The Complex Interpretation and Management of Zika Virus Test Results

Kenneth W. Lin, MD, MPH, John D. Kraemer, JD, MPH, Rachael Piltch-Loeb, MSPH, and Michael A. Stoto, PhD

Zika virus disease provides the latest example of a critical nexus between public health and clinical practice. Interpreting Zika virus test results is complicated by the absence of a single testing approach with superior validity across contexts and populations. Molecular tests are highly specific, variably sensitive, and have a short window period. Serologic tests identify antibodies against Zika virus and are more likely than molecular tests to cross-react with other related viruses, reducing specificity. The type of test performed and timing relative to possible Zika virus exposure depend on public health guidance, testing algorithms, test availability, and capacity. Guidance from the Centers for Disease Control and Prevention and local health departments have changed throughout the course of the US epidemic based on prevalence, geography, and clinical concerns. Women with a low pretest probability of infection should be counseled against testing. Women with a high pretest probability of Zika virus infection should still receive enhanced prenatal monitoring and newborn evaluation, regardless of the test result. An appropriate interpretation of results depends on what tests are used, patient characteristics, and reasons for testing. Clinicians should take these factors into account in shared decision making discussions with pregnant women about Zika virus testing. (J Am Board Fam Med 2018;31:924–930.)

Keywords: **Centers for Disease Control and Prevention (US), Decision Making, Pregnancy, Probability, Public Health, Sensitivity and Specificity, Serologic Tests, Zika Virus**

Zika virus disease provides the latest example of a critical nexus between public health and clinical practice. Clinicians rely on national recommendations and state and local health department guidance on how and when to conduct screening and diagnostic testing. Whether testing is done, which tests are used, the accuracy of results, and whether results are reported also depend on test availability, patient demand, where transmission is thought to be occurring, and public awareness of these factors. Public health guidance depends on surveillance data, which are generated primarily from case reports based on clinical tests initiated by physicians.[1] Finally, the interpretations of test results for individual patients rely on estimates of disease prevalence, which are from public health surveillance.

Clinicians have found it challenging to implement public health recommendations regarding Zika virus testing and fetal and infant surveillance,[2] and some have argued that the shifting nature of these recommendations means that clinicians cannot simply rely on algorithms from the Centers for Disease Control and Prevention (CDC) to determine whom to test.[3] This article aims to help clinicians understand the rationale for public health testing and screening guidance, the importance of appropriate testing, and how to interpret results under less than ideal circumstances. We address both screening (for asymptomatic individuals who might have been exposed) and diagnostic testing (for individuals with symptoms) and focus on

This article was externally peer reviewed.
Submitted 15 February 2018; revised 12 June 2018; accepted 15 June 2018.
From the Department of Family Medicine, Georgetown University Medical Center, Washington, DC (KWL); Department of Health Systems Administration, Georgetown University, Washington (JDK, MAS); New York University College of Global Public Health, New York, NY (RP-L).
Funding: none.
Conflict of interest: none declared.
Corresponding author: Kenneth W. Lin, MD, MPH, Georgetown University Medical Center, Department of Family Medicine, 3900 Reservoir Road NW Preclinical Science GB-01A, Washington, DC 20007 (E-mail: Kenneth.Lin@georgetown.edu).

J Am Board Fam Med: first published as 10.3122/jabfm.2018.06.180061 on 9 November 2018. Downloaded from http://www.jabfm.org/ on 10 April 2021 by guest. Protected by copyright.

women of childbearing age, because most testing scenarios that clinicians encounter will be in women who are pregnant or considering pregnancy. We begin by describing the performance of available tests and show how interpreting test results depends on 5 "Ws": who gets tested and the risk that they have been infected; what type of test is done; when the test is done; where the individual lives or has traveled; and why was the test performed (eg, in response to symptoms, known exposure, concerns about pregnancy complications, or for active surveillance purposes). These factors, in turn, influence the test's performance characteristics and the interpretation of the results for patients.

Zika Virus Test Types and Performance

Interpreting Zika virus test results is complicated by the absence of a single testing approach with superior validity across contexts and populations. Rather, there is substantial variation across 3 dimensions: (1) what the test seeks to detect; (2) the test's sensitivity and specificity under idealized conditions; and (3) moderators that affect test validity under real world conditions, such as pregnancy status, the timing of a test, what fluids are tested, and cross-reactivity with other, similar viruses.

The US Food and Drug Administration (FDA) has authorized 2 classes of Zika virus tests for human use: molecular and serologic (Table 1). Molecular tests identify individuals with a current infection by identifying Zika virus RNA in blood serum or urine. Most molecular tests use polymerase chain reaction (PCR), although 1 uses transcription-mediated amplification.

Exact estimates of sensitivity and specificity are not available because there is no gold standard comparison. However, currently available molecular tests have high specificity—they correctly identify patients without Zika virus—under idealized conditions.[4] Their sensitivity varies substantially, however. The tests currently authorized for use in the United States have labeled limits of detection ranging across 3 orders of magnitude.[5] As a result, while some tests are extremely sensitive,[6] the least sensitive tests would have failed to detect over half of the cases in a large Nicaraguan cohort.[7]

Several factors influence the sensitivity of molecular tests, of which the timing of the test is most important. These tests generally cease returning a

Table 1. Zika Test Types and Characteristics

Class of Test	Specific Type of Test	Estimated Sensitivity	Estimated Specificity	Risk of Cross-Reactivity	Timing
Molecular: identify Zika RNA	Polymerase chain reaction; transcription-mediated amplification	Incompletely characterized; tests currently authorized for US use have labeled limits of detection across three orders of magnitude. So, while some are extremely sensitive, the least sensitive tests would have failed to detect more than half of positive cases in a recent, large Nicaraguan cohort.	Incompletely characterized but expected to be high.	Expected to be rare.	Only positive while the person is viremic. Window period is normally short, but will cease positive results within a few weeks after symptoms resolve. Mild and nonspecific symptoms for many patients complicate correct timing.
Serologic: identify antibody against Zika	Enzyme-linked immunosorbent assay	37% to 100% in various studies.	66% to 100% in various studies. Risk of false positives calls for confirmation by plaque reduction neutralization test under certain situations in CDC algorithm.	8% to 40% in various studies, which would reduce effective specificity when cross-reacting viruses are likely present.	Most tests identify IgM, which usually develops within a few days after symptoms and decline after about three months (though it sometimes be detected for over a year). A few tests identify IgG, which develops later, although as early as 10 days after symptoms in some cases, but persists for years.

CDC, Centers for Disease Control and Prevention.

J Am Board Fam Med: first published as 10.3122/jabfm.2018.06.180061 on 9 November 2018. Downloaded from http://www.jabfm.org/ on 10 April 2021 by guest. Protected by copyright.

positive test once a person is no longer viremic, usually around 2 weeks after symptom onset[8] to a maximum of a few weeks after symptoms resolve.[5,9] Furthermore, only a small fraction of infected people develop symptoms that are likely to be identified as Zika virus,[10,11] complicating the correct timing of tests. Several studies suggest that whole-blood samples have higher virus levels and that detectable virus may persist longer than in serum or urine samples.[12] Coinfection with related viruses, which tends to reduce virus levels, may reduce sensitivity[13]; however, cross-reactivity, which would reduce test specificity, is rarely reported.[5] Finally, limited evidence suggests that pregnant women may have higher and longer-lasting viremia, which would increase the test's sensitivity.[14]

Serologic tests, on the other hand, use the enzyme-linked immunosorbent assay (ELISA) to identify antibodies against Zika virus,[15] which indicates past infection. All US tests identify immunoglobulin M (IgM), which develop shortly (usually a few days) after symptom onset and decline after about 3 months (although IgM can sometimes be detected for over a year).[10] A few tests identify IgG, which develops later, although as early as 10 days after symptoms in some cases, but persists for years.[16] Under ideal conditions, serologic tests have sensitivities ranging from 37% to 100% and specificities between 66% and 100%.[15]

The performance of serologic tests depends substantially on the timing of testing relative to infection. Immediately after infection, antibodies against Zika virus will not have developed yet. Too long after infection, the IgM antibody against Zika virus will no longer be present. IgG will persist but cannot distinguish recent from previous infection.[17] Serologic tests are more likely to cross-react with viruses that are related to Zika virus, including dengue, West Nile virus, and yellow fever virus. The risk of cross-reactivity depends on where a person has lived and traveled. While limited data exist, 1 commercially available test found cross-reactivity 19% of the time for IgG and 8% for IgM.[4] Another test cross-reacted in 40% of cases where dengue but not Zika virus IgM was present.[17]

Because there is a significant risk of false positives and cross-reaction with ELISA tests, the CDC recommends that negative tests be considered definitive but positive or indeterminate tests be followed up with a plaque reduction neutralization test for both Zika virus and dengue. The plaque reduction neutralization test is highly accurate and usually able to differentiate between antibodies against Zika virus and other related viruses, but it can only be run by CDC or other specialized labs. It takes up to 4 weeks for results and, like all antibody tests, it cannot definitely determine when infection occurred.[10]

Because of the differences in the sensitivity and specificity of available tests, clinicians must know which tests were done and when they were done relative to the approximate time of infection (estimated by the time of symptom onset and/or known exposure) to properly interpret the results. Any test's positive and negative predictive value, however, also depends on the pretest probability of infection (see Sidebar below). Therefore, it is also important to understand patient characteristics, including why they were tested.

Indications for Testing

Whether one is tested for Zika virus at all, what type of test is used, and when the test is done depend on the likelihood that one has been infected (eg, travel to an area of known transmission or contact with someone exposed) and the consequences of that infection (especially for children of women exposed during pregnancy). The type of test performed and timing relative to exposure depend on public health guidance, testing algorithms, test availability, and capacity. Whether and what type of testing is done also depends on where state and local health departments believe transmission is occurring.

Early in the US Zika virus outbreak, the only laboratories capable of testing samples were state and local health departments. Because testing capacity was limited, they (working in collaboration with the CDC) determined whether a sample was eligible to be tested by using algorithms that involve clinical criteria, especially (1) symptoms such as fever, rash, arthralgia, and conjunctivitis and associated conditions such as Guillain-Barré syndrome; (2) high-risk situations, such as pregnancy, and discovery of prenatal or neonatal outcomes, such as microcephaly or other specified conditions; (3) and "epidemiologic linkage," a combination of risk factors, including recent travel to areas with ongoing transmission; having sexual contact with

J Am Board Fam Med: first published as 10.3122/jabfm.2018.06.180061 on 9 November 2018. Downloaded from http://www.jabfm.org/ on 10 April 2021 by guest. Protected by copyright.

Table 2. Zika Virus Screening Protocols (NYC Health + Hospitals, Oct. 2016)

Criteria for testing
1. Pregnant women who
a. traveled while pregnant to an area with Zika virus transmission **OR**
b. had unprotected sex (vaginal, anal, or oral) with a partner who spent time in an area with Zika virus transmission
2. Persons who develop/developed compatible symptoms during or within 4 weeks of travel to an area with Zika virus transmission
3. Neonates with suspected or confirmed microcephaly or intercranial calcifications born to women who
a. traveled while pregnant to an area with Zika virus transmission **OR**
b. had unprotected sex (vaginal, anal, or oral) with a partner who spent time in an area with Zika virus transmission
4. Anyone who developed Guillain-Barré syndrome after spending time in an area with active Zika virus transmission
5. Other special conditions with epidemiological linkage to a confirmed or probably case of Zika virus infection including
a. recipient of blood, blood products, or organ transplant **OR**
b. suspected transfusion-associated transmission, **OR**
c. suspected mosquito-borne transmission, **OR**
d. any other unusual clinical manifestation or suspected route of exposure
Laboratory testing, if indicated, can be performed at DOHMH or at a specified commercial laboratory.
Patient specimens from travel-associated cases of suspected Zika virus infection are sent to the commercial laboratory for testing and do not require the clinician to call DOHMH.
Clinicians are instructed to call DOHMH for testing in all nontravel-associated cases of suspected Zika virus disease.

DOHMH, Department of Health and Mental Hygiene.

partners who recently traveled to such an area; being a recipient of blood, blood products, or an organ transplant from a person with known infection; or clinical suspicion of mosquito-borne transmission. For example, Table 2 illustrates the criteria used by the New York City Health and Hospitals department in early 2016 to determine whether someone was eligible to be tested. Other jurisdictions likely followed the CDC's guidance less formally, taking into account local testing capacity.

Early in the outbreak, only those with known risks were eligible to be tested, so the pretest probability of infection likely was relatively high. As time progressed, testing became more available and lab capacity constraints were relaxed. In addition, private laboratories began to offer Zika virus testing through an emergency order from the Food and Drug Administration. Although the CDC recommends that clinicians contact their state or local health department to request Zika virus testing,[10] private laboratories can be accessed independently by providers and patients. Private labs and services, including Personal Labs, Quest Diagnostics, and LabCorp, offer both reverse transcription-PCR and ELISA Zika virus tests independently of state and local health departments. Patients may pay out of pocket for some private tests, with costs ranging from $500 to $3000 (LabCorp sales representative, personal communication).[18] Tests that are independently requested by patients are not covered by insurance, creating a potential bias toward those who have the availability to pay for a test (if test results are even being reported). There is wide state-by-state variation in private labs. Some states do not allow for private Zika virus testing. The cost, location, and availability of private tests vary, adding to the complexity of tracking potential Zika virus cases.

As a consequence of the increasing capacity, tests became more easily available to individuals who did not meet the CDC criteria, so, on average, the pretest probability of infection likely dropped. Because testing can be costly, its use likely varied by income, and because testing capacity varied geographically, the pretest probability likely varied from location to location as well.

Why Patients Request Testing

Patient requests for Zika virus testing are driven by awareness and knowledge, risk perception based on geography and travel, pregnancy concerns, symptoms, and government and media messages. According to surveys conducted over the course of 2016, women, older adults, non-Hispanic white adults, those with higher incomes, and those with higher education were more likely to be aware of Zika virus risk.[19,20] Awareness did not necessarily equate to knowledge; only 38% of persons aware of Zika virus knew it could be sexually transmitted, cause birth defects, and be asymptomatic. However, knowledge of particular characteristics of Zika virus's effects decreased as the awareness of risk increased.[19] Understanding about Zika virus also varied in specific, targeted populations. Berenson

J Am Board Fam Med: first published as 10.3122/jabfm.2018.06.180061 on 9 November 2018. Downloaded from http://www.jabfm.org/ on 10 April 2021 by guest. Protected by copyright.

and colleagues[21] reported that women attending prenatal clinics in southern Texas in summer 2016 had low levels of knowledge: 60% were not aware Zika virus can be sexually transmitted. This variation in knowledge and awareness suggests different individuals seek Zika virus tests and engage with their clinician about Zika virus.

Because Zika virus infection increases the risk of microcephaly and other serious neurologic problems in fetuses and neonates of infected women,[22] women who were in an area with active transmission or whose sexual partner may have been exposed and who later learn they are pregnant might desire testing to inform their decisions about undergoing additional fetal surveillance or carrying a pregnancy to term. A woman also might elect to delay pregnancy if her partner tested positive for Zika virus or had a known exposure.

A patient may also seek testing if displaying symptoms, especially after travel. Symptoms of Zika virus infection, such as fever, rash, and joint pain, are relatively nonspecific and could reflect similar mosquito-borne viruses or even flu-like symptoms. Guidelines recommended that testing be ordered in the context of the patient or their sexual partner having traveled to a Zika virus endemic area.

Finally, clinicians confronting a novel disease threat often look to practice guidelines to decide what to do. Guidelines from the CDC and local health departments have changed throughout the course of the US Zika virus epidemic based on prevalence, geography, and clinical concerns.

Clinical Scenarios

The drivers of Zika virus testing outlined above highlight the varying reasons and motivations for initiating a Zika virus test. Health departments/facilities have developed complex algorithms to initiate Zika virus testing, but the guidelines are subject to change and the meaningful interpretation of a positive or negative Zika virus test result depends on understanding how test and context-dependent factors interact. The sensitivity and specificity of any test depends on what type of test was done and when it was done relative to the time of exposure. Furthermore, the interpretation of a positive or negative test also depends on the pretest probability of infection, which is a function of who was tested, where he or she lives or has traveled, and why the test was performed. We provide 3 scenarios to illustrate these points.

Scenario 1: Low Pretest Probability

Suppose a woman attends a routine antenatal visit in Minneapolis, where there is no local Zika virus transmission. She has flu-like symptoms but no history of travel to an affected area and no recent sexual partners who have traveled to an affected area. There is no indication for ordering a Zika virus test in this patient, and it is not recommended. However, because it was in the news, she requests a Zika virus test. Her likelihood of Zika virus infection is very small, perhaps 1 in 10,000 (though likely much lower). She is given a well-performing IgM ELISA test with 99% sensitivity and 95% specificity. In this situation, a positive result would only have a positive predictive value (PPV) of 1 in 500, reflecting the very low likelihood of an actual history of Zika virus infection. A negative result would rule out Zika virus with near certainty.

Scenario 2: High Pretest Probability

At the opposite end of the spectrum, consider a pregnant woman who lives in Puerto Rico and presents to her physician with classic Zika virus symptoms: fever, muscle and joint pain, and rash. In this case, we assume her pretest probability of Zika virus infection is 80%. She is given an appropriate reverse transcription-PCR test that has been shown not to cross-react with dengue fever virus or other likely infections. Limited data are available on sensitivity and specificity but assume 99% sensitivity and 95% specificity. In this scenario, a positive test is 98.8% likely to signal actual Zika virus infection. Even in the situation where there is a 50% chance she is coinfected with dengue and her test has a 10% likelihood of cross-reacting (which would be worse performance than what seems to be likely for PCR tests), she would still be 97.6% likely to actually have Zika virus if her test were positive. Negative results in either situation are about 96% likely to rule out Zika virus. Of course, if she were given 1 of the least-sensitive PCR tests (suppose 50%), the predictive value of a positive test would remain high (95%) but would fall greatly for a negative test (31%). Because a negative test result would not rule out the possibility of Zika virus infection, prenatal surveillance for fetal abnormalities and newborn referrals to hearing, vision, and

J Am Board Fam Med: first published as 10.3122/jabfm.2018.06.180061 on 9 November 2018. Downloaded from http://www.jabfm.org/ on 10 April 2021 by guest. Protected by copyright.

neurologic evaluations would still be warranted. In this situation, testing the woman has relevance primarily for public health surveillance.

Scenario 3: Intermediate Pretest Probability

Suppose a patient has only a 25% pretest probability of infection. Perhaps she had nonspecific symptoms 2 months ago, early in her pregnancy, after traveling briefly to Brazil. She has no other risk factors for Zika virus and lives a part of the United States with no local transmission. She is given the same well-performing IgM ELISA as the woman from Minneapolis. In this case, a positive test signals an 86.8% likelihood of infection; it is likely but uncertain that she has been infected with Zika virus in the past several months, and her travel history may make it unlikely that infection occurred before her pregnancy (if it occurred). A negative result excludes Zika virus with near certainty. Suppose, however, that she were instead given a PCR test, which her low level of viremia this long after putative infection would render insensitive (perhaps 20%) but otherwise performs the same as before. Now, a positive test is only 57% likely to signal infection and a negative test is 78% likely to signal noninfection.

Even at a higher likelihood of infection, intermediate risks are hard to interpret. Suppose the patient had a 50% pretest probability of infection; maybe she stayed a few weeks in Brazil and her symptoms are ambiguous but more consistent with Zika virus. Now, her well-performing ELISA returns positive and negative predictive values of 95% and 99%, respectively. Her poorly advised PCR test returns 80% and 54% positive and negative predictive values, respectively. Also, suppose she is given a less well-performing ELISA, which is plausible given the relatively limited information about the performance of particular tests on the market. If her test has 70% sensitivity and specificity, the approximate range of some tests on the market,[17] her positive and negative predictive value drop to 70% each.

Implications for Clinicians

What follows from these scenarios? First, women who have a low pretest probability of infection should be counseled against testing. Conversely, since a negative test cannot "rule out" Zika virus infection in women with a high pretest probability of infection, enhanced prenatal monitoring and newborn evaluation should still occur, regardless of the test result. Second, an interpretation of the results depends on what tests are used; patient characteristics, such as where the individual lives or has traveled; and why was the test performed (eg, in response to symptoms, known exposure, concerns about pregnancy complications, or for active surveillance purposes). Third, many of these ambiguities leading to potential false positives can be resolved through an adherence to CDC's sequential testing algorithms,[10] but this will sometimes require plaque reduction neutralization tests, which are of limited availability. Now that the CDC only recommends universal testing for pregnant women who present with Zika virus-compatible symptoms or ongoing Zika virus exposure throughout pregnancy, clinicians should take all these factors into account in shared decision-making discussions with pregnant women about whether to test or not.

Sidebar: Definitions of Test Characteristics

Screening tests are often described in terms of sensitivity and specificity. Sensitivity describes the test's ability to detect cases where they actually exist. Sensitivity is defined as probability that test is positive, given that condition is present. Specificity describes the likelihood that the test will avoid false positives, that is to be negative when the condition is not present. Specificity is defined as the probability that, if the condition is not present, the test will be negative.

Sensitivity and specificity describe how well a test performs given the "truth," that is, if the person being tested has or does not have the condition of interest. In practice, however, one knows the test result and wants to know whether the patient has the condition. Epidemiologists use PPV and negative predictive value (NPV) to describe how well a test distinguishes between individuals with and without the condition. PPV is defined as the probability that the condition is present, given that the test is positive; NPV is the probability the condition is not present, given that the test is negative.

Unlike sensitivity and specificity, the positive and negative predictive values depend on the prevalence of the condition. For example, if a test has 80% sensitivity and 90% specificity and the prevalence of the condition is 10%, the PPV is only 47.1%. This is because in a group of 1000 individuals, 100 of whom have the condition, there will be

J Am Board Fam Med: first published as 10.3122/jabfm.2018.06.180061 on 9 November 2018. Downloaded from http://www.jabfm.org/ on 10 April 2021 by guest. Protected by copyright.

90 false positives (10% of 900) and only 80 true positives (80% of 100). When the prevalence is 1%, only 8 of 107 positive tests are for people who actually have the condition, so the PPV is only 7.5%. On the other hand, nearly all the individuals with negative test values do not in fact have the condition, so the NPV is 891/893 (99.8%).

To see this article online, please go to: http://jabfm.org/content/31/6/924.full.

References

1. Piltch-Loeb R, Kraemer J, Lin KW, Stoto MA. Public health surveillance for Zika virus: data interpretation and report validity. Am J Public Health; 23 August 2018. [E-pub ahead of print].
2. Morain SR, Wootton SH, Eppes C. A devastating delay - Zika and the implementation gap. N Engl J Med 2017;377:1505–7.
3. Goldfarb IT, Jaffe E, Lyerly AD. Responsible care in the face of shifting recommendations and imperfect diagnostics for Zika virus. JAMA 2017;318: 2075–2076.
4. Charrel RN, Leparc-Goffart I, Pas S, de Lamballerie X, Koopmans M, Reusken C. Background review for diagnostic test development for Zika virus infection. Bull World Health Organ 2016;94:574–584D.
5. Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks. Washington DC: Government Accountability Office (GAO); May 2017.
6. Paz-Bailey G, Rosenberg ES, Doyle K, et al. Persistence of Zika virus in body fluids - preliminary report. N Engl J Med. In press.
7. Waggoner JJ, Gresh L, Vargas MJ, et al. Viremia and clinical presentation in Nicaraguan patients infected with Zika virus, chikungunya virus, and dengue virus. Clin Infect Dis 2016;63:1584–90.
8. Fontaine A, de Laval F, Belleoud D, Briolant S, Matheus S. Duration of Zika viremia in serum. Clinical Infectious Diseases. 2018;67:1143–1144.
9. Barzon L, Percivalle E, Pacenti M, et al. Reply to Fontaine. Clin Infect Dis 2018;67:1144–1145.
10. Centers for Disease Control and Prevention. Guidance for US laboratories testing for Zika virus infection, July 24, 2017. Available from: https://www.cdc.gov/zika/laboratories/lab-guidance.html. Published 2017. Accessed October 4, 2017.
11. Flamand C, Fritzell C, Matheus S, et al. The proportion of asymptomatic infections and spectrum of disease among pregnant women infected by Zika virus: systematic monitoring in French Guiana, 2016. Euro Surveill 2017;22:17–00102.
12. Mansuy JM, Mengelle C, Pasquier C, et al. Zika virus infection and prolonged viremia in whole-blood specimens. Emerg Infect Dis 2017;23: 863–5.
13. Lustig Y, Mendelson E, Paran N, Melamed S, Schwartz E. Detection of Zika virus RNA in whole blood of imported Zika virus disease cases up to 2 months after symptom onset, Israel, December 2015 to April 2016. Euro Surveill 2016;21:30269.
14. Suy A, Sulleiro E, Rodó C, et al. Prolonged Zika virus viremia during pregnancy. N Engl J Med 2016; 375:2611–3.
15. Ren P, Ortiz DA, Terzian ACB, et al. Evaluation of Aptima Zika virus assay. J Clin Microbiol 2017;55: 2198–203.
16. Rabe IB, Staples JE, Villanueva JM, et al. Interim guidance for interpretation of Zika virus antibody test results. MMWR Morb Mortal Wkly Rep 2016; 65:543–6.
17. Safronetz D, Sloan A, Stein DR, et al. Evaluation of 5 commercially available Zika virus immunoassays. Emerg Infect Dis 2017;23:1577–1580.
18. Rabin RC. Want a Zika test? It's not easy. New York Times 2016 September 19, 2016.; Sect. Well.
19. Abramson D, Piltch-Loeb R. U.S. public's perception of Zika risk: awareness, knowledge, and receptivity to public health interventions. New York City, NY: New York University College of Global Public Health; 2016.
20. March of Dimes/NORC The Zika virus: gaps in Americans' knowledge and support for government action. Chicago, IL: March of Dimes/NORC at the University of Chicago; 2016.
21. Berenson AB, Trinh HN, Hirth JM, Guo F, Fuchs EL, Weaver SC. Knowledge and prevention practices among U.S. pregnant immigrants from Zika virus outbreak areas. Am J Trop Med Hyg 2017;97: 155–62.
22. Johansson MA, Mier-y-Teran-Romero L, Reefhuis J, Gilboa SM, Hills SL. Zika and the risk of microcephaly. N Engl J Med 2016;375:1–4.

J Am Board Fam Med: first published as 10.3122/jabfm.2018.06.180061 on 9 November 2018. Downloaded from http://www.jabfm.org/ on 10 April 2021 by guest. Protected by copyright.