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Transmission of Yellow Fever Vaccine Virus Through Breast-Feeding --- Brazil, 2009

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In April, 2009, the state health department of Rio Grande do Sul, Brazil, was notified by the Cachoeira do Sul municipal health department of a case of meningoencephalitis requiring hospitalization in an infant whose mother recently had received yellow fever vaccine during a postpartum visit. The Field Epidemiology Training Program of the Secretariat of Surveillance in Health of the Brazilian Ministry of Health assisted state and municipal health departments with an investigation. This report summarizes the results of that investigation, which determined that the infant acquired yellow fever vaccine virus through breast-feeding. The mother reported 2 days of headache, malaise, and low fever occurring 5 days after receipt of yellow fever vaccine. The infant, who was exclusively breast-fed, was hospitalized at age 23 days with seizures requiring continuous infusion of intravenous anticonvulsants. The infant received antimicrobial and antiviral treatment for meningoencephalitis. The presence of 17DD yellow fever virus was detected by reverse transcription--polymerase chain reaction (RT-PCR) in the infant's cerebrospinal fluid (CSF); yellow fever--specific immunoglobulin M (IgM) antibodies also were present in serum and CSF. The infant recovered completely, was discharged after 24 days of hospitalization, and has had normal neurodevelopment and growth through age 6 months. The findings in this report provide documentation that yellow fever vaccine virus can be transmitted via breast-feeding. Administration of yellow fever vaccine to breast-feeding women should be avoided except in situations where exposure to yellow fever viruses cannot be avoided or postponed.

On March 23, the mother, aged 22 years, delivered a healthy female infant at 39 weeks' gestational age by elective cesarean delivery. During that same month, a yellow fever epidemic had spread to a nonendemic area in Rio Grande do Sul state where the mother resided (1). On April 7, when the mother was 15 days postpartum, she visited her health-care provider to have the sutures removed from her caesarean incision. While in the provider's office, she received 17DD yellow fever vaccine. She had not been vaccinated for yellow fever previously. On April 12, 5 days after receiving the vaccine, she reported a headache, malaise, and low fever, which persisted for 2 days. The mother did not seek medical care for her symptoms.

On April 15, 2009, the mother's infant, aged 23 days, developed fever, and irritability and refused to nurse. The next day, the infant exhibited seizure-like activity and was admitted to the hospital for evaluation of possible meningoencephalitis. Upon admission, the infant experienced unilateral left upper extremity clonic convulsions of increasing frequency requiring intravenous diazepam (0.15 mg). Perioral cyanosis was noted and oxygen saturation measured by arterial blood gas was pO_2 60 (normal: pO_2 80--100). A chest radiograph showed no infiltrate. Peripheral white blood cell (WBC) count was 25,400/mm³ (normal: 5,000--20,000 WBC/mm³) and platelet count was

393,000/mm³ (normal: $\geq 150,000$ platelets/mm³). Laboratory examination of CSF was unremarkable, with a WBC count of 1/mm³ (normal: 0--5 WBC/mm³), slight elevation of protein (67 mg/dL [normal: 15--45 mg/dL]), and decreased glucose concentration (37 mg/dL [normal: 42--78 mg/dL]). Gram stain of the CSF specimen revealed no bacteria. The infant received oxygen therapy, intravenous dipyrone (0.1 mL every 6 hours) and phenytoin (10 mg every 12 hours), and empiric treatment for bacterial infection with ampicillin and gentamicin. On April 18, empiric acyclovir treatment was added. No specimens for bacterial or fungal cultures were obtained. Other etiologies for meningoencephalitis were ruled out by testing of serum and CSF samples for dengue-specific IgM; viral culture for herpes simplex, cytomegalovirus, and varicella; and RT-PCR for enteroviruses, all of which were negative.

The infant alternated between periods of somnolence and irritability, without clinical improvement. On April 19, convulsions became more frequent (one episode every 10 minutes) and difficult to control, with persistent perioral cyanosis, resulting in transfer to the pediatric ICU for continuous infusion of anticonvulsants and monitoring of oxygen saturation. A second CSF examination showed a WBC count of 128/mm³, a protein concentration of 106 mg/dL, and a glucose concentration of 24 mg/dL. Computerized tomography of the head demonstrated bilateral symmetrical areas of diffuse low density suggestive of inflammation consistent with encephalitis.

After the second CSF examination on April 19, the mother mentioned receiving yellow fever vaccine 8 days before the infant's onset of symptoms, and a serum and CSF sample from the infant were sent to the arbovirus reference laboratory at Adolfo Lutz Institute in São Paulo, Brazil, to test for the presence of 17DD yellow fever vaccine virus. Yellow fever-specific IgM antibodies were detected in serum and CSF. Yellow fever viral RNA was amplified by RT-PCR (2,3) from a CSF specimen collected on April 19; the nucleotide sequence of the amplified PCR product was identical to 17DD yellow fever vaccine virus. No breast milk or maternal serum was collected for yellow fever virus testing.

The infant recovered completely and was discharged from the hospital without sequelae on May 10, 2009. Follow-up of the infant showed normal neurodevelopment and growth through age 6 months. The Brazilian Committee on Vaccine-Associated Adverse Events classified the child's encephalitis as yellow fever vaccine--associated neurologic disease. To rule out the possibility that the infant had received yellow fever vaccine inadvertently, the investigators reviewed all procedures documented in the medical record performed between the infant's birth and onset of symptoms. The child had received intramuscular vitamin K and hepatitis B vaccine on the day of birth. Two other children born on the same day had received hepatitis B vaccine from the same lot of vaccine as the one registered in the child's vaccination record, and neither experienced similar symptoms.

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Editorial Note

This report describes the first laboratory-confirmed case of yellow fever vaccine--associated neurologic disease occurring in an infant secondary to the transmission of yellow fever vaccine virus through breast milk. The infant described in this report also is the youngest reported case of yellow fever vaccine--associated neurologic disease. The presence of yellow fever-specific IgM in CSF, and 17DD yellow fever vaccine viral RNA in the CSF of the infant indicates transmission and infection with yellow fever vaccine. Following primary vaccination, IgM antibodies generally appear 4--7 days after receipt of vaccine (4). Maternal IgM antibodies can be excreted in breast milk and the presence of serum IgM in the infant alone is not diagnostic of yellow fever virus infection. The detection of IgM antibodies in the infant's CSF indicates intrathecal antibody production in response to a nervous system infection because IgM does not normally cross the blood brain barrier (5).

Based on the mother's receipt of yellow fever vaccine on April 7, and onset of symptoms in the infant on April 15, the infant's infection likely occurred during the expected peak of viremia following vaccination. Neurologic adverse events, including encephalitis, have been described previously in association with yellow fever vaccination; children aged <6 months have the highest incidence of vaccine-associated neurologic events (6). However, only one previous episode of encephalitis, which was not confirmed as vaccine-associated, has been described in an infant exposed to yellow fever vaccine virus through breast-feeding (Public Health Agency of Canada, personal communications, 2009).

Yellow fever vaccine is a live, attenuated virus preparation made from various strains of the 17D yellow fever virus lineage. In Brazil, yellow fever vaccine from the 17DD strain is produced by Bio-Manguinhos, a public sector vaccine manufacturer of the Oswaldo Cruz Foundation of the Brazilian Ministry of Health. Yellow fever vaccine--associated neurologic disease (YEL-AND, formerly known as postvaccinal encephalitis) is reported to occur at a rate of 0.4 cases per 100,000 persons vaccinated in the U.S. population, with highest rates reported among persons aged ≥ 60 years (1.6 per 100,000) (6). However, the incidence among infants aged <6 months has been estimated as 0.5--4.0 cases per 1,000 infants vaccinated (4). For this reason, administration of 17D-derived yellow fever vaccines is contraindicated in infants aged <6 months (4,7,8).

Yellow fever virus, either wild-type or 17D, has not been reported to have been isolated from or detected in human breast milk. West Nile virus (WNV), another flavivirus, has been detected in milk from WNV-infected, lactating women (9), and one case of probable WNV transmission through breast-feeding has been reported (10). The actual risk for 17DD virus transmission through breast-feeding cannot be characterized because the number of breast-feeding women who have been vaccinated without negative sequelae in their infants is unknown. Based on the theoretical risk for yellow fever vaccine virus transmission through breast milk, the Advisory Committee on Immunization Practices recommends that yellow fever vaccination of nursing mothers be avoided, except when travel of nursing mothers to high-risk yellow fever--endemic areas cannot be avoided or postponed (7). Vaccine recommendations from the World Health Organization do not include considerations for breast-feeding mothers (8).

In Brazil, yellow fever vaccination is recommended for all residents of municipalities considered at risk for yellow fever transmission, and for travelers to at-risk areas (1). As a result of this investigation, the Brazilian Ministry of Health is revising its recommendations to caution against administration of yellow fever vaccine to breast-feeding women, except in situations where the risk for contracting yellow fever is unavoidable. Further studies on excretion of 17DD virus in breast

milk of vaccinated, lactating women would help to define a risk period for viral transmission in cases where vaccination of nursing mothers is necessary.

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What is already known on this topic?

Administration of yellow fever vaccine is contraindicated in children aged <6 months because of increased risk for vaccine-associated encephalitis; the Advisory Committee on Immunization Practices cautions against vaccinating breast-feeding women to avoid the potential risk for transmission of yellow fever vaccine virus to breast-feeding infants.

What is added by this report?

This report describes laboratory-confirmed, breast-feeding--associated transmission of 17DD yellow fever vaccine virus from a recently vaccinated mother; the affected infant developed postvaccinal encephalitis requiring hospitalization.

What are the implications for public health practice?

Health-care personnel should be aware that yellow fever vaccine virus can be transmitted through

breast-feeding, and administration of yellow fever vaccine to breast-feeding women should be avoided except in situations where exposure to circulating yellow fever viruses cannot be avoided.

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