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S.C. Department of Health and Environmental Control

South Carolina Health Alert Network

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CDC Health Advisory

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Prolonged IgM Antibody Response in People Infected with Zika Virus: Implications for Interpreting Serologic Testing Results for Pregnant Women

Summary

In July 2016, CDC issued Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure – United States, July 2016 https://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm) that includes Zika virus immunoglobulin M (IgM) testing of pregnant women. However, some flavivirus infections can result in prolonged IgM responses (>12 weeks) that make it difficult to determine the timing of infection, especially in testing of asymptomatic people. Emerging epidemiologic and laboratory data indicate that Zika virus IgM can persist beyond 12 weeks in a subset of infected people. Therefore, detection of IgM may not always indicate a recent infection. Although IgM persistence could affect IgM test interpretation for all infected people, it would have the greatest effect on clinical management of pregnant women with a history of living in or traveling to areas with Zika virus transmission. Pregnant women who test positive for IgM antibody may have been infected with Zika virus and developed an IgM response before conception.

For asymptomatic pregnant women with a history of living in or traveling to areas with Zika virus transmission, Zika virus nucleic acid test (NAT) testing at least once per trimester is recommended, in addition to IgM testing as previously recommended. If positive, this may provide a more definitive diagnosis of recent Zika infection. However, a negative NAT does not rule out recent infection because viral ribonucleic acid (RNA) declines over time. Other diagnostic methods, such as NAT testing of amniocentesis specimens or serial ultrasounds, may provide additional information to help determine whether the IgM test results suggest a recent infection. Providers should counsel women on the limitations of all tests. In addition, providers may wish to consider IgM testing as part of pre-conception counseling to establish baseline IgM results before pregnancy; however, preconception negative IgM results might have limited value for

women at ongoing risk of Zika infection. NAT testing should be performed for any pregnant woman who becomes symptomatic or who has a sexual partner who tests positive for Zika virus infection.

Recommendations

For asymptomatic pregnant women with possible Zika virus exposure before conception, (particularly women who lived in or traveled to areas with posted CDC Zika Travel Notices https://wwwnc.cdc.gov/travel/page/zika-information), CDC recommends that healthcare providers take these steps:

1) Screen pregnant women for risk of Zika exposure and symptoms of Zika. Promptly test pregnant women with NAT if they become symptomatic during their pregnancy or if a sexual partner tests positive for Zika virus infection.
2) Conduct NAT testing at least once per trimester, unless a previous test has been positive.*
3) Consider NAT testing of amniocentesis specimens if amniocentesis is performed for other reasons.†
4) Counsel pregnant women each trimester on the limitations of IgM and NAT testing. For more information about Zika virus testing, see: https://www.cdc.gov/zika/pdfs/living_in.pdf. For more information about counseling before testing, see: https://www.cdc.gov/zika/pdfs/pretestingcounselingscript_livingin.pdf.
5) Consider IgM testing to determine baseline Zika virus IgM levels as part of preconception counseling.§ For more information about preconception counseling, see: https://www.cdc.gov/zika/pdfs/preconception-counseling.pdf

Recommendations for testing symptomatic pregnant women, remain unchanged (https://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm). However, if a symptomatic pregnant woman is IgM positive and NAT negative, and lived in or traveled to an area with a posted CDC Zika Travel Notice (https://wwwnc.cdc.gov/travel/page/zika-information), healthcare providers should recognize that the positive IgM result does not necessarily indicate recent infection.

CDC will update clinical management (https://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm) and laboratory testing (https://www.cdc.gov/zika/laboratories/lab-guidance.html) recommendations as new information becomes available.

Background

Some flavivirus infections have been reported to result in prolonged IgM responses that make it difficult to differentiate recent from prior infections in areas with ongoing transmission. For dengue virus, IgM was determined to persist for 6 months (179 days [95% confidence interval, 155 to 215 days]) for primary infections and 4.6 months (139 days [95% confidence interval, 119 to 167 days]) after infection with another flavivirus[1]. IgM antibodies against West Nile virus, another flavivirus related to Zika virus, have been detected in asymptomatic, infected blood donors for at least three months after they donated blood, and almost half of tested patients with West Nile virus infection had serum IgM antibodies >1 year after infection[2,3] .

Recent findings suggest that Zika virus infection may also result in IgM persistence that may make it difficult to differentiate prior from recent infections. A recent study in Puerto Rico of symptomatic patients with NAT-confirmed Zika virus infection detected Zika virus IgM in 100% (28/28) of participants at 8 to 15 days after symptom onset, and 87% (52/60) at greater than 60 days after symptom onset[4]. Unpublished data on the symptomatic patients from this ongoing study show a median time to first negative Zika virus IgM as 4 months (122 days [range 8-210 days]). More data are needed to accurately estimate the proportion of persons who are likely to have Zika IgM persist beyond 12 weeks after infection.

IgM test results can also be difficult to interpret because of cross-reactivity with other flaviviruses, particularly dengue virus, when a person has been previously infected or vaccinated with a related flavivirus. During 2016, Puerto Rico had limited dengue virus transmission and, therefore, people who tested positive for Zika IgM antibody could be assumed to have had recent Zika virus infection. However, if dengue virus transmission were to increase, guidance for interpretation of Zika virus IgM testing results may need to be reconsidered.

NAT testing may be useful in testing pregnant women as an indicator of current infection and increased risk to the fetus. In the same study from Puerto Rico discussed above, viral RNA was detected in 36% (10/28) of participants at 8–15 days after symptom onset, 21% (27/129) at 16–30 days after symptom onset, and 4% (3/79) more than 60 days after symptom onset4 . A limited number of studies have demonstrated detection of viral nucleic acid in some pregnant women for even longer periods after symptom onset. For example, three of the five pregnant women included in the study from Puerto Rico had detectable RNA at 46 days and one still had detectable RNA at 80 days after symptom onset[4]. In another case series, some pregnant women had Zika virus RNA detectable up to 107 days after symptom onset[5].

For More Information

Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure - United States, July 2016. MMWR Morb Mortal Wkly Rep. 2016 Jul 25;65(29):739-44.https://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm

Guidance for U.S. Laboratories Testing for Zika Virus Infection. https://www.cdc.gov/zika/laboratories/lab-guidance.html

Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Persons with Possible Zika Virus Exposure - United States, September 2016. MMWR Morb Mortal Wkly Rep. 2016 Oct 7;65(39):1077-1081. https://www.cdc.gov/mmwr/volumes/65/wr/mm6539e1.htm?s_cid=mm6539e1_w

References

1. Prince HE, Matud JL. Estimation of dengue virus IgM persistence using regression analysis. Clin Vaccine Immunol 2011;18: 2183-5.
2. Roehrig JT, Nash D, Maldin B, et al. Persistence of virus-reactive serum immunoglobulin M antibody in confirmed West Nile virus encephalitis cases. Emerg Infect Dis 2003;9:376-9. http://dx.doi.org/10.3201/ eid0903.020531
3. Busch MP, Kleinman SH, Tobler LH, et al. Virus and antibody dynamics in acute West Nile virus infection. J Infect Dis 2008;198:984-93. http:// dx.doi.org/10.1086/591467
4. Paz-Baily G, Rosenberg ES, Doyle K, et al. Persistence of Zika virus in body fluids— Preliminary report. N Engl J Rep 2017. DOI: 10.1056/NEJMoa1613108
5. Suy A, Sulleiro E, Rodó C, et al. Prolonged Zika virus viremia during pregnancy. N Engl J Med. 2016;375:2611-2613.
6. Reynolds MR, Jones AM, Petersen EE, et al. Vital signs: Update on Zika virus–associated birth defects and evaluation of all U.S. infants with congenital Zika virus exposure — U.S. Zika pregnancy registry, 2016. MMWR Morb Mortal Wkly Rep 2017;66:366-373.

Footnotes

* Birth defects have been reported in a higher proportion of fetuses or infants whose mothers were infected during the first trimester of pregnancy than in later trimesters. In pregnancies with symptom onset or exposure during the first trimester that were

limited to those with laboratory-confirmed Zika virus infection, 15% of completed pregnancies had reported birth defects of the type seen with congenital Zika infection6 .

† Consideration of amniocentesis should be individualized, because data about its usefulness in diagnosing congenital Zika virus infection are limited. The presence of Zika virus RNA in the amniotic fluid might indicate fetal infection; however, a negative result does not exclude congenital Zika virus infection

§ Preconceptional IgM testing is recommended to establish a baseline IgM level before pregnancy. However, given the limitations of interpreting IgM testing, the results of these tests should not be used to guide decisions about pregnancy timing for women living in areas with ongoing risk of transmission.

DHEC contact information for reportable diseases and reporting requirements

Reporting of **Zika** is consistent with South Carolina Law requiring the reporting of diseases and conditions to your state or local public health department. (State Law # 44-29-10 and Regulation # 61-20) as per the DHEC 2017 List of Reportable Conditions available at:
http://www.scdhec.gov/Library/CR-009025.pdf

Federal HIPAA legislation allows disclosure of protected health information, without consent of the individual, to public health authorities to collect and receive such information for the purpose of preventing or controlling disease. (HIPAA 45 CFR §164.512).

Regional Public Health Offices – 2017

Mail or call reports to the Epidemiology Office in each Public Health Region

MAIL TO:

Lowcountry	Midlands	Pee Dee	Upstate
4050 Bridge View Drive, Suite 600 N. Charleston, SC 29405 Fax: (843) 953-0051	2000 Hampton Street Columbia, SC 29204 Fax: (803) 576-2993	145 E. Cheves Street Florence, SC 29506 Fax: (843) 661-4859	200 University Ridge Greenville, SC 29602 Fax: (864) 282-4373

CALL TO:

Lowcountry	Midlands	Pee Dee	Upstate
Berkeley, Charleston, Dorchester Phone: (843) 953-0043 Nights/Weekends: (843) 441-1091	**Kershaw, Lexington, Newberry, Richland** Phone: (803) 576-2749 Nights/Weekends: (888) 801-1046	**Chesterfield, Darlington, Dillon, Florence, Marlboro, Marion** Phone: (843) 661-4830 Nights/Weekends: (843) 915-8845	**Anderson, Oconee** Phone: (864) 260-5581 Nights/Weekends: (866) 298-4442
Beaufort, Colleton, Hampton, Jasper Phone: (843) 322-2453 Nights/Weekends: (843) 441-1091	**Chester, Fairfield, Lancaster, York** Phone: (803) 286-9948 Nights/Weekends: (888) 801-1046	**Clarendon, Lee, Sumter** Phone: (803) 773-5511 Nights/Weekends: (843) 915-8845	**Abbeville, Greenwood, McCormick** Phone: (864) 260-5581 Nights/Weekends: (866) 298-4442
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For information on reportable conditions, see http://www.scdhec.gov/Health/FHPF/ReportDiseasesAdverseEvents/ReportableConditionsInSC/

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Categories of Health Alert messages:

Health Alert	Conveys the highest level of importance; warrants immediate action or attention.
Health Advisory	Provides important information for a specific incident or situation; may not require immediate action.
Health Update	Provides updated information regarding an incident or situation; unlikely to require immediate action.
Info Service	Provides general information that is not necessarily considered to be of an emergent nature.