

## EDITORIAL



## Zika Virus and Microcephaly

Eric J. Rubin, M.D., Ph.D., Michael F. Greene, M.D., and Lindsey R. Baden, M.D.

Zika virus has been sweeping through South and Central America, with more than a million suspected cases during the past few months, along with a substantial increase in reporting of infants born with microcephaly.<sup>1,2</sup> Thus far, the two outbreaks have largely been epidemiologically associated in time and geography. However, Mlakar and colleagues<sup>3</sup> now report in the *Journal* molecular genetic and electron-microscopic data from a case that helps to strengthen the biologic association.

This group cared for a pregnant European woman in whom a syndrome compatible with Zika virus infection developed at 13 weeks of gestation while she was working in northeastern Brazil. She subsequently returned to Europe, where ultrasonographic examinations performed late in the pregnancy showed a small fetal head and brain calcifications as had been seen in other cases linked to Zika virus.<sup>4</sup> After approval by national and hospital ethics boards, the patient chose a late-pregnancy termination.

At autopsy, the fetal brain was grossly diseased, with findings that included a very small brain (weight, 84 g), a complete absence of cerebral gyri, severe dilation of both cerebral lateral ventricles, dystrophic calcifications throughout the cerebral cortex, and hypoplasia of the brain stem and spinal cord, including Wallerian degeneration of the long descending spinal tracts. Particles consistent with Zika virus were visualized on electron microscopy, and a large amount of viral genomic RNA was present in the brain but in no other organs. The viral sequence was similar to that of other recent Zika virus isolates. No evidence of any fetal genetic abnormalities or other pathogens was found.

The findings of this case report do not provide absolute proof that Zika virus causes microcephaly. The standard criteria for proving causation (with modifications) are still those that were formulated by Robert Koch in 1890, which require the isolation of the causative organism, reinfection of a susceptible person in whom the characteristic disease develops, and then repeated isolation of the organism.<sup>5</sup> However, Koch's criteria are difficult to apply, particularly for rare, devastating, and untreatable manifestations of an illness. Often, as in this case, we must rely on a combination of scientific and epidemiologic evidence. And the evidence in this case report makes the link stronger.

Zika virus has spread explosively since its introduction into South America and has now been found throughout Central America and the Caribbean. The full extent of disease is not clear — most infections are asymptomatic and many are associated with only mild disease.<sup>6</sup> But the apparent risk of microcephaly was enough for the World Health Organization to declare a public health emergency of international concern on February 1.

What more do we need to know to help us manage and control this outbreak? Certainly, understanding the disease better could have long-term benefits, including the development of protective vaccines. However, it is the information that we do not yet have that has potential immediate applications.

Although many authorities are counseling women who are pregnant or could become pregnant to avoid travel to affected areas, the millions of women who live in these places are faced with enormous uncertainty, and as the virus spreads,

many more will be affected. For example, assuming the association between Zika virus and microcephaly exists, we do not know whether the timing of the infection during pregnancy has an effect on the risk of fetal abnormalities, nor do we have any idea of the magnitude of that risk. The development of rapid, scalable diagnostic tests is needed, since the current polymerase-chain-reaction assay detects viral RNA and thus should be positive only during the period of viremia, which may be relatively short. Current serologic assays have considerable cross-reactivity with other flaviviruses, including those that are endemic in the same areas (as in the case now being reported), and serologic assays specific for Zika virus are not easily available. Thus, it may be difficult to determine retrospectively whether a woman has been infected. This will be particularly difficult in areas where dengue virus and other pathogens can cause symptoms similar to those of the Zika virus. In addition, it is unclear whether asymptomatic or minimally symptomatic disease poses a risk to the fetus. It is possible that as is the case with mumps, early infection could result in fetal loss rather than malformations. And, as in this case report, ultrasonography may detect severe fetal abnormalities only very late in gestation — in many cases, too late to terminate the pregnancy. Is there a sensitive test that can be applied earlier? And is previous infection protective?

Although we need a good deal of research to define critical aspects of infection, there is much to do immediately. A vulnerable point for Zika virus transmission is the mosquito vector. Unfortunately, mosquito-control efforts have failed to curtail the spread of many similar pathogens, including dengue and chikungunya viruses, which are carried by the same aedes species and

are spreading in the same communities currently affected by the Zika virus. Perhaps this new threat will help boost such control efforts with the use of both old and new approaches. Women need to have access to relevant health care services, including contraception, diagnostics, and pregnancy-termination services. And the many affected children need to have care. Coming shortly after the global response to the Ebola virus, the rapid spread of the Zika virus reminds us how connected we all are.<sup>7</sup> Once again, an outbreak is going to challenge our public health infrastructure and require a substantial response.

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

From the Department of Immunology and Infectious Diseases, Harvard School of Public Health (E.J.R.), and the Department of Obstetrics and Gynecology, Massachusetts General Hospital (M.F.G.) — both in Boston.

This article was published on February 10, 2016, at NEJM.org.

1. Fauci AS, Morens DM. Zika virus in the Americas — yet another arbovirus threat. *N Engl J Med*. DOI: 10.1056/NEJMp1600297.
2. Schuler-Faccini L, Rjibeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65:59-62.
3. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. *N Engl J Med*. DOI: 10.1056/NEJMoa1600651.
4. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol* 2016;47:6-7.
5. Koch R. 1891. *Über bakteriologische Forschung Verhandlung des X Internationalen Medicinischen Congresses, Berlin, 1890, 1, 35.* August Hirschwald, Berlin. (In German.) Xth International Congress of Medicine, Berlin.
6. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;360:2536-43.
7. Sands P, Mundaca-Shah C, Dzau VJ. The neglected dimension of global security — a framework for countering infectious-disease crises. *N Engl J Med*. DOI: 10.1056/NEJMs1600236.

DOI: 10.1056/NEJMe1601862

Copyright © 2016 Massachusetts Medical Society.