

Special Communication

What Does Zika Virus Mean for the Children of the Americas?

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As Zika virus infection spreads across the Latin American and Caribbean region and then into the southern United States, we can expect to see thousands of additional children born with microcephaly and possibly many more newborns or even older infants with signs of more subtle but significant neurologic defects and developmental delays. Just as human immunodeficiency virus (HIV)/AIDS created a "new normal" in the field of pediatrics beginning in the 1990s, can we expect new paradigms in child health from Zika virus?

By the end of last year we had all seen the pictures of severely microcephalic Brazilian and Colombian newborns, subsequently followed by devastating images of perinatal outcomes even worse than first imagined. The first cranial ultrasonograms of Zika virus-associated microcephaly published in January 2016 revealed cerebral calcifications and ventriculomegaly, consistent with a congenital infection.¹ Follow-up radiologic studies confirmed these findings but also showed us a profoundly diminished brain parenchymal volume due to absent brain tissue and interruptions in cortical development, in addition to a hypoplasia of the cerebellum, brainstem, and corpus callosum.²⁻⁴ It was observed that congenital Zika virus infection and microcephaly resembled a fetal brain disruption sequence that was first described in the 1980s and 1990s by pediatric geneticists who found destruction or loss of brain tissue, reductions in intracranial pressure, and then subsequent collapse of the fetal skull.⁵⁻⁷ The link between Zika virus, microcephaly, and this fetal brain disruption sequence was then confirmed,⁸⁻¹⁰ as was a link to a previous 2013 outbreak of Zika virus infection in French Polynesia.¹¹

We are beginning to understand the sequence of events at the molecular and cellular levels responsible for Zika virus' destructive power. Decades after it was first identified in Africa, Zika virus underwent mutations that transformed it from a virus that caused focal epidemics into one with pandemic properties and the ability to infect almost entire Pacific Island populations in a period of weeks or months, before entering Brazil in 2013.^{12,13} Many of the mutations appear in the virus gene encoding nonstructural protein 1, which is linked to flavivirus replication and pathogenicity, presumably allowing it to replicate more efficiently in human tissues.¹³ Human neuronal tissue is the particular target based on evidence showing that the virus selectively infects cortical neural progenitor cells that give rise to the fetal brain.¹⁴ A pre-M protein involved in virus assembly and maturation has also been shown to be affected.¹⁴

Thus, within less than a year after the first microcephaly cases were reported in northeastern Brazil, the scientific and medical communities identified, isolated, and elucidated the microbial pathogenic properties of what I call "the virus from hell." It is every parent's nightmare—a virus that can cause an explosive epidemic, infecting hundreds if not thousands of pregnant women, crossing their placenta, and ultimately halting the development of the fetal brain.

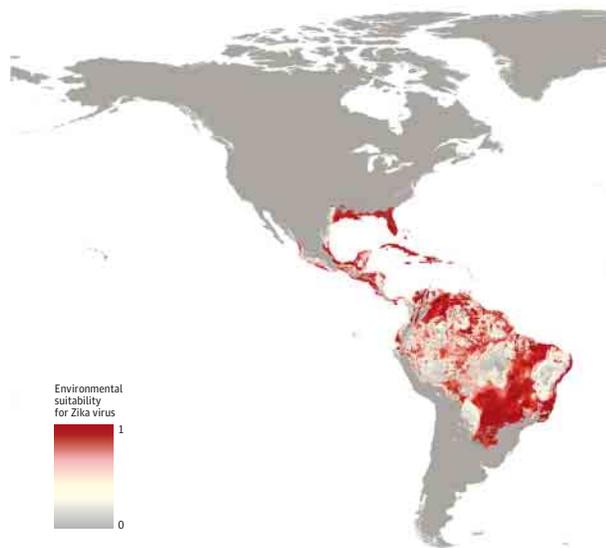
After ripping through the island populations of Micronesia and French Polynesia, the Asian strain of Zika virus infected 1.5 million Brazilian individuals in less than 2 years. The fact that urban centers in northeastern Brazil—cities such as Recife and Salvador—were the ones affected the most is not a coincidence. We have learned that 3 major factors determine where Zika virus infection will emerge: high concentrations of the *Aedes aegypti* mosquito, urban crowding, and poverty.¹⁵

All of these factors were in play in northeastern Brazil cities where the first clusters of microcephaly cases were noted, as they were in Colombia, the second major Latin American country to be affected. From there we can predict where the virus will strike next. High concentrations of the *A aegypti* mosquito, crowding, and poverty converge in the Central American countries of El Salvador, Guatemala, Honduras, and Nicaragua; parts of Mexico such as the Mayan villages in Yucatan; and in the Caribbean nation of Haiti, where owing to its depleted health system we can expect a humanitarian catastrophe to unfold. Poor areas of Puerto Rico will be affected, as will urban centers of the continental United States where *A aegypti* numbers are their highest and poverty is at its worst. Those factors combine mostly in poor neighborhoods of major Gulf Coast cities such as Houston and Galveston, Texas, and New Orleans, Louisiana, as well as Florida¹⁶ (Figure). With a combined population of approximately 60 million individuals, more than 1 million pregnancies could be at risk in US Gulf Coast states.

Within 9 months from now—by the end of 2016 and into early 2017—pediatricians working in poor urban areas of the Americas (including the US Gulf Coast) where Zika virus is now emerging can expect to see babies with microcephaly and the full-blown fetal brain disruption sequence. However, we might also expect many additional newborns to show evidence of significant but less obvious neurologic and cognitive deficits. Possibly some of these infants will have been infected with Zika virus later in gestation, allowing them to avoid the full force of the virus' neurotropic properties. Based on evidence that Zika virus can pass through the blood-brain barrier to cause meningoencephalitis in adults,¹⁸ is it also possible that an infant or young child infected with Zika virus could also show evidence of neurodegenerative disease and developmental delays? Beyond Zika virus, many neglected tropical diseases exhibit important mental health effects.¹⁹ The full pediatric neurologic and psychiatric impact of Zika virus infection will take time to sort out and may not be fully realized for years.

Pediatricians and pediatric subspecialists, including child neurologists, psychiatrists, physiatrists, and behavioral and infectious disease experts, as well as physician-scientists will need to mobilize quickly to get ahead of this fast-moving train. According to the World Health Organization, up to 4 million people could be infected with Zika virus by the end of 2016. Therefore, it is likely that

Figure. Environmental Suitability for Human Zika Virus Infection in the Western Hemisphere

Adapted from Messina et al.¹⁷

tens of thousands of children could be affected by a spectrum of neurologic and psychiatric illness in the next year and beyond.

Could this new virus emerging in the western hemisphere change pediatric practice? As a new pediatric infectious diseases fellow and attending physician during the 1990s, I was impressed by the rapid rise of pediatric HIV/AIDS and our steep learning curve on how to manage and treat this new disease. Both Zika virus and HIV are neurotropic viruses with long-term consequences for childhood neurologic and developmental outcomes. Given the possibility of 4 million Zika virus cases across the Americas, we might revisit how the specialty of pediatrics responded to the HIV/AIDS crisis 30 years ago and possibly look to that model for how we might establish a road map for addressing this new virus infection.

We are just now waking up to a new normal as we learn more about the complete mental health effects of Zika virus infection.

We will likely need to educate and train a new generation of primary care providers, including pediatricians and pediatric nurse practitioners. We will need to assemble interdisciplinary teams of pediatric specialists in neonatology, neurology, psychiatry, rehabilitation medicine, and infectious diseases to organize diagnostic, clinical management, and treatment approaches and algorithms for this new illness. We will need new programs of child advocacy. Because Zika virus may equally affect North America, Central America, and South America, we will need to expand how we work together across international boundaries. Zika virus will require us to dissolve any existing north-south divisions across pediatrics in the Americas. The next few years will be a challenging period as the number of congenital and pediatric Zika virus infections continues to increase from the current epidemic that first exploded in the western hemisphere in 2013.

ARTICLE INFORMATION

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