

**THE AUTHORS REPLY:** Diacon and colleagues have evaluated the application of the simplified outcome definitions to MDR tuberculosis in the data set from the TMC207-C208 trial, a randomized, double-blind, placebo-controlled phase 2b trial of a new treatment for MDR tuberculosis.<sup>1</sup> In this trial, patients were followed beyond the standard of clinical practice. There were 26 post-baseline visits with participants, and three sputum samples were collected for liquid-culture examination at each visit. Although a single positive culture for *Mycobacterium tuberculosis* after 6 months of antituberculosis therapy is considered to be a treatment failure according to the simplified TBNET definitions, it is promising to see that the application of these definitions to the cure rates from the TMC207-C208 trial data set were similar to the cure rates as defined by the WHO.<sup>2</sup> The more intensive bacteriologic monitoring used in the TMC207-C208 trial indicates that the use of the simplified definitions is unlikely to result in a marked overstatement of the proportion of patients with cure. Data from ongoing clinical trials will allow further evaluation of the simplified outcome definitions.

We agree with Brust and colleagues that laboratory capacities in countries with a high burden of tuberculosis must be expanded to allow for high-quality culture of *M. tuberculosis* and that monthly monitoring of sputum cultures from patients receiving treatment for MDR tuberculosis is recommended in order to identify those patients for whom therapy has failed.<sup>3,4</sup> The simplified outcome definitions support bacteriologic monitoring. Close monitoring of patients is suggested even after the end of treatment for at least 1 year in order to identify those who have

disease recurrence. However, despite sufficient laboratory capacity, we noted that monitoring in the continuation phase of MDR tuberculosis treatment is infrequently performed in Europe. We are concerned that more than half the patients for whom MDR tuberculosis treatment “failed” were not identified in accordance with the WHO definitions in the European cohort because their therapy was not changed — a requirement for the outcome of “failure” according to WHO definitions.<sup>2</sup> It should be emphasized that to improve treatment outcomes in MDR tuberculosis, clinical training for the best care of patients and availability of appropriate drugs are as important as building laboratory capacity.

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Since publication of their letter, the authors report no further potential conflict of interest.

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3. Mitnick CD, White RA, Lu C, et al. Multidrug-resistant tuberculosis treatment failure detection depends on monitoring interval and microbiological method. *Eur Respir J* 2016;48:1160-70.
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## Prolonged Zika Virus Viremia during Pregnancy

**TO THE EDITOR:** We describe a case of Zika virus (ZIKV) infection during pregnancy in a Colombian woman. She was infected in December 2015 while she was visiting her home country. At 9 weeks' gestation, she had a self-limited maculopapular, nonconfluent rash for 3 days that affected her trunk, arms, and legs; she had no fever or other concurrent symptoms. She was screened for ZIKV and other flaviviruses.

A reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay (RealStar Zika Virus RT-PCR Kit 1.0, Altona Diagnostics) of a serum sample was positive for ZIKV, and testing remained positive for 89 days (or 107 days after the onset of symptoms, until 29 weeks' gestation), in six consecutive blood samples. Testing for ZIKV in the urine, vagina, and endocervix was negative. No fetal brain abnormalities were observed on

**Table 1. Patient Data.\***

Variable	Jan. 27, 2016	Feb. 4, 2016	Feb. 11, 2016	Feb. 26, 2016	March 8, 2016	March 21, 2016	April 11, 2016	April 25, 2016	May 30, 2016	June 30, 2016	July 25, 2016
Gestational age	11 wk	12 wk	13 wk 4 days	15 wk 5 days	17 wk 2 days	19 wk 1 day	22 wk 1 day	24 wk 1 day	29 wk 1 day	33 wk 4 days	37 wk 1 day
Forehead pain	+	+	+	+	+	-	-	-	-	-	-
ZIKV IgG antibodies	+	+	+	+	+	+	+	+	+	+	+
ZIKV IgM antibodies	-		†	+	+						
ZIKV PRNT titer	256	512	1024	1024							
ZIKV RT-PCR of serum (Ct)	+ (35)		+ (35)	+ (33)	+ (35)		+ (36)	+ (37)			
ZIKV RT-PCR of urine				-	-						
ZIKV RT-PCR of vagina, cervix, and cervicovaginal-lavage fluid					-						
ZIKV RT-PCR of amniotic fluid (Ct)						+ (28)					
Neurosonography		Normal		Normal		Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	-
ZIKV RT-PCR of placenta											
ZIKV RT-PCR of membranes and umbilical cord											
ZIKV RT-PCR of breast milk											

\* Plus signs indicate positive tests, and minus signs negative tests. Ct denotes cycle threshold value, PRNT plaque reduction neutralization test, RT-PCR reverse transcriptase–polymerase chain reaction, and ZIKV Zika virus.

† This value is undetermined.

scans obtained at 12 and 15 weeks' gestation. Neurosonography performed at 20, 24, and 29 weeks' gestation revealed bilateral mild ventriculomegaly and a shortened corpus callosum. The posterior fossa was normal. The brain parenchyma had calcifications and severe atrophy. Similar findings were seen on magnetic resonance imaging (MRI). No other anomalies were found in the fetus or the placenta. An RT-PCR assay of the amniotic fluid was positive for ZIKV, and screening was negative for dengue virus, chikungunya virus, cytomegalovirus, varicella-zoster virus, parvovirus B19, *Toxoplasma gondii*, and sexually transmitted infectious agents (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma hominis*, *Ureaplasma parvum*, *M. genitalium*, *U. urealiticum*, and *Trichomonas vaginalis*). The ZIKV viral load in the amniotic fluid was higher than that in the maternal serum (cycle threshold values, 28 vs. 35; RT-PCR cycle threshold values were used as an indirect marker of viral load). Results of targeted genetic testing of the amniotic fluid by means of microarray-based comparative genomic hybridization (SurePrint G3 Unrestricted CGH ISCA v2 Microarray Kit, 8x60K, Agilent Technologies) were normal.

The baby was delivered at 37 weeks' gestation because of suspected growth restriction. At this time, RT-PCR assays of the maternal serum, urine, amniotic fluid, placenta, membranes, and umbilical cord were negative for ZIKV. RT-PCR assays of the neonatal serum, urine, and cerebrospinal fluid were also negative. Postnatal ultrasonography and MRI studies confirmed the presence of microcephaly with a thinned corpus callosum and brain atrophy with parenchymal calcifications. (Table 1 shows the evolution of laboratory and ultrasonographic findings in the mother and the baby.)

ZIKV has been documented to be detectable in maternal blood by means of molecular techniques during the acute phase of the infection (the first 5 days after the onset of clinical symptoms).<sup>1</sup> Driggers et al. (June 2 issue)<sup>2</sup> detected ZIKV RNA in maternal serum 8 weeks after the onset of clinical symptoms. They suggested that persistent viremia may occur as a consequence of viral replication in the fetus or placenta. In our case, certain findings would support this hypothesis. First, the viral load in the amniotic fluid was higher than that in the maternal serum. Second, the viral load in the maternal serum

remained stable (cycle threshold value, approximately 35) for 14 weeks and then became negative, instead of decreasing progressively, as would be expected. Third, neutralizing antibodies and ZIKV RNA were present in the maternal serum. In addition, RT-PCR assays of the maternal urine were negative, while testing of the maternal serum was positive. According to previous studies,<sup>3</sup> ZIKV RNA would be detectable in urine longer than in serum, so an RT-PCR assay of the maternal urine would be expected to be positive in the presence of maternal viremia. For all these reasons, we would hypothesize that the persistent viremia that was detected in the mother could be the result of viral replication in the fetus or placenta, which thus acts as a reservoir.

We presume that the RT-PCR testing of neonatal samples was negative because the clinical infection occurred during prenatal life; hence, it is possible that ZIKV antibodies developed in the baby's immune system before birth. In summary, persistent ZIKV RNA in maternal serum could be a sign of fetal infection, and thus the fetus may play a role in persistent maternal viremia.

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