The Emerging Zika Virus Epidemic in the Americas
Research Priorities

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On February 1, 2016, the World Health Organization declared a "public health emergency of international concern" regarding neurological disorders associated with the rapid emergence of Zika virus (ZIKV) in the Americas. Since being detected in Brazil in early 2015, ZIKV has spread extensively, with most countries in Latin America and the Caribbean now reporting local transmission of the virus. An association between congenital ZIKV infection and birth defects, most prominently microcephaly, has prompted intense concern among health officials and the public.

The current ZIKV epidemic follows a trend that started more than 500 years ago with introduction of the yellow fever mosquito, *Aedes aegypti*, from Africa into the Americas. The invasion of *A aegypti* led to epidemics of old world arboviral diseases such as yellow fever (1647), dengue fever (1780), dengue hemorrhagic fever (1982), and chikungunya (2013), which share the same mosquito vector and urban transmission cycle as ZIKV. The worldwide call for new initiatives to combat ZIKV must be informed by decades of basic and applied research on dengue and other closely related arboviruses. This Viewpoint will focus on research priorities to better understand and effectively respond to the ZIKV crisis.

New Diseases From an Old Virus?

Zika virus is a flavivirus related to dengue, West Nile, and yellow fever viruses.[1,2] Sequence analyses show that ZIKV isolates from South America are similar to those from French Polynesia, suggesting that the virus was introduced to Brazil by an infected traveler or mosquito from the South Pacific. However, the virus sequences are not identical, and there is even greater divergence from historical African isolates. Much of this difference likely represents random genetic drift, but even minor changes to the viral genome could have a significant effect on human disease.

As an example, a single amino acid change in its surface glycoprotein enables chikungunya virus to use *Aedes albopictus* mosquitoes as a vector, facilitating epidemic spread into new areas. It is unknown whether specific changes in ZIKV (ie, new viral strains) are responsible for the unexpected disease patterns in the current pandemic. Cell culture, mosquito, and vertebrate animal models are needed to compare the replication, pathogenesis, and transmission of historical and contemporary ZIKV strains. Molecular tools to map viral genetic determinants that contribute to increased transmission and disease also are needed.

Diagnostic Dilemmas

Currently available serological tests cannot reliably distinguish ZIKV infection from other flaviviruses, severely hampering studies of ZIKV spread and disease. The public health response to this epidemic depends on rapid development of accurate diagnostics. Most flavivirus infections remain unrecognized or cause an undifferentiated febrile illness, and therefore, surveillance based on clinical criteria alone can be misleading. In addition, because flavivirus infections cause acute infections that are rapidly cleared by the human immune response, detection of viral nucleic acid or antigens in the peripheral blood is typically limited to a narrow window of 1 to 5 days after the onset of symptoms.[3]

Serology, a mainstay of viral surveillance and diagnosis, is confounded by extensive antibody cross-reactivity between flaviviruses.[3] The presence of immunoglobulin G antibodies that bind to ZIKV could result from past infection with any of several flaviviruses or prior vaccination with a flavivirus vaccine. This is not simply an academic scenario because ZIKV is emerging in areas with transmission of all 4 dengue serotypes, yellow fever vaccination, and dengue vaccines approved or in trials. In most metropolitan areas in Latin America at risk of ZIKV transmission, dengue seroprevalence in adults is likely to exceed 90%.[4]

Perhaps the most immediate research priority is the development of simple serological diagnostic assays for tracking the spread of ZIKV and for studying links between ZIKV infection and severe clinical manifestations. Currently, an immunoglobulin M (IgM) enzyme-linked immunosorbent assay is the only assay that can be used to test whether an individual has been recently exposed to ZIKV. However, the IgM assay has poor specificity in people who have been previously exposed to another flavivirus (ie, most people living in high-risk areas of Latin America and the Caribbean).

Although flavivirus cross-reactive antibodies dominate the human immune response, exposed individuals develop antibodies that target unique epitopes for each flavivirus, and such virus-specific antibodies are linked to protection against dengue virus.[5] Building on approaches developed for dengue and West Nile viruses, the major ZIKV-specific epitopes targeted by human antibodies need to be defined and mapped to develop more specific diagnostics.

Pathogenesis and Clinical Complications

Following a mosquito bite, keratinocytes and dendritic cells in the skin are presumed to be the initial targets of ZIKV infection. Viremia develops some 1 to 5 days later, and the virus is cleared from circulation within 2 weeks of infection. The cellular and tissue tropism of ZIKV in humans is not completely understood, and there is a need

for basic pathogenesis studies to understand the tropism, immune response, and pathogenic mechanisms of ZIKV.

Even though many questions remain surrounding transplacental transmission and teratogenic effects of ZIKV, accumulating evidence strongly suggests a causal role in the development of birth defects. In addition to the timing and geographic distribution of microcephaly cases relative to ZIKV infections, studies of infants and fetuses with microcephaly have detected ZIKV RNA in placenta, amniotic fluid, and fetal tissues; viral particles, antigen, and complete viral genome in brain tissue; and ZIKV IgM in amniotic fluids.[6] A recent report also documented severe ocular abnormalities involving the macula and optic disc among infants with microcephaly born in Brazil after a regional ZIKV outbreak.[7]

Many viruses acquired in pregnancy have different fetal transmission rates by trimester in which a pregnant woman is infected. Viruses tend to be more easily transmitted at later gestational ages, but have more severe effects on the fetus if transmitted earlier in pregnancy. Conversely, the risk of cytomegalovirus sequelae in infants may be as low as 6% with second trimester infection, and there appears to be an extremely low to no risk during the third trimester.[8]

The overall perinatal transmission rate of ZIKV, with resultant fetal infection, is not known, nor is it known whether vertical transmission rates differ by gestational age at the time of exposure or severity of maternal infection. Furthermore, among fetuses infected with ZIKV, the rate that newborns are significantly affected at birth is unknown, as well as whether the virus can be transmitted during labor and delivery or through breastfeeding.

The amniotic fluid of a fetus infected with cytomegalovirus does not become positive by polymerase chain reaction until at least 7 weeks after transmission. Because the sensitivity of cytomegalovirus polymerase chain reaction is lower during the initial 21 gestational weeks, amniocentesis is usually performed after 21 gestational weeks for a suspected infection, unless the fetus already shows sonographic signs of infection. This is likely to be true for ZIKV, but remains unknown. Zika virus seems to have a tropism for fetal brain tissue, but the entire spectrum of clinical findings for congenital ZIKV infection has not been adequately characterized.

Many ultrasonographic findings of fetal viral infections can be identified as early as 18 to 20 gestational weeks, but microcephaly may not be reliably diagnosed until after 24 to 28 weeks of gestation and in some cases may not be evident until birth. The full spectrum of potential developmental defects caused by fetal ZIKV infection is unknown, but other manifestations seem likely and may aid in fetal diagnosis. The currently identified microcephaly cases may represent the most severe effects of ZIKV infection, and many other infants who were infected may have better outcomes.

Given the potential for an epidemic of developmental defects due to congenital ZIKV infection, studies are needed to understand the probability of transplacental transmission upon ZIKV infection during pregnancy; the risk of transmission at different stages of gestation; the spectrum of effects caused by congenital ZIKV infection; and additional factors that may contribute to transplacental transmission and teratogenic potential of ZIKV. Evidence-based recommendations regarding prenatal screening for ZIKV infection and associated congenital abnormalities, including the roles of diagnostic procedures such as ultrasound and amniocentesis as well as information about possible outcomes and options for intervention, must be developed. In addition, the effect of prior flavivirus immunity (eg, from dengue virus infection or vaccination) on ZIKV pathogenesis and disease severity must be understood.

Conclusions

The size of the current ZIKV epidemic, its potential for further spread, and the potential teratogenic effects of this virus require development of ZIKV-specific diagnostic agents and a better understanding of pathogenic mechanisms. The association between ZIKV infection and microcephaly has been the cause of much alarm and has been the driving force behind a substantial public health response and a drive to develop vaccines and antivirals to combat ZIKV infection.

Zika virus represents just the most recent example of an epidemic of vector-borne disease brought about by the introduction of a virus to a new host population and ecological landscape. Although current research priorities must focus on the immediate need to develop specific diagnostic tools and understand the teratogenic potential of ZIKV, public health efforts to address the current epidemic must be informed by experience with previous outbreaks of viruses transmitted by *Aedes* mosquitoes.

ARTICLE INFORMATION

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