Medical News & Perspectives

Zika: Worse Than Thalidomide?

Jeff Lyon

A moment of truth is at hand for health experts tracking Zika virus in Latin America and the Caribbean. Thousands of pregnant women who were infected in the past year by Zika, just as it was unmasked as a devastating threat to fetuses, are at the point of giving birth.

Alarmed by the scientific consensus that the Zika virus was behind a 20-fold spike in microcephaly cases reported last year in Brazil, investigators are anxious to see what befalls this new wave of mothers and infants.

Research suggests that nearly a third of deliveries in mothers infected with Zika will involve severe birth complications, including microcephaly, fetal cerebral calcification, and central nervous system alterations (Brasil P et al. *NEJM*. doi:10.1056/NEJMoa1602412 [published online March 4, 2016]). But as evidence mounts that the virus' strong affinity for neural stem cells may also cause subtler central nervous system damage, the medical community fears that the current tragedy may give way to an equally horrific second act that will play out over years as exposed children who seemed unscathed at birth exhibit serious neurological ills as they age. Expectations range from auditory and visual problems to cognitive delays and seizure disorders.

Accordingly, the World Health Organization recently called for broadening the definition of Zika-related pathology beyond microcephaly, noting "Zika virus is an intensely neurotropic virus that particularly targets neural progenitor cells, but also—to a lesser extent—neuronal cells in all stages of maturity. ... [I]t is possible that many thousands of infants will incur moderate to severe neurological disabilities." (http://who.int/bulletin/volumes/94/6/16-17-1776990/en/)

The outlook is bleak enough that some authorities speak of the Zika epidemic in the same breath as the thalidomide and rubella disasters of the 1960s. Citing these earlier crises, Hal C. Lawrence III, MD, chief executive officer of the American College of Obstetricians and Gynecologists, predicted that the Zika virus' full toll may not be known "for years downstream."

Edwin Trevathan, MD, MPH, former director of the Center for Disease Control and Prevention's National Center on Birth Defects and Developmental Disabilities, echoed this sentiment, noting the likelihood that Zika will leave long-lasting scars on developing brains is "close to 100 percent."

"Frankly [it] poses a much more serious long-term risk to the health of a generation than the more obvious microcephaly in a few infants," says Trevathan, a pediatric neurologist who serves on the American Academy of Pediatrics' Zika Task Force. When asked to compare Zika's threat to thalidomide and rubella, he said, "depending on the rapidity with which an effective vaccine can be developed and distributed effectively, the ability to marshal resources to do appropriate science, and large-scale prevention efforts, Zika has the potential to be much worse and to have an impact that continues over a much longer period of time."

Researching Long-term Outcomes

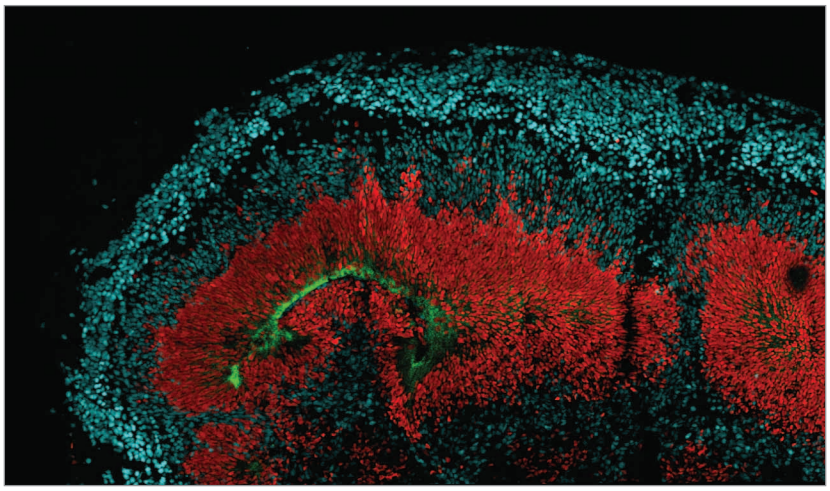
Mindful of the need to get ahead of the crisis scientifically, the CDC and the National Institutes of Health (NIH) are currently taking steps to launch major prospective studies of Zika's prenatal and postnatal effects.

The NIH effort, dubbed ZIP for Zika and Infants in Pregnancy, calls for tracking 10 000 pregnant women in Puerto Rico, Brazil, Colombia and other countries where the virus, is prevalent. The women will be followed up from their first trimester through delivery, and their infants for at least the first year of life. Mothers and newborns who do not contract Zika during the course of the study will serve as controls.

"We'll be looking at [birth] outcomes," said Catherine Spong, MD, acting director of the National Institute of Child Health and Human Development, whose agency is collaborating with the National Institute of Allergy and Infectious Diseases, the National Institute of Environmental Health Sciences, and the Fundação Oswaldo Cruz (Fiocruz), a research organization linked to the Brazilian Ministry of Health.

Of primary concern, Spong said, is the ongoing health of children born to mothers infected with Zika who showed no signs of neurological insult at birth. "We'll be able to observe over time how well they meet certain developmental milestones. Do their eyes track you when you move around a room? Can they turn over at the proper age? Do they crawl, stand and walk at the appropriate time?"

Formal assessment tools may be mobilized as well, she said. "There are a battery



Elizabeth Di Lullo

Zika virus may disrupt brain development by infecting neural stem cells (red) via AXL receptors (green).

of instruments available—motor and sensory inventories, cognitive tests, Bayley scales. The issue for me is that these children live in South and Central America and we want to make certain we use instruments that are standardized for that population."

The study will also focus on a child's in utero environment, Spong said. "We'll look at what time point women contracted Zika during pregnancy, as that is one of our big questions: What are the risks involved with infection during different trimesters?"

Although a previous study in Colombia suggested that infection in the third trimester is not linked to structural abnormalities at birth, it is currently unknown whether late gestational exposure may cause neurological abnormalities to surface later in childhood (Pacheco O et al. *NEJM*. doi:10.1056/NEJMoa1604037 [published online June 15, 2016]).

"We are also including both symptomatic and asymptomatic women, since we now know our fears were well-founded that even in the asymptomatic cases, the fetus can be affected," noted Spong. Information on confounders, for example prior maternal infection with dengue and other flaviviruses, will also be collected to see if such prior exposure may affect Zika virus potency.

The NIH study should shed light on another urgent question: Can unexposed infants and toddlers, whose brains are still relatively plastic, be damaged if a mosquito carrying the virus bites them?

"We'll have a group of children who were not infected by Zika during pregnancy but contract it in early childhood. We'll be able to see how they are affected," Spong said.

Fiocruz President Paulo Gadelha, MD, PhD, called the study "essential to elucidating the scientific complexity of the Zika virus. It will be fundamental to developing prevention and treatment strategies against the disease."

For its part, the CDC plans to monitor outcomes in infants born to nearly 400 US mothers who have tested positive for Zika during pregnancy, including any who were infected domestically since reporting of local cases began in Florida in late July. Like the NIH study, the effort will only follow up the youngsters for their first year. But a second CDC study will go much further. Using its Zika Active Pregnancy Surveillance registry, the agency will follow up exposed youngsters up to age 3 years in Puerto Rico, where a public health emergency was declared by the US Dept. of Health and Human Services on Aug. 5, 2016.

As of Aug. 12, 2016, the island was reporting 10,690 cases of Zika infection, including 1,035 pregnant women, but CDC experts say they believe that is an undercount. Researchers have estimated that the number of pregnant women who will ultimately be infected with Zika during the Puerto Rican outbreak will fall between 5900 and 10 300 (Ellington S et al.*JAMA Pediatr*. doi:10.1001/jamapediatrics.2016.2974 [published online August 19, 2016]). They further project that 100 to 270 cases of microcephaly could result between mid-2016 and mid-2017 in the absence of effective interventions .

By extending its Puerto Rican study to 2- and 3-year-olds, the CDC will obtain much more data about how the young brain evolves after Zika infection. Researchers can test more definitively for hearing and visual disturbances and can pick up delays in acquiring speech.

Anne Schuchat, MD, principal deputy director of the CDC, asserted that the agency will be alert to signs that Zika exposure can have insidious aftereffects. "The brain continues to develop after birth" she said, suggesting that it remains vulnerable.

More Funding Needed

Both Spong and Schuchat expressed regret that their studies cannot observe children to school age, when more informative cognitive measurements and tests for disorders such as autism can be administered.

"We would like to go to 5 years of age," Schuchat noted. "But that will depend on whether we get additional resources." Spong echoed this sentiment. "We could take things out further than a year, but other factors affect what we can do," she said.

Their implication was clear: no money is available to support more prolonged observation. Ideally, the studies might extend into adolescence when any association between Zika and mental illness might reveal itself, Spong suggested. Exposure to influenza virus during pregnancy, for example, has been linked to heightened risk of schizophrenia and bipolar disorder in adolescent offspring (Brown AS et al. *Arch Gen Psychiatry*. 2004;61[8]:774-780) (Parboosing R et al. *JAMA Psychiatry*. 2013;70[7]:677-685.).

But neither Schuchat nor Spong would directly address Congress' failure to approve the White House's $1.1 billion funding request for Zika research and prevention before it recessed for 6 weeks in early July.

"Read my silence," said Spong.

To spur more research, the NIH announced a special funding opportunity for outside investigators who wish to tackle Zika, promising rapid review of grant proposals and quick disbursement of cash http://grants.nih.gov/grants/guide/pa-files/PAR-16-106.html). The customary wait time of 9 to 10 months has been shrunk to 2 to 4 months.

Spong says the response has been "robust," adding, "I've never seen such an announcement in the 20 years I've been at NIH." But without Congressional action, most of this new funding must be diverted from other areas of NIH-backed medical research.

Unlocking Zika Mysteries

Those already involved in Zika research continue to plug away at deciphering the virus, which joins rubella and cytomegalovirus as pathogens that cause only mild maternal illness but are potent teratogens in offspring. Though it was isolated in 1947, Zika is woefully understudied because it wasn't recognized as a serious threat until little more than a year ago. "We don't even know what we don't know," said Alan Harris, MD, an infectious disease specialist at Rush University Medical Center and the University of Illinois College of Medicine at Chicago.

The science that *is* emerging about the virus, however, is deeply unsettling.

For one thing, after vertical transmission, Zika has been shown to infiltrate radial glial cells, the neural stem cells that give rise to the neurons and astrocytes that will form the fetal cerebral cortex. Recent studies suggest that the virus gains entry to these progenitor cells via the AXL protein receptors that dot their surface. Once inside the cells, the virus somehow inhibits their growth, proliferation, and differentiation. AXL receptors are also present on the stem cells of the retina, which might explain visual problems sometimes encountered in Zika-infected newborns. (Nowakowski TJ et al. *Cell Stem Cell*. 2016;18[5]:591-596) (Wu K-Y et al. *Cell Res*. 2016 26[6]:645-654).

Equally troubling, while the virus generally clears the blood within 7 days, in

pregnant women, it can be detected in the blood for at least 70 days. The prevailing hypothesis, according to David O'Connor, PhD, a microbiologist at the University of Wisconsin-Madison who studies Zika in macaque monkeys, is that the virus, which seems to freely cross the placenta, travels from the mother to the fetus, which then sheds more virus that reinfects the mother in what he called "a feedback loop."

The significance? While the fetus is most vulnerable during the first trimester, when the central nervous system is forming, it may be under attack by the virus for months afterward, when more subtle central nervous system insults may occur.

Finally, Zika seems capable of hiding from the host cells' ability to mount an immune response. According to John W. Schoggins, PhD, of the University of Texas Southwestern Medical Center, when he and his colleagues infected human neural precursor cells with the virus, the cells did not seem to display the normal cell intrinsic immunity (Schoggins JW et al. *Cell Rep.* 2016; 15[11]:2315-2322). The virus continued to replicate in many cells for the life of the 28-day in vitro experiment. "There was a very subpar immune response," Schoggins says. "The virus may have a mechanism, as do many viruses, to evade such a response."

This might be troublesome, he says. "We don't yet know the long-term consequences. One possibility, supported by our data and other published studies, is that the virus persists long-term in the brain, which could cause continual neuronal injury." Schoggins cautioned against drawing too many conclusions, however. "All of our work is done in culture, and in the developing brain, you would also have other cells, glials and so on. It's possible there is a different process going on in the fetus that we can't mimic in cell culture."

Reasons for Hope and Worry

If there is a bright spot, O'Connor said, it is that "[i]n areas where there has been explosive transmission, say Brazil, it's going to be a short-lived problem that will resolve itself. A critical threshold will be reached where the population acquires natural immunity."

On the other hand, he said, when a virus like Zika sweeps through a community, it takes a huge economic and health toll, "a spectrum that creates enormous anxiety. And in the longer term, if it turns out that only some of the abnormalities are evident at birth, that anxiety is going to continue for years, with uncertainty over the prognosis kids will have in the future."

The long-term ramifications, according to Schuchat, are "pretty scary." ■