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American Academy of Pediatrics
Webinar Series on Zika Virus Syndrome
Recognizing Microcephaly and Other Presentations of Zika Virus Syndrome
January 10, 2017
Question and Answers

Question	Answer
1. How are possible asymptomatic cases identified? Are these babies whose mother has tested positive?	Infants born to women with laboratory evidence of confirmed or possible Zika virus infection should be evaluated for congenital Zika virus infection in accordance with CDC interim guidance for health care providers caring for infants with possible Zika virus infection, whether or not they have any visible abnormalities. The full spectrum of congenital Zika virus syndrome is not well established, and case reports demonstrate variability. Any infant who tests positive for Zika infection who does not have any clinical evidence of abnormalities should be managed according to the above-referenced guidance.
2. Are there any twin pregnancies and is it inevitable that both twins are affected?	Zika virus infection during pregnancy is a cause of a spectrum of anomalies including microcephaly and other brain defects, and has been linked to other abnormalities among fetuses and infants infected with Zika virus before birth. There is currently no information regarding whether Zika virus can infect only one of a pair of twins during pregnancy. We know from other infections, however, that this is possible; it is also possible that both twins get infected but have different disease manifestations. Studies are underway that could provide data to address this question, and CDC is collecting information on all pregnant women with Zika virus infection and their infants in the US including territories. CDC guidance will be updated when additional data become available.
3. Thanks for this informative talk. We (a Caribbean country) are seeing a trend of several babies at birth with lower OFC's, not as low as microcephaly. How would you manage this in between group?	The CDC recommendations for the management of infants born to mothers in areas of active Zika virus transmission without evidence of abnormalities consistent with congenital Zika syndrome (CZS) are outlined in the Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection. For infants with no evidence of such abnormalities (including infants with lower OFC's, but not microcephaly) residing in an area of active Zika transmission and whose mothers have not been diagnosed with Zika virus infection, a postnatal head ultrasound can be considered in addition to routine newborn care and hearing screen. If abnormalities are identified in infants based on postnatal ultrasound, healthcare

	providers should provide clinical management as outlined in the above referenced guidance. In addition, infants should be evaluated for other causes of congenital anomalies, including genetic conditions and other congenital infections, as indicated, based on the specific clinical finding for each infant, consistent with best clinical practices and standards of care.
4. Can prior Zika infection in the mother have a protective effect on fetus/infant in future pregnancy if mother continues to live in endemic Zika area?	We expect that the neutralizing, mainly IgG, antibodies to flaviviruses should persist for many years, as described in CDC's Interim Guidance for Interpretation of Zika Virus Antibody Test Results. This is believed to confer prolonged, possibly lifelong, immunity. Theoretically, a woman should be immune after a Zika virus infection. Based on research in Rhesus macaques given Zika virus, the macaques appear to be immune to further infections (http://www.nature.com/articles/ncomms12204). Since there remain many unanswered questions about the relationship of Zika virus and the altered immune status of the pregnant woman, a conservative approach would be to recommend that all pregnant women take measures to avoid Zika virus exposure, precautions against mosquito bites, and barrier methods of protection against sexual exposure from potentially infected males.
5. Can you speak about the sensitivity and specificity of laboratory diagnosis of Zika - Is PCR vs antibody testing more appropriate in childhood? How long do children shed the virus? Should we be testing blood, spinal fluid, or urine?	The current testing recommendations for postnatal infection in children is in line with the testing recommendations for adults. Serum and urine and urine are the primary diagnostic specimens for Zika virus infection. Other specimen types such as plasma, whole blood, and cerebrospinal fluid are authorized for use with some tests that have received an FDA Emergency Use Authorization. For all diagnostic testing conducted on specimen types other than serum, it is also necessary to obtain a concurrent serum specimen for reflex IgM testing. For diagnosis of postnatal Zika virus disease, testing algorithms should be used to determine test order based on time between symptom onset and specimen collection (https://www.cdc.gov/zika/laboratories/lab-guidance.html). The CDC's Zika virus testing technology continues to evolve, and researchers continue to learn about the performance characteristics of these tests. IgM serologic testing (antibody-based testing) is considered very sensitive on serum collected in the recommended interval (2-12 weeks) relative to exposure or symptom onset; however, negative test results should be interpreted with caution, considering all possible exposure risks and timing of exposure relative to sample collection. A positive IgM result does not always indicate Zika virus infection and can be difficult to interpret because cross-reactivity with related flaviviruses (e.g., dengue, Japanese encephalitis, West Nile, yellow fever) can occur. A positive Zika virus IgM result may also reflect previous vaccination against a related flavivirus. Further

	information regarding performance data, including available data on specificity and sensitivity, is available through the FDA website on Zika MAC-ELISA testing at: Zika MAC-ELISA Instructions for Use. Zika virus usually remains in the blood of an infected person for about a week. Although persistence of Zika virus RNA in serum for longer periods has been demonstrated in some populations (e.g., pregnant women), there are limited data on viral persistence in infants/children.
6. Is there historical data to trend Zika congenital defects to measure rates for comparison?	The CDC is currently working to assess historical trends in the types of birth defects that are now classified as potentially Zika-related. CDC is using data from birth defects surveillance systems and pregnancy registries. We hope to have information available soon.
7. Is it possible for a clinician to order ZikV IgG. What labs provide ZikV IgG?	PRNT, or plaque reduction neutralization test, is a neutralizing antibody test that is used to confirm Zika IgM results. Neutralizing antibodies to Zika virus develop shortly after IgM antibodies and consist primarily of IgG antibodies. PRNT assays measure the titer of neutralizing antibody for a virus and provide a quantitative value of how much neutralizing antibody is present to specific flavivirus species. Conversely, IgM and IgG assays typically measure only the qualitative/semi-quantitative presence of antibody, not the concentration. Because IgM antibody develops early in response to an infection, the presence of IgM antibody helps in the evaluation of Zika virus infection because it suggests a recent infection. This is in contrast to IgG, which is not able to identify the timing of an infection. Our Zika virus testing technology continues to evolve, and we continue to learn about the performance characteristics of these tests. Further information on laboratory testing is provided in Guidance for U.S. Laboratories Testing for Zika Virus Infection and will be updated as new information becomes available.
8. We recently cared for a patient with congenital Zika syndrome in our NICU (positive Zika IgM, still awaiting confirmatory PRNT results from CDC). The patient had many features which have already been described (including severe	Zika virus infection during pregnancy is a cause of microcephaly and serious brain anomalies; the full spectrum of congenital Zika syndrome includes structural anomalies and functional disabilities secondary to nervous system damage, as described in Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. Our genetics experts report some discussion of diaphragmatic elevation in association with congenital Zika syndrome at clinical meetings, but currently there have been no published reports of this phenomenon in the medical literature. CDC continues to evaluate the evolving

microcephaly, arthrogyposis) but was also noted to have significant elevation of the right hemidiaphragm. Do you know if this feature has been described with congenital Zika syndrome previously? I could not find anything in the published literature.	evidence base and will update recommendations when additional data become available.
9. Can you say more about case coordination for those children and families who need multiple services? Who is doing the active case coordination and are there good case examples that can be shared?	The primary medical home should be doing the care coordination. Realistically, we know that lots of primary care practices are ill equipped for this. A complex care clinic or a cerebral palsy clinic at the regional children's hospital would be a good place to refer these families to. I don't have any good examples of this for Zika. But the AAP has a lot of clinical reports that would be relevant to folks wondering about care coordination. The following materials from the *Manage Children with Medical Complexity in Your Practice* webinar are now available on the COCWD Web site here. • Webinar recording • Webinar slides • Audience questions/answers that were not addressed during the live webinar due to time constraints For more information about children with medical complexity, view the recently published AAP COCWD clinical report "Recognition and Management of Medical Complexity," co- authored by the webinar's guest faculty Dennis Kuo, MD, MHS, FAAP, and Amy Houtrow, MD, PhD, MPH, FAAP and "Patient- and Family-Centered Care Coordination: A Framework for Integrating Care for Children and Youth Across Multiple Systems".
10. What is the longest follow-up so far for microcephaly and what other clinical manifestations would you anticipate for these babies in the future?	The longest known follow-up of children with congenital Zika virus-associated microcephaly is among some children who are in Brazil, who were born in the late Summer-Fall of 2015. So the oldest kids with congenital Zika (that I know about) are only about 15 months old or so. I know that there are cohorts of these children being followed in Brazil, and also in Puerto Rico (who are younger), but detailed reports of these cohorts are not available yet.

	However, we know much more about the outcome of children who have the types of brain malformations that I demonstrated in the lecture, as children can have these abnormalities of abnormal brain development from other causes as well. I think we can fairly reliably predict the types of clinical manifestations that these children will have, and I have outlined them in a recent article (which I have attached) and are summarized in Table 1. Note that the bottom line is that children without microcephaly at birth (congenital microcephaly), but who later manifest developmental abnormalities and seizures (usually with acquired microcephaly), will often have difficult to treat seizures (sometimes infantile spasms), and developmental delays across several domains. Of note is that we anticipate that some, perhaps many, of these children will have hearing impairment, and so hearing screens in these children are important. See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5132043/
11. What labs do I need to do if I suspect Zika?	There are three types of tests that can be performed: Molecular, Serologic, and Plaque Reduction Neutralization Testing. Infant serum, urine, fetal membranes, placenta and umbilical cord can all be tested. You can learn more about procedures for testing for Zika virus here: https://www.cdc.gov/zika/hc-providers/test-specimens-at-time-of-birth.html. Testing options vary by state and the time it takes to get results can vary. Pre-approval is required by the Centers for Disease Control and Prevention (CDC) prior to submission of any tissue specimens. For pre-approval please contact pathology@cdc.gov and eocevent189@cdc.gov.
12. In California, do you have confirmed cases with Zika?	As of January 13, 2017, the California Department of Public Health reports 472 total cases of Zika virus infection. 73 of those cases are pregnant women, and there have been 3 live born infants with birth defects. See: http://www.cdph.ca.gov/HealthInfo/discond/Documents/TravelAssociatedCasesofZikaVirusinCA.pdf.
13. Can you tell us about the current research? For instance, what progress is being made on testing or vaccines or treatments?	The National Institutes of Health, National Institute of Allergy and Infectious Disease (NIAID) is working on the development of a Zika virus vaccine by funding numerous organizations for research and development. The NIAID reports that early-stage trials examine whether an experimental vaccine is safe and generates immune responses in vaccinated volunteers. A safe and effective, fully licensed Zika vaccine will likely not be available for several years.

	Currently, there are several vaccines that are in Phase 1 clinical trials. This linked Washington Post article details the three furthest along vaccine candidates (as of January 12, 2017).
14. For babies severely affected, wouldn't comfort care be more appropriate?	Comfort care or palliative care can be an appropriate strategy for care of severely affected babies born with congenital Zika virus syndrome should the parents and doctors decide on that approach. Palliative care clinicians can assist parents in making decisions about the care of their child. The AAP Section on Hospice and Palliative Medicine and the Committee on Hospital Care produced the policy Pediatric Palliative Care and Hospice Care Commitments, Guidelines, and Recommendations to guide pediatricians. Like other congenital conditions, children with Congenital Zika Virus Syndrome will need care by a team of subspecialists. This can be very overwhelming for parents, so the AAP Council on Children with Disabilities has produced a webinar on managing medical complexity in your practice.
15. The question is, is there a specific trimester during pregnancy when complications are more prominent?	There is some research that suggests that a higher proportion of pregnant women who were infected in the first trimester had babies with abnormalities consistent with congenital Zika virus syndrome. A preliminary report from the U.S. Zika Pregnancy Registry found that as of September 22, 2016, overall, about 6% of fetuses or infants whose mothers had laboratory evidence of possible Zika virus infections during pregnancy are affected by birth defects. Of the total, 11% of pregnant women with Zika virus symptoms or exposure during the first trimester and laboratory evidence of possible Zika virus infection had a fetus or infant with a birth defect.
16. When shall the timeframe of monitoring be longer than 1 year?...referrals &/or many needs may develop {further} after 1 year.	At this time, the Center for Disease Control and Prevention Zika Pregnancy Registry follows pregnant women and infants who test positive for Zika virus for one year after birth. We do not know if that timeframe will be extended beyond one year. However, the pediatrician should continue to monitor the infant beyond one year for possible developmental delays. The AAP recommends use of the Bright Futures Periodicity Schedule for guidance on screenings that should be performed from infancy to adolescence.
17. Are there specific professional development / training topics for early childhood educators to provide safe, quality care for a child affected by Zika Virus?	At this point, we are not aware of any professional development or trainings for early childhood educators specifically about caring for children affected by Zika virus. The Head Start Early Childhood Development Teaching and Learning Web site offers various resources for child care staff working with children with disabilities. Additionally, the Centers for Disease Control and Prevention, in collaboration with the American Academy of Pediatrics and many other organizations, has developed a training series for early child care providers called "Watch Me! Celebrating Milestones and Sharing Concerns" which helps providers learn how to watch for signs of developmental delay. This course is offered for continuing education (CE) credit.

	Each state will have its own Zika State Action Plan which may describe training and services available to early childhood educators who care for children affected by congenital Zika virus syndrome. Depending on the state, children born with congenital Zika virus syndrome may automatically be enrolled in early intervention services. Early intervention services offices coordinate care between pediatricians, subspecialists, and other services the child may need.
18. Are there now studies that show there are more intense/long term effects from the Zika virus for toddlers, older children & adults?	There is one article, "Characteristics of Children Aged <18 Years with Zika Virus Disease Acquired Postnatally — U.S. States, January 2015–July 2016" on this topic. This study found that the effects of the virus were generally mild in children and young adults, but that there can be a risk of serious complications in anyone infected with the virus. The authors urge clinicians to be aware of the patient's risk for the virus and to refer to CDC guidance for healthcare providers caring for infants and children with suspected Zika virus.
19. Are there guidelines for anticipatory guidance for sexually active adolescents regarding risk for transmission?	The CDC has a Web page with guidance on prevention of sexual transmission of Zika virus. This site does not specifically speak to sexually active adolescents, but is relevant to anyone who is sexually active. The AAP Adolescent Health Web page has many resources for prevention education, including condom and contraception policy statements, around adolescents and sexually transmitted infections.
20. What is the estimated cost of care for a family whose child is diagnosed with Zika virus?	The Center for Disease Control and Prevention (CDC)birth defects specialists have reported that a single child with birth defects can usually cost $10 million dollars to care for or more. See the transcript from the Zika Summit Press Conference by Dr Friedan, former Director of the CDC, in which this information is reported: https://www.cdc.gov/media/releases/2016/t0404-zika-summit.html.
21. Any suggestions with regard to making possible Zika exposure on our newborn blood screening program? Relative to unknown exposed?	At this point neither the CDC nor the AAP recommend universal newborn blood screening for Zika virus. However, the CDC does recommend that all pregnant women are verbally screened to understand possible exposure to Zika virus. If there is a risk of exposure, testing should be conducted. Similarly, for infants born to mothers with risk factors for maternal Zika virus infection or physical abnormalities at birth that may point to congenital Zika virus syndrome, testing should be conducted. The CDC has comprehensive information about testing on its Web site.
22. Did you say that other viruses, like CMV can cause these types of birth defects?	Yes, other infections or viruses are known to cause congenital birth defects in infants. The more common viruses linked to congenital infections include the Cytomegalovirus (CMV), Herpes, Rubella (German measles), Parvovirus, Varicella (chickenpox), Enteroviruses, and now Zika virus. Though these viruses can cause similar manifestations in newborns, researchers have found that congenital Zika virus infection causes 5 unique manifestations: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices

	with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia and symptoms of extrapyramidal involvement. See the full article on these findings here.
23. What's the position of the AAP on testing for ZIKV in the third trimester?	The AAP supports the CDC recommendations for testing, which can be found on the recommendations for healthcare professionals Web site. Please also see the CDC's Clinical Guidance for Healthcare Providers Caring for Pregnant Women.