Guillain–Barré syndrome	Paired serum and urine; testing of cerebrospinal fluid should be considered	Serum; testing of cerebrospinal fluid should be considered	Nerve conduction studies Cerebrospinal fluid chemical analysis
Presenting for preconception screening	Not recommended	Not recommended	Not recommended
Pregnant women			
Possible ZIKV exposure; symptomatic	Paired serum and urine (ASAP, up to 12 weeks after onset of illness)	Serum (ASAP, up to 12 weeks after onset of illness)	Ultrasonography (at 18–22 weeks of gestation) Serial ultrasonography (every 3–4 weeks)†‡ No universal recommendation for amniocentesis§
Possible ongoing ZIKV exposure; asymptomatic	Paired serum and urine (at initial visit and during each trimester)	Not recommended	Ultrasonography (at 18–22 weeks of gestation) Serial ultrasonography (every 3–4 weeks)†‡ No universal recommendation for amniocentesis§
Possible recent ZIKV exposure; no ongoing exposure; asymptomatic	Paired serum and urine (ASAP, up to 12 weeks after onset of illness)†	Serum (ASAP, up to 12 weeks after onset of illness)†	Ultrasonography (at 18–22 weeks of gestation) Serial ultrasonography (every 3–4 weeks)†‡ No universal recommendation for amniocentesis§
Possible ZIKV exposure; fetus has findings on ultrasound consistent with congenital ZIKV infection	Paired serum and urine (ASAP, up to 12 weeks after onset of illness) Amniotic fluid¶ Testing of placental and fetal tissues after delivery should be considered	Serum (ASAP, up to 12 weeks after onset of illness)	Ultrasonography (at 18–22 weeks of gestation) Serial ultrasonography (every 3–4 weeks)†‡ No universal recommendation for amniocentesis§
Newborns			
No findings of congenital Zika syndrome; mother had possible ZIKV exposure (not laboratory-confirmed) or was not tested	Not recommended	Not recommended	Physical and neurologic examination at birth and at each follow-up visit
No findings of congenital Zika syndrome; mother had laboratory-confirmed ZIKV exposure during pregnancy	Paired serum and urine (within 2 days after birth)	Serum (within 2 days after birth)	Physical and neurologic examination at birth Head circumference retested 24 hours after birth Ultrasonography of the head by 1 month of age; consider MRI if available Ophthalmologic examination by 1 month of age AABR testing by 1 month of age

Findings of congenital Zika syndrome; mother had possible ZIKV exposure during pregnancy	Paired serum and urine (within 2 days after birth)	Serum (within 2 days after birth)	Same as for an infant without congenital Zika syndrome findings who is born to a mother with laboratory-confirmed exposure during pregnancy Screening for other causes of fetal abnormalities (genetic, infectious, toxic, or metabolic) Referral to developmental specialist, family support service, and additional consultations‖
Stillbirth or neonatal death; mother had possible or laboratory-confirmed ZIKV exposure during pregnancy	Placental and fetal tissues[46]	Not recommended	Repeat serologic test in mother if previous results were negative Autopsy

* Adapted from Centers for Disease Control and Prevention[60,61] and World Health Organization[62] recommendations. AABR denotes automated auditory brainstem response, and ASAP as soon as possible.
† The need for testing is determined on a case-by-case basis.
‡ There is not a strong consensus for the timing of testing.
§ Amniocentesis has not been universally recommended because of the risk of false negative results and potential for iatrogenic pregnancy loss. The decision to pursue amniocentesis should be discussed with mothers who have laboratory-confirmed ZIKV infection.
¶ Amniotic fluid is tested if amniocentesis is performed as part of clinical care.
‖ Additional consultations may include infectious disease specialist, clinical geneticist, neurologist, or other clinical specialists, depending on clinical findings in the infant.

unexpected consequences of ZIKV infections during pregnancy. However, the response to the Zika crisis, including the declaration by the WHO of a public health emergency of international concern, was enormous, as exemplified by the identification of the causal link between ZIKV and birth defects, more than 6000 scientific publications on ZIKV, approval of new diagnostic tests, and development of vaccine candidates that have entered clinical trials — all within the past 3 years.[72] Furthermore, the pandemic increased positive awareness about critical social justice issues, such as stigma toward and isolation of families of infants with congenital Zika syndrome, the reproductive rights of women, and access to safe abortion and contraception in Latin America.[73] Of note, although abortion policies remained unchanged in many countries, the ZIKV outbreak in Brazil was associated with a decrease of more than 100,000 births between September 2015 and December 2016, which may have resulted from postponement of pregnancies and an increase in clandestine abortions.[74]

The experience of the pandemic highlights important deficiencies in our understanding of ZIKV (Table S2 in the Supplementary Appendix) and the barriers to translating evidence into implementable guidelines, especially in low- and middle-income countries.[72] The pandemic is illustrative of the universal failure of vector-control programs in regions where rapid urbanization and interconnectivity promote epidemic spread. However, new vector-control approaches, such as those that involve genetically modified mosquitoes, wolbachia-transfected mosquitoes, and pyriproxyfen-based larvicide, are under evaluation.[75] Current diagnostic testing remains suboptimal for the detection of congenital ZIKV infections, which in turns hampers implementation of clinical management. Although the pandemic has subsided, we lack sufficient information on ZIKV seroprevalence to evaluate the potential for future epidemics among the more than 2 billion people who live in regions at risk for ZIKV transmission (Fig. 1).[37] Furthermore, the majority of this population resides in resource-poor settings in which there is no access to diagnostic testing and limited capacity to conduct screening and evaluation of pregnant women and infants who have been exposed to ZIKV infection — a difficult task to implement even in high-resource countries.[72]

The ZIKV pandemic has waned, but the virus still poses a public health threat, as shown by continued reports of outbreaks in Asia, India, and Africa. Although at present we do not have the tools to predict where and when the next large epidemic will happen, the large numbers of susceptible persons residing in aedes-infested regions make a reemergence of ZIKV likely. Thus, there is a critical need to mobilize support and improve capacity in low- and middle-income countries to respond to future ZIKV epidemics and the next emerging pathogens.

Dr. Ko reports holding pending patent PCT/US2018/031540 on methods and compositions for the detection of flavivirus infections, licensed to the University of Pittsburgh. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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