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Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015

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In early 2015, an outbreak of Zika virus, a flavivirus transmitted by *Aedes* mosquitoes, was identified in northeast Brazil, an area where dengue virus was also circulating. By September, reports of an increase in the number of infants born with microcephaly in Zika virus-affected areas began to emerge, and Zika virus RNA was identified in the amniotic fluid of two women whose fetuses had been found to have microcephaly by prenatal ultrasound. The Brazil Ministry of Health (MoH) established a task force to investigate the possible association of microcephaly with Zika virus infection during pregnancy and a registry for incident microcephaly cases (head circumference ≥2 standard deviations [SD] below the mean for sex and gestational age at birth) and pregnancy outcomes among women suspected to have had Zika virus infection during pregnancy. Among a cohort of 35 infants with microcephaly born during August–October 2015 in eight of Brazil's 26 states and reported to the registry, the mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy, 25 (71%) infants had severe microcephaly (head circumference >3 SD below the mean for sex and gestational age), 17 (49%) had at least one neurologic abnormality, and among 27 infants who had neuroimaging studies, all had abnormalities. Tests for other congenital infections were negative. All infants had a lumbar puncture as part of the evaluation and cerebrospinal fluid (CSF) samples were sent to a reference laboratory in Brazil for Zika virus testing; results are not yet available. Further studies are needed to confirm the association of microcephaly with Zika virus infection during pregnancy and to understand any other adverse pregnancy outcomes associated with Zika virus infection. Pregnant women in Zika virus-affected areas should protect themselves from mosquito bites by using air conditioning, screens, or nets when indoors, wearing long sleeves and pants, using permethrin-treated clothing and gear, and using insect repellents when outdoors. Pregnant and lactating women can use all U.S. Environmental Protection Agency (EPA)-registered insect repellents according to the product label.

An outbreak of Zika virus infection was recognized in northeast Brazil in early 2015 (*1*). In September 2015, health authorities began to receive reports from physicians in this region of an increase in the number of infants born with microcephaly. In October, the MoH confirmed an increase in birth prevalence of microcephaly in northeast Brazil, compared with previously reported estimates (approximately 0.5/10,000 live births), which are based on review of birth certificates and include descriptions of major congenital anomalies. The MoH rapidly established a microcephaly registry in Brazil. On November 17, 2015, the MoH reported the increase in microcephaly cases, and possible association of microcephaly with Zika virus infection during pregnancy on its website;* and the Pan American Health Organization (PAHO) published an alert regarding the increase in occurrence of microcephaly in Brazil (*2*). In December, PAHO reported the identification of Zika virus RNA by reverse transcription-polymerase chain reaction (RT-PCR) in amniotic fluid samples from two pregnant women whose fetuses were found to have microcephaly by prenatal ultrasound, and the identification of Zika virus RNA from multiple body tissues, including the brain, of an infant with microcephaly who died in the immediate neonatal period (*3*). These events prompted new alerts from the MoH, the European Centre for Disease Prevention and Control (*4*), and CDC (*5*) concerning the possible association of microcephaly with the recent outbreak of Zika virus infection.

*http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saudedivulga-boletim-epidemiologico.

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A comprehensive protocol for notification and investigation of all infants with microcephaly and all women with suspected Zika virus infection during pregnancy was developed by the MoH and implemented nationwide. In addition, the Brazilian Society of Medical Genetics established the Zika Embryopathy Task Force (SBGM–ZETF), which includes clinical geneticists, obstetricians, pediatricians, neurologists, and radiologists, to review all incident cases of microcephaly as well as all infants born to mothers with suspected Zika virus infection during pregnancy. Task force members collect data concerning the pregnancy (including exposure history, symptoms, and laboratory testing), physical examination of the infant, and any additional studies using a standardized spreadsheet. Microcephaly was defined as neonatal head circumference ≥2 SD below the mean for gestational age and sex of the infant at birth. Infection with Zika virus is difficult to confirm retrospectively because serological immunological tests might cross-react with other flaviviruses, especially dengue virus (*6*). Therefore a mother's report of a rash illness during pregnancy was used as a proxy indicator of potential Zika virus infection.

Although 37 infants with microcephaly were evaluated, only 35 cases are included in this report. Two infants with microcephaly were excluded from the original cohort of 37 babies: one had autosomal recessive microcephaly with sibship recurrence, and one had cytomegalovirus infection. Overall, 26 (74%) mothers of infants with microcephaly reported a rash during the first (n = 21) or second (5) trimester (Table). Residence in or travel during pregnancy to areas where Zika virus is circulating was confirmed for all mothers, including women without a history of rash. Twenty-five (74%) infants had severe microcephaly (head circumference >3 SD below the mean for gestational age). Computed tomography scans and transfontanellar cranial ultrasounds showed a consistent pattern of widespread brain calcifications, mainly in the periventricular, parenchymal, and thalamic areas, and in the basal ganglia, and was associated in approximately one third of cases with evidence of cell migration abnormalities (e.g., lissencephaly, pachygyria). Ventricular enlargement secondary to cortical/subcortical atrophy was also frequently reported. Excessive and redundant scalp skin, reported in 11 (31%) cases, also suggests acute intrauterine brain injury, indicating and arrest in cerebral growth, but not in growth of scalp skin. Four (11%) infants had arthrogryposis (congenital contractures), indicative of central or peripheral nervous system involvement (*7*). All 35 infants in the cohort tested negative for syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus infections. CSF samples from all infants enrolled in the cohort were sent to a reference laboratory in Brazil for Zika virus testing; the results are not yet available.

Discussion

Microcephaly usually results from abnormal brain development. The long-term consequences of microcephaly depend on underlying brain anomalies and can range from mild developmental delays to severe motor and intellectual deficits, like cerebral palsy. In addition to congenital infections, microcephaly can result from chromosomal abnormalities; exposure to drugs, alcohol, or other environmental toxins; premature fusion of the bones of the skull (craniosynostosis); and certain metabolic disorders. The sudden increase in the number of infants born with microcephaly associated with cerebral damage characteristically seen in congenital infections in a region where an outbreak of a newly circulating virus has recently occurred is suggestive of a possible relationship. The association between maternal infections and congenital anomalies has long been recognized, especially when infection occurs during the first 12 weeks of pregnancy (*8*). Brazil's vaccination program has eliminated some infections that result in congenital anomalies, such as rubella. Congenital infections can affect multiple organ systems, and many are associated with specific brain damage, including microcephaly, calcifications (predominantly periventricular, but also in the basal ganglia and in cerebral parenchyma), ventriculomegaly, neuronal migration disorders (pachygyria, polymicrogyria, lissencephaly, and schizenchephaly), cerebellar hypoplasia, and white matter anomalies (*8*). Ongoing surveillance and evaluation of new cases are important to describe the phenotypic spectrum of potential Zika virus-associated congenital infections. In addition, special studies, including case-control studies, are needed to confirm the association, determine the magnitude of the potential risk, and identify other possible risk factors.

CDC recently tested samples from two pregnancies that ended in miscarriage and from two infants with microcephaly who died shortly after birth. All four cases were from Brazil and were positive for Zika virus infection, indicating that the infants had become infected during pregnancy. Zika virus was present in the brain of the full term infants, and genetic sequence analyses show that the virus in all four cases was the same as the Zika virus strain currently circulating in Brazil. All four mothers reported having experienced a febrile rash illness during their pregnancies.[†]

Prevention strategies established by the MoH include aggressive efforts to eliminate mosquito breeding areas by removing standing water containers, as well as recommendations for personal protective measures, including preventing mosquito bites among pregnant women by applying insect repellents, wearing long-sleeved shirts and long pants, and using mosquito nets,

[†] http://www.cdc.gov/media/releases/2016/t0116-zika-virus-travel.html.

Summary

What is already known about this topic?

An outbreak of Zika virus infection, a flavivirus transmitted by *Aedes* mosquitoes, was first recognized in northeastern Brazil in early 2015. In September, a sharp increase in the number of reported cases of microcephaly was reported in areas affected by the outbreak.

What is added by this report?

The Brazil Ministry of Health developed a case definition for Zika virus–related microcephaly (head circumference ≥2 standard deviations [SD] below the mean for sex and gestational age at birth). A task force and registry were established to investigate Zika virus–related cases of microcephaly and to describe the clinical characteristics of cases. Among the first 35 cases of microcephaly reported to the registry, 74% of mothers reported a rash illness during pregnancy, 71% of infants had severe microcephaly (>3 SD below the mean), approximately half had at least one neurologic abnormality, and among 27 who had neuroimaging studies, all were abnormal. Cerebrospinal fluid from all infants is being tested for Zika virus; results are not currently available.

What are the implications for public health practice?

The increased occurrence of microcephaly associated with cerebral damage characteristically seen in congenital infections in Zika virus-affected areas is suggestive of a possible relationship. Additional studies are warranted to confirm the association and to more fully characterize the phenotype. In addition to removing potential breeding areas for mosquitoes, pregnant women in Zika-affected areas should wear protective clothing, apply a U.S. Environmental Protection Agency (EPA)-approved insect repellent, and sleep in a screened room or under a mosquito net.

TABLE. Main phenotypical findings of the first 35 patients enrolled in the Brazilian Society of Medical Genetics–Zika Embryopathy Task Force Registry — Brazil, 2015

Characteristic	n (%)
Reported maternal rash during pregnancy	
First trimester	21 (57)
Second trimester	5 (14)
Not reported	9 (26)
Sex	
Female	21 (60)
Male	14 (40)
Gestational age at birth (34)*	
Term	31 (91)
Preterm	3 (9)
Weight	
≥2,500g	26 (74)
<2,500g	9 (26)
Defect	
Head circumference >3 SD	25 (71)
Head circumference >2 SD to 3 SD	10 (29)
Excessive and redundant scalp skin	11 (31)
Talipes (clubfoot)	5 (14)
Arthrogryposis (contractures)	4 (11)
Other defects (microphthalmia)	1 (3)
Abnormal funduscopic examination (11)	2 (18)
Neurologic examination	
Any abnormality	17 (49)
Hypertonia/Spasticity	13 (37)
Hyperreflexia	7 (20)
Irritability	7 (20)
Tremors	4 (11)
Seizures	3 (9)
Neuroimaging (27)	
Any abnormality	27 (100)
Calcifications	20 (74)
Ventricular enlargement	12 (44)
Neuronal migration disorders (lissencephaly, pachygyria)	9 (33)

Abbreviation: SD = standard deviations.
* Number of patients sampled was less than total (35).

as well as risk communication and community mobilization (*3*). Pregnant and lactating women can use all EPA-registered insect repellents according to the product label.

This findings in this report are subject to at least four limitations. First, historical birth prevalence of microcephaly in Brazil, approximately 0.5 cases per 10,000 live births, calculated from birth certificates, was lower than expected estimates of 1–2 cases per 10,000 live births (*9*), which might indicate general underascertainment of microcephaly in Brazil. However, during the second half of 2015 alone, >3,000 suspected cases of microcephaly (approximately 20 cases per 10,000 live births) were reported to the MoH through the special notification protocol, suggesting a sharp increase in birth prevalence, although the special notification protocol might have also increased case reporting. Second, before the November MoH alert, although descriptions of congenital anomalies were reported, infant head circumference was not routinely recorded. Hence, it is possible that mild cases of microcephaly might not have been reported. Since the MoH alert and the attendant media coverage of the outbreak, surveillance for microcephaly and physician reporting of suspected cases have increased. Third, because Zika virus infection was not laboratory-confirmed in infants or their mothers, the history of a nonspecific rash illness during pregnancy is subject to recall bias and might have resulted in misclassification of potential Zika virus exposure. Finally, this report does not comment on other features characteristic of intrauterine infections such as hepatosplenomegaly, rash, and chorioretinitis, or on some features that have been reported in cases with presumed Zika including hearing loss, pale maculas, and swallowing difficulties.

As of January 2016, there has been confirmed autochthonous transmission of Zika virus in 19 countries in the Americas outside Brazil (*10*). Although other countries in the Americas, including Uruguay and Argentina, have not reported autochthonous Zika virus, the presence of a competent vector, *Ae. aegypti*, in these countries poses a potential risk for further spread of the virus.

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References

1. Campos GS, Bandeira AC, Sardi SI. Zika virus outbreak, Bahia, Brazil. Emerg Infect Dis 2015;21:1885–6. http://dx.doi.org/10.3201/eid2110.150847.
2. Pan American Health Organization. Epidemiological alert. Increase in microcephaly in the northeast of Brazil—epidemiological alert. Washington DC: World Health Organization, Pan American Health Organization; 2015. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32636&lang=en.
3. Pan American Health Organization. Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas—epidemiological alert. Washington DC: World Health Organization, Pan American Health Organization; 2015. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32405&lang=en.
4. European Centre for Disease Prevention and Control. Rapid risk assessment: microcephaly in Brazil potentially linked to the Zika virus epidemic. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2015. http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment-Nov-2015.pdf.
5. CDC. Recognizing, managing, and reporting Zika virus infections in travelers returning from Central America, South America, the Caribbean, and Mexico. CDC Health Advisory. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. http://emergency.cdc.gov/han/han00385.asp.
6. Hall JG. Arthrogryposis multiplex congenita: etiology, genetics, classification, diagnostic approach, and general aspects. J Pediatr Orthop B 1997;6:159–66. http://dx.doi.org/10.1097/01202412-199707000-00002.
7. Lanciotti RS, Kosoy OL, Laven JJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis 2008;14:1232–9. http://dx.doi.org/10.3201/eid1408.080287.
8. Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, Mor G. Viral infections during pregnancy. Am J Reprod Immunol 2015;73:199–213. http://dx.doi.org/10.1111/aji.12355.
9. EUROCAT European Surveillance of Congenital Anomalies. Prevalence tables. Ispra, Italy: EUROCAT European Surveillance of Congenital Anomalies; 2015. http://www.eurocat-network.eu/accessprevalencedata/prevalencetables.
10. Hennessey M, Fischer M, Staples JE. Zika virus spreads to new areas—region of the Americas, May 2015–January 2016. MMWR Morb Mortal Wkly 2016;65(3).

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