Research suggests that many disparities in overall health and well-being are rooted in early childhood (1,2). Stressors in early childhood can disrupt neurologic, metabolic, and immunologic systems, leading to poorer developmental outcomes (1). However, consistent, responsive caregiving relationships and supportive community and health care environments promote an optimal trajectory (3,4). The first 8 years of a child’s life build a foundation for future health and life success (5–7). Thus, the cumulative and lifelong impact of early experiences, both positive and negative, on a child’s development can be profound. Although the health, social service, and education systems that serve young children and their families and communities provide opportunities to support responsive relationships and environments, efforts by these systems are often fragmented because of restrictions that limit the age groups they can serve and types of services they can provide. Integrating relationship-based prevention and intervention services for children early in life, when the brain is developing most rapidly, can optimize developmental trajectories (4,7). By promoting collaboration and data-driven intervention activities, public health can play a critical role in both the identification of at-risk children and the integration of systems that can support healthy development. These efforts can address disparities by reducing barriers that might prevent children from reaching their full potential.

**Developmental Trajectories**

Healthy child development includes not only physical developmental domains but also emotional, behavioral, cognitive, language, and general learning competencies. The human brain undergoes rapid growth during childhood, driven in part by a child’s acquisition and integration of skills across many developmental domains. Development in all domains is finely integrated across neural circuitry, allowing for more complex learning and tasks over time (8). Skill acquisition depends on children being ready to learn and can be envisioned as a developmental trajectory. Exposure to adversity and stressors such as poverty, lack of safety and stability in the home environment, and lack of access to quality early education can negatively affect a child’s development (1,2). These exposures can lead to an “at-risk or vulnerable” trajectory and in severe cases, a “delayed or disordered”

This is another in a series of occasional MMWR reports titled CDC Grand Rounds. These reports are based on grand rounds presentations at CDC on high-profile issues in public health science, practice, and policy. Information about CDC Grand Rounds is available at https://www.cdc.gov/about/grand-rounds.
trajectory (5). Conversely, protective factors provided in a child’s home or community environment, such as consistent and responsive caregiving relationships and coordinated health care and other services, can reduce and even ameliorate the impact of adverse circumstances, allowing children to reach or return to a healthy trajectory (2,5).

Chronic stressors in early childhood, such as poverty, can have cumulative lifetime effects on learning, earnings, and health (3). Language differences associated with socioeconomic status have been documented as early as age 18 months (9). Vocabulary skills by age 3 years predict third grade reading, which in turn predicts high school graduation rates (10–12). High school graduates achieve increased earning potential and are less likely to have chronic diseases, such as diabetes, chronic pain, and symptoms of mental disorders than are non-graduates (13). High school graduates are also more likely to report good health and visit a health professional, important markers of positive health outcomes (13).

Identifying Vulnerable Children and Informing Action

Screening, early identification, and linkage to services can prevent vulnerable children (i.e., children at risk for or with a developmental delay) from progressing to levels of higher risk (14). For disadvantaged groups, early intervention can yield the greatest social and economic returns (15). For example, an economic analysis of two similar early childhood interventions for socioeconomically disadvantaged children, Carolina Abecedarian Project and the Carolina Approach to Responsive Education, identified a 7.3 benefit/cost ratio and a 13.7% rate of return per annum when examining the long-term health, crime reduction, educational, and employment benefits of program participation (15).

Public health surveillance data characterize population-level impacts and can be used to inform public health action. For example, recent analyses identified treatment patterns for young children with attention-deficit/hyperactivity disorder that were not aligned with the American Academy of Pediatrics’ (AAP) recommendations (16). These data have led to collaborations to 1) increase awareness of recommendations for behavior therapy before medication for preschool children, 2) increase available behavioral therapy options for providers and families, and 3) inform state and local decision-makers about best practices (16). Surveillance data continue to inform and monitor the impact of these collaborations and other early childhood initiatives.

Screening measures inclusive of social determinants of health provide opportunities for strengthening protective factors through family, community, and health care connections (3). Public health activities to improve early detection and referral to treatment include the Early Hearing Detection and Intervention* programs to identify hearing loss in infants; online tools developed by CDC and AAP for identifying motor delays1; and Learn the Signs. Act

---

1 https://www.cdc.gov/ncbddd/hearingloss/ehdi-programs.html.
2 http://motordelay.aap.org.
Early\textsuperscript{5} for children with or at risk for developmental disabilities. These tools leverage state, provider, and family-level actions to reduce the time to diagnosis and initiation of services.

**Integrating Support Services for Vulnerable Children and Their Families**

A large number of service agencies work to support optimal child development, but many have specific age requirements (e.g., early intervention, preschool, or school age), or provide specific types of services (e.g., developmental, health, social welfare, or educational). Too often, vulnerable children are identified but do not meet strict criteria for services of the agencies contacted, leaving them without needed services. An example of a program that has reduced service gaps by integrating available services for children is Help Me Grow.\textsuperscript{5} Help Me Grow serves as a centralized point of entry for both state- and community-based services where families of vulnerable children are matched to service agencies that offer the support they need (14). Through a single information line, vulnerable children who are likely to meet eligibility criteria are linked to one or more publicly funded early intervention services, preschool special education services, and interventions for children with special health care needs. Vulnerable children at risk because of environmental or biologic factors, but who do not meet eligibility requirements for the described services are linked to other community-based programs and services through Help Me Grow. In 2015 alone, Help Me Grow served 42,511 children and their families. Promising evaluation results have led some states to embed the Help Me Grow model within various federal initiatives, including the Health Resources and Services Administration’s Maternal, Infant, and Early Childhood Home Visiting and Early Childhood Comprehensive Systems and the Substance Abuse and Mental Health Services Administration’s Project LAUNCH (Linking Actions for Unmet Needs in Children’s Health) program.

**Integrating Behavioral and Physical Health**

Behavioral health services can promote the health and development of children when high-quality services can be accessed by the children who need them (17). Nationally representative data from 2011–2012 suggest that 15% of U.S. children aged 2–8 years have a parent-reported mental, behavioral, or developmental disorder (18), and children living in small rural areas have a higher prevalence (19%) than children living in urban areas (15%) (19). In 2012, nearly $14 billion in medical expenditures for mental disorders among children were spent across all payment types (private insurance, public insurance, out of pocket, and other); these costs were higher than those for any other health condition (e.g., chronic obstructive pulmonary disease and asthma, trauma-related conditions, and acute respiratory infections).\textsuperscript{**} However, only an estimated 20% of children and youth with behavioral problems receive mental health services (17). In particular, children in rural communities often have less access to early childhood interventions and behavioral health care services highlighting the need for behavioral health care in alternative settings and coordinated care solutions (20).

Mental, behavioral, and developmental disorders in young children have been associated with potentially modifiable family, community, and health care factors (18,19). Two-generation approaches that support the health, educational achievement, economic self-sufficiency, and wellbeing of both children and their caregivers have indicated some beneficial effects on early childhood literacy and language development (3,7). Within primary care, screening and referral to appropriate services for maternal depression can support the parent-child relationship and enhance both child and maternal health (3). For children facing circumstances that put them at risk, such as poverty, enhancing these maternal-child protective factors might be particularly important for reducing the negative effects of stressors on long-term child health (3). Furthermore, pediatric primary care can expand beyond anticipatory guidance by promoting protective factors and resiliency through evidence-based interventions that address parental self-care, positive parenting strategies, and parent-child relationship building (3,7). By coordinating and integrating care across medical systems and community providers, the prevention- and patient-focused medical home (family-centered coordinated primary care) model promotes both behavioral and physical health.

**Promoting Supportive Relationships Across Multiple Contexts**

Early childhood objectives outlined in Healthy People 2020\textsuperscript{††} highlight the need to support parents and caregivers, create supportive communities, increase access to high-quality health care, and increase the proportion of children ready for school in all domains of healthy development. Programs that create connections across the early learning and home environments by supporting family engagement in learning have demonstrated positive impacts on young children’s academic success and development (7,8). However, gaps exist in access to high quality early care and education, training, and evidence-based resources to support family engagement partnerships (7,8). A 2016 AAP policy statement aimed at ameliorating the health and developmental impacts of poverty describes the importance


\textsuperscript{††} https://www.healthypeople.gov/node/3498/objectives#4816.
of effective interventions and strategies focused on economic aid, access to comprehensive care coordination, early care and education, early identification of children and families in need of services, and promotion of protective factors through family support programs (3). The common thread for these approaches is the focus on both risk factors and protective factors for the entire family across multiple systems, not simply on the child with an identified condition in a single context.

**Importance of Integration and Collaboration**

Early childhood represents a period of growth that lays the foundation for successful learning, development, and health; disparities emerge early and widen over time (6). Intervening in early childhood can prevent the development of diseases and disorders among at-risk and vulnerable children but will require collaboration. Strategies that foster consistent and responsive caregiving relationships and supportive environments can improve outcomes for both parent and child (7). Parents and early care providers can work together to provide the responsive interactions and consistent environments that nurture the development of young children. Practitioners can screen and identify children early, promote family strengths, and refer to services before risks progress. States and communities can use surveillance data to drive action around early childhood investments. Partners within public health can use data-informed approaches to prevent health disparities by facilitating service linkages across health, social, and educational systems. Timely referral and better integrated services might help children at low or moderate risk reach their full potential by returning to healthy developmental trajectories.

**Conflict of Interest**

No conflicts of interest were reported.

---

**References**

Georgia, a country in the Caucasus region of Eurasia, has a high prevalence of hepatitis C virus (HCV) infection. In April 2015, with technical assistance from CDC, Georgia embarked on the world’s first program to eliminate hepatitis C, defined as a 90% reduction in HCV prevalence by 2020 (1,2). The country committed to identifying infected persons and linking them to care and curative antiviral therapy, which was provided free of charge through a partnership with Gilead Sciences (1,2). From April 2015 through December 2016, a total of 27,595 persons initiated treatment for HCV infection, among whom 19,778 (71.7%) completed treatment. Among 6,366 persons tested for HCV RNA ≥12 weeks after completing treatment, 5,356 (84.1%) had no detectable virus in their blood, indicative of a sustained virologic response (SVR) and cure of HCV infection. The number of persons initiating treatment peaked in September 2016 at 4,595 and declined during October–December. Broader implementation of interventions that increase access to HCV testing, care, and treatment for persons living with HCV are needed for Georgia to reach national targets for the elimination of HCV.

In 2015, an estimated 5.4% of the adult population of Georgia (approximately 150,000 persons) had chronic HCV infection, and of those, nearly two thirds were unaware of their infection (Georgia Ministry of Labour, Health, and Social Affairs [MoLHSA], unpublished data, 2016). Populations with the highest rates of HCV infection include men, persons aged 30–59 years, persons with a history of injection drug use, and persons with a history of receipt of blood products (MoLHSA, unpublished data, 2016). Initially, when the program was launched in April 2015, national guidelines limited treatment to HCV-infected persons with advanced liver disease, defined as one or both of the following: F3 or F4 by METAVIR fibrosis score (a system used to assess the histological extent of hepatic inflammation and fibrosis in patients with hepatitis C infection) on transient elastography or FIB-4 score (a noninvasive test based on a combination of biochemical values and patient age) >3.25 (3,4). In June 2016, treatment eligibility criteria were expanded to include all HCV-infected persons, regardless of disease severity.

HCV screening programs began in January 2015, before the launch of the program, and screening services continue to be provided at various settings at no cost (Table). During

Table. Number of screening tests* for hepatitis C virus (N = 472,890) and percentage testing positive, by group screened — Georgia, 2015–2016

<table>
<thead>
<tr>
<th>Group screened/Location of screening</th>
<th>No. screening tests</th>
<th>% HCV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood donors</td>
<td>168,121</td>
<td>1.3</td>
</tr>
<tr>
<td>NCDC</td>
<td>83,910</td>
<td>17.5</td>
</tr>
<tr>
<td>Pregnant women/ANCs</td>
<td>53,852</td>
<td>0.4</td>
</tr>
<tr>
<td>Hospitalized patients†</td>
<td>48,025</td>
<td>4.9</td>
</tr>
<tr>
<td>Persons who inject drugs</td>
<td>44,410</td>
<td>45.0</td>
</tr>
<tr>
<td>Tbilisi citizens§</td>
<td>26,159</td>
<td>13.8</td>
</tr>
<tr>
<td>Outpatients†</td>
<td>18,900</td>
<td>7.4</td>
</tr>
<tr>
<td>Prisoners</td>
<td>14,053</td>
<td>37.4</td>
</tr>
<tr>
<td>Military recruits</td>
<td>11,217</td>
<td>1.5</td>
</tr>
<tr>
<td>HCV screening or treatment center</td>
<td>2,453</td>
<td>31.4</td>
</tr>
<tr>
<td>Persons living with HIV</td>
<td>1,790</td>
<td>24.9</td>
</tr>
<tr>
<td>Total</td>
<td>472,890</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Abbreviations: ANC = antenatal clinic; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NCDC = National Centers for Disease Control and Public Health headquarters and regional centers. 

* Number of HCV screening tests (not individual persons) reported to NCDC. 
† Data are from November 1–December 30, 2016. 
§ Screening centers operated by the city of Tbilisi.

January 2015–December 2016, a total of 472,890 HCV screening tests* were conducted, 50,962 (10.8%) of which were positive for HCV antibody. The highest rate of HCV antibody—positive screening tests (45.0%) was among persons who attended programs providing services for persons who inject drugs; the lowest rate (0.4%) was among women attending antenatal clinics (Table). Persons who screen positive for HCV antibody are referred to the treatment program for confirmation of chronic HCV infection using polymerase chain reaction (PCR) testing for detection of HCV RNA. Once chronic HCV infection is confirmed, the person is invited to enroll in the treatment program.

When the treatment program began on April 28, 2015, four treatment centers operated in Georgia, all located in Tbilisi, the capital and largest city. By December 2016, the number of treatment centers had increased to 27 nationwide. From the start to December 31, 2016, a total of 58,223 persons with positive HCV antibody test results sought confirmation of chronic HCV infection through the treatment program, among whom 38,113 (65.5%) initiated a diagnostic evaluation, including confirmation of HCV infection by

*Hepatitis C virus rapid tests by all screening programs except blood banks that mostly used enzyme immunoassay.
PCR testing; of those who initiated a diagnostic evaluation, 30,046 (78.8%) were confirmed as having chronic HCV infection and completed the diagnostic workup, and 27,595 (91.8%) of whom began treatment. Men accounted for 23,062 (83.6%) of all persons starting treatment, including 9,180 men aged 40–49 years, representing one third of all persons who initiated treatment (Figure 1). The average number of persons starting treatment each month increased nearly 300% from April 2015–May 2016 (661 per month) to June–December, 2016 (2,619 per month), peaking in September 2016 at 4,595. A decline occurred from October through December 2016 (Figure 2). During the initial phase of the program (April, 2015–May, 2016), when treatment was prioritized for persons with more severe liver disease, most patients initiating treatment (9,088 of 9,259; 98.2%) had advanced liver disease (≥F3 METAVIR fibrosis score or FIB-4 score >3.25). After the expansion of treatment criteria to allow treatment for all persons with HCV infection (beginning June 1 through December 31, 2016), most persons initiating treatment (14,368 of 18,336; 78.4%) had less severe liver disease (<F3 METAVIR fibrosis score or FIB-4 score <1.45) (Figure 2).

As of December 31, 2016, a total of 19,778 persons completed treatment, and 6,366 (32.2%) eligible patients received testing for SVR (undetectable HCV RNA ≥12 weeks after treatment completion) (5). SVR was observed for 5,356 (84.1%) persons tested, indicating that they were cured of their infection. Among the 75.0% (4,774/6,366) who received sofosbuvir (without ledipasvir) treatment regimens, 3,793 (79.5%) achieved SVR, and among the 25.0% (1,592 of 6,366) who received ledipasvir/sofosbuvir-based treatment regimens, 1,563 (98.2%) achieved SVR. Among 537 (1.9%) persons who did not complete treatment, 371 (69.1%) died from their liver disease or another cause during the course of treatment, and the other 166 (30.1%) discontinued treatment for other reasons.

FIGURE 1. Number of persons initiating treatment for hepatitis C virus infection, by sex and age group — Georgia, April 2015–December 2016*

* The age group “18–29 years” includes five female patients aged 13–17 years.

FIGURE 2. Number of persons initiating treatment for hepatitis C virus infection and cumulative number initiating treatment, by severity of liver disease* and month — Georgia, April 2015–December 2016

* Less severe liver disease defined as <F3 METAVIR fibrosis score and/or FIB-4 score <1.45; advanced liver disease defined as ≥F3 METAVIR fibrosis score and/or FIB-4 score >3.25.
Discussion

Since the launch of the Georgia HCV Elimination Program in April 2015, progress has been made in providing treatment to and curing persons infected with HCV, including a 300% increase in the average monthly number of patients initiating treatment during the second half of 2016. These gains are attributed to an increase in the number of treatment sites, expansion of treatment eligibility criteria, and introduction of a newer, highly effective all-oral combination antiviral drug (ledipasvir/sofosbuvir) (6). However, enrollment in the treatment program declined considerably during the last 3 months of 2016. This decline is likely because of patients’ lack of awareness of their infection status or lack of access to the treatment program for HCV-infected persons who were aware of their infection. The data in this report suggest that a substantial proportion of persons tested and found positive for HCV antibodies are not successfully referred for evaluation of HCV infection. Through December 2016, approximately 20% of the estimated 150,000 Georgians living with HCV infection entered the treatment program. Increased measures to identify infected persons and link them to care and treatment are needed to reach the 2020 elimination goal of 90% reduction in HCV prevalence.

At the launch of the program in 2015, national serologic survey data revealed about one third of HCV-infected Georgians were aware of their infection (MoLHSA, unpublished data, 2016). Data are lacking on how many of the approximately 51,000 persons who screened positive for HCV during 2015 and 2016 accessed the program to receive confirmatory testing (which unlike initial screening, is not free of charge) and entered the treatment program if chronic HCV infection was confirmed. Changes in government policies that target large at-risk populations, offer free HCV confirmatory testing and additional diagnostic evaluation for patients with confirmed HCV infection, increase the number of providers that can provide testing and treatment services, and support campaigns to expand public awareness and demand for HCV services can increase HCV screening and treatment rates.

Although approximately 470,000 HCV screening tests were reported during 2015–2016, many at-risk Georgians remain unscreened. HCV prevalence varied markedly across different screening settings and programs: screening conducted at antenatal clinics yielded a low proportion of persons screening positive, and screening at corrections and harm-reduction facilities yielded high HCV prevalence rates. Targeted provision of testing and linkage to care services might increase the detection of persons with HCV infection, and thereby, the number entering the treatment program.

Summary

What is already known about this topic?

An estimated 150,000 persons in the country of Georgia (5.4% of the adult population) are infected with hepatitis C virus (HCV). In April 2015, in collaboration with CDC and other partners, Georgia launched a program to eliminate HCV by 2020. An important strategy is the identification of HCV-infected persons and provision of curative antiviral therapy.

What is added by this report?

During April 28, 2015–December 31, 2016, a total of 27,595 HCV-infected persons started therapy, 19,778 (71.7%) of whom completed treatment. Among 6,366 (32.2%) who completed treatment and were tested for treatment response, 5,356 (84.1%) were cured of their HCV infection. The average number of persons who initiated treatment each month increased threefold from April 2015–May 2016, when treatment was limited to persons with severe liver disease, to June–December 2016, after expansion of the eligibility criteria to allow treatment of all HCV-infected persons. During the last 3 months of 2016, the number of persons entering the treatment program declined steadily, suggesting that identification and linkage to care of HCV infected persons in the country might be slowing.

What are the implications for public health practice?

The Georgia HCV Elimination Program has made substantial progress since its launch in April 2015; the country has demonstrated the ability to scale up HCV care and treatment services rapidly. Enhancing HCV testing and linkage to care and treatment services are critical to reaching the 2020 HCV elimination goal. Lessons learned from the Georgia elimination program can inform programs in other countries striving to eliminate HCV as a public health threat.

Reaching the 2020 HCV elimination goals will require innovative strategies to increase awareness, expand access to high-quality screening, and remove diagnostic and treatment barriers which may include costs associated with confirmatory testing and diagnostic workup, stigma, and distance to treatment centers. Increased impact can be achieved by providing services at primary care settings and settings serving populations at high risk (e.g., syringe service programs for injection drug users).

Elimination of HCV infection in Georgia hinges not only on strategies that identify, treat, and cure persons of their infection, but also on those that prevent new infections. To ensure a comprehensive approach to HCV elimination, MoLHSA developed a Strategic Plan for Elimination of Hepatitis C in Georgia (7). In addition to proposing actions to improve HCV screening and linkage to care, the plan identifies strategies for preventing new infections, including improving safety of the blood supply, ensuring infection control in health care settings, and providing persons who inject drugs with harm-reduction services.
The findings in this report are subject to at least three limitations. First, data from the screening and treatment programs could not be independently verified and might be subject to data entry errors. Second, the screening data reported might include persons who received repeat testing; thus it is not known whether each HCV antibody test represents a single person screened. Finally, HCV screening data are not linked to treatment data, and as a result, this analysis could not assess the effectiveness of linkage of screening to the care and treatment program.

Despite notable progress during the first 20 months of the Georgia HCV elimination program, challenges to Georgia achieving the national targets for HCV elimination by 2020 remain. High-quality screening, innovative linkage-to-care strategies, and cost-effective and simplified diagnostic and treatment regimens are needed. Provision of free-of-charge services for HCV screening, diagnosis, care, and treatment in settings serving populations at high risk for HCV infection and in primary care settings can decrease barriers to access of treatment services. MoLHSA is working with CDC and other international partners to address challenges and introduce innovative strategies. Pangenotypic direct-acting antiviral drugs that are effective across the different genotypes of HCV, point-of-care HCV RNA testing, and HCV core antigen testing are likely to be introduced in late 2017 or 2018 and could have a substantial impact on improving access and simplifying diagnosis and treatment. Information systems capable of linking screening and treatment data are being developed to improve efficiencies. With increased access to HCV treatment services and full implementation of the country’s strategic plan, Georgia can achieve the goal for HCV elimination in 2020. Lessons learned from this program can inform similar initiatives in other countries and help curb the global epidemic of viral hepatitis (8).

Acknowledgment

Gilead Sciences had no role in the conduct of the research or preparation of this report.
Outbreak of Septic Arthritis Associated with Intra-Articular Injections at an Outpatient Practice — New Jersey, 2017

Kathleen Ross, MPH1,2; Jason Mehr, MPH1; Barbara Carothers1; Rebecca Greeley, MPH1; Isaac Benowitz, MD3; Lisa McHugh, MPH1; David Henry, MPH4; Lisa DiFedele, MPH1; Eric Adler, MPH1; Shereen Naqvi4; Edward Lifshitz, MD1; Christina Tan, MD1; Barbara Montana, MD1

On March 6, 2017, the New Jersey Department of Health (NJDOH) was notified of three cases of septic arthritis in patients who had received intra-articular injections for osteoarthritic knee pain at a private outpatient practice. The practice voluntarily closed the next day. NJDOH, in conjunction with the local health department and the New Jersey Board of Medical Examiners, conducted an investigation and identified 41 cases of septic arthritis associated with intra-articular injections administered during 250 patient visits at the same practice, including 30 (73%) patients who required surgery. Bacterial cultures of synovial fluid or tissue from 15 (37%) patients were positive; all recovered organisms were oral flora. An infection prevention assessment of the practice identified multiple breaches of recommended infection prevention practices, including inadequate hand hygiene, inappropriate use of pharmacy bulk packaged (PBP) products as multiple-dose containers and handling PBP products outside of required pharmacy conditions, and preparation of syringes up to 4 days in advance of their intended use. No additional septic arthritis cases were identified after infection prevention recommendations were implemented within the practice.

Investigation and Response
On March 6, 2017, Monmouth County Regional Health Commission No. 1 (MCRHC) notified NJDOH that three patients were hospitalized for septic arthritis after receiving intra-articular injections for osteoarthritic pain relief at practice A, a private outpatient facility where procedures were performed by two staff physicians with the aid of two medical assistants. On March 7, practice A voluntarily closed in response to a large number of reports of severe knee pain and swelling. On March 8, NJDOH notified the New Jersey Board of Medical Examiners, which oversees physician licensure, to facilitate and coordinate a joint investigation.

A confirmed case of septic arthritis was defined as any one of the following in a patient who received intra-articular injections at practice A during March 1–6, 2017: 1) isolation of any microorganism from synovial fluid or tissue collected from the injected joint, 2) positive Gram stain of synovial fluid, 3) synovial fluid white blood cell count of >20,000/mm³, and 4) recipient of intravenous antibiotics or surgical debridement for a clinical diagnosis of septic arthritis.

Among 250 patient visits involving knee intra-articular injections at practice A during March 1–6, NJDOH identified 41 confirmed cases (16%) of septic arthritis. Patients had been scheduled over 3 consecutive clinic days (March 1, March 2, and March 6) with no apparent clustering by appointment time; the same physician administered all injections on these 3 days. Information on time of symptom onset was available for 38 (93%) of 41 patients and ranged from zero to 65* days after injection; 35 (92%) of the 38 patients developed symptoms within 48 hours of the procedure. Thirty (73%) of the 41 patients required surgery.

All 41 patients had synovial fluid or knee tissue obtained during surgery collected for culture, and cultures were positive for 15 (37%) patients. Bacteria recovered included *Streptococcus mitis-oralis* (10 patients), *Abiotrophia defectiva* (two), *Staphylococcus aureus* (two), *Actinomycyes odontolyticus* (one), alpha-hemolytic *Streptococcus* (one), *Eikenella corrodens* (one), *Haemophilus parainfluenzae* (one), *Neisseria oralis* (one), *Streptococcus gordonii* (one), *Streptococcus intermedius-milleri* (one), *Streptococcus sanguinis* (one), and *Veillonella* (one); five patients had polymicrobial infections. Cultures from 26 (63%) patients were negative. All recovered organisms are commonly found in oral flora (1,2). In addition to bacteria recovered from culture of synovial fluid or tissue, *Staphylococcus aureus* was isolated from the blood of two patients.

On March 13, MCRHC, NJDOH, and the New Jersey Division of Consumer Affairs representing the New Jersey Board of Medical Examiners conducted an unannounced visit to practice A to inspect the premises, interview staff members, observe infection prevention practices, and review records. Because the practice remained closed to patients at this time, mock procedures were observed during the visit.

Multiple breaches in infection prevention recommendations were identified. Staff members did not have access to a hand-washing sink, and alcohol-based hand rub was not available in medication preparation or treatment areas. Staff members, operating under the mistaken belief that PBP products could be used as multiple-dose containers outside of pharmacy conditions (e.g., use of a laminar flow hood, appropriate garbing, staff training, and environmental monitoring), accessed a pharmacy conditions, and preparation of syringes up to 4 days in advance of their intended use. No additional septic arthritis cases were identified after infection prevention recommendations were implemented within the practice.

For further information, contact: Melissa Carlon, health department, NJDOH, 74顺德 Rd, Piscataway, NJ 08854; phone: 732-757-5000, ext. 2076; email: melissa.carlon@nj.gov.
Summary
What is already known about this topic?
Single-use medications, including pharmacy bulk packaged (PBP) products, typically lack antimicrobial preservatives and can become contaminated and serve as a source of microorganisms when handled inappropriately. Use of a PBP product as a multiple-dose container outside of pharmacy conditions could contaminate the container and serve as a source of pathogens for multiple patients.

What is added by this report?
In March 2017, an outbreak of 41 cases of septic arthritis associated with intra-articular injections administered at an outpatient practice occurred in New Jersey. A public health investigation identified multiple breaches of recommended infection prevention practices during the preparation and administration of PBP products, which are intended for single-use, in accordance with standards outlined by the United States Pharmacopeial Convention.

What are the implications for public health practice?
No additional septic arthritis cases were identified after infection prevention recommendations were implemented within the practice. The findings from this investigation highlight the need for better adherence to and oversight of basic infection prevention recommendations and sterile compounding standards in outpatient settings.

50 mL PBP container of contrast material up to 50 times to prepare syringes for multiple patients, with the septum of the container cleaned with alcohol only before the initial draw. Staff members prepared injections in a separate room, away from the patient treatment area; however, pharmacy conditions necessary for batch preparation of syringes and use of PBP products were not in place. In addition, injectable medications were drawn into syringes by medical assistants up to 4 days in advance of procedures, contrary to the recommended practice of administering medication from single-dose vials within 1 hour of preparation (3).

Injections were initiated using a needle and syringe filled with local anesthetic. After injecting the anesthetic, the physician removed the syringe, leaving the needle within the intra-articular space. A second syringe containing contrast material from the PBP container was then attached to the needle hub and used to facilitate fluoroscopic needle placement. This was followed by replacement with a third syringe containing a glucocorticoid or hyaluronic acid–based product. The physician did not wear a face mask during joint injection procedures and used nonsterile gloves to manipulate the needle hub during procedures.

Practice A was advised to immediately stop batch preparation of syringes and use of PBP products for multiple patients and to hire an infection preventionist to assess staff competency and ensure that hand hygiene, standard precautions, and safe injection practices were followed. No additional cases occurred after these measures were implemented.

Discussion
An investigation of 41 cases of septic arthritis associated with intra-articular injections at an outpatient practice in New Jersey identified multiple breaches of recommended infection prevention practices during the preparation and administration of PBP products, which are intended for use in a pharmacy setting, using standards outlined by the United States Pharmacopeial Convention (USP) (3,4). PBP products are restricted to preparation of admixtures only in a suitable work area as defined by USP, such as in a laminar flow hood, and handled in accordance with sterile compounding standards outlined by the manufacturer and USP (3,4). CDC guidelines call for medications labeled as “single-dose” or “single-use” to be used for only one patient (5,6). Single-use medications, including PBP products, typically lack antimicrobial preservatives and can become contaminated and serve as a source of microorganisms when handled inappropriately (6).

In this outbreak, all pathogens isolated were oral flora. CDC recommends that health care personnel wear face masks for spinal injection procedures that require injection of material or insertion of a catheter into epidural or subdural spaces (e.g., myelogram, administration of spinal or epidural anesthesia, or intrathecal chemotherapy) (5). Multiple outbreaks have demonstrated the risk for bacterial meningitis associated with droplet transmission of oral flora from health care personnel to patients during spinal injection procedures. The Association for Professionals in Infection Control and Epidemiology recommends the use of a face mask to contain respiratory droplets when preparing and injecting material into an intra-articular space (7). The use of multiple syringes with a single intra-articular needle could serve as a conduit for organisms to enter directly into the joint space if the needle hub is left exposed to potential respiratory droplets. Although this is a potential mechanism for a single case, it is unlikely to explain the large number of cases identified in this outbreak.
No additional septic arthritis cases were identified after infection prevention recommendations were implemented within the practice. The findings from this investigation highlight the need for better adherence to and oversight of basic infection prevention recommendations and sterile compounding standards in outpatient settings (8,9).

Conflict of Interest
No conflicts of interest were reported.

References
Sanofi Pasteur, the manufacturer of the only yellow fever vaccine (YF-VAX) licensed in the United States, has announced that their stock of YF-VAX is totally depleted as of July 24, 2017. YF-VAX for civilian use will be unavailable for ordering from Sanofi Pasteur until mid-2018, when their new manufacturing facility is expected to be completed. However, YF-VAX might be available at some clinics for several months, until remaining supplies at those sites are exhausted. In anticipation of this temporary total depletion, in 2016, Sanofi Pasteur submitted an expanded access investigational new drug application to the Food and Drug Administration to allow for importation and use of Stamaril. The Food and Drug Administration accepted Sanofi Pasteur’s application in October 2016.

Manufactured by Sanofi Pasteur in France, Stamaril is not licensed in the United States, but is licensed and distributed in approximately 70 countries, and has comparable efficacy and safety to YF-VAX (1). During the interim period until YF-VAX is available again for use in the United States, Stamaril will be available in a limited number of designated clinics, selected to provide access to vaccine in U.S. states and certain territories (1). Clinicians and travelers can find clinics offering Stamaril vaccine and those clinics that might have remaining doses of YF-VAX online at https://wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search. Consideration will be given to adding more clinics if critical gaps in vaccine access are identified. CDC and Sanofi Pasteur continue to collaborate on contingency planning to address this situation.

Information about which countries require yellow fever vaccination for entry and for which countries CDC recommends yellow fever vaccination is available at https://wwwnc.cdc.gov/travel/.

No conflicts of interest were reported.

Reference
Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States (Including U.S. Territories), July 2017

Titilope Oduyebo, MD; Kara D. Polen, MPH; Henry T. Walke, MD; Sarah Reagan-Steiner, MD; Eva Lathrop, MD; Ingrid B. Rabe, MBChB; Wendi L. Kuhner-Tallman, PhD; Stacey W. Martin, MSc; Allison T. Walker, PhD; Christopher J. Gregory, MD; Edwin W. Ades, PhD; Darin S. Carroll, PhD; Maria Rivera, MPH; Janice Perez-Padilla, MPH; Carolyn Gould, MD; Jeffrey B. Nemhauser, MD; C. Ben Beard, PhD; Jennifer L. Harcourt, PhD; Laura Viens, MD; Michael Johansson, PhD; Sascha R. Ellington, MSPH; Emily Petersen, MD; Laura A. Smith, MA; Jessica Reichard, MPA; Jorge Munoz-Jordan, PhD; Michael J. Beach, PhD; Dale A. Rose, PhD; Ezra Barzilay, MD; Michelle Noonan-Smith; Denise J. Jamieson, MD; Sherif R. Zaki, MD; Lyle R. Petersen, MD; Margaret A. Honein, PhD; Dana Meaney-Delman, MD

On July 24, 2017, this report was posted as an MMWR Early Release on the MMWR website (https://www.cdc.gov/mmwr).

CDC has updated the interim guidance for U.S. health care providers caring for pregnant women with possible Zika virus exposure in response to 1) declining prevalence of Zika virus disease in the World Health Organization’s Region of the Americas (Americas) and 2) emerging evidence indicating prolonged detection of Zika virus immunoglobulin M (IgM) antibodies. Zika virus cases were first reported in the Americas during 2015–2016; however, the incidence of Zika virus disease has since declined. As the prevalence of Zika virus disease declines, the likelihood of false-positive test results increases. In addition, emerging epidemiologic and laboratory data indicate that, as is the case with other flaviviruses, Zika virus IgM antibodies can persist beyond 12 weeks after infection. Therefore, IgM test results cannot always reliably distinguish between an infection that occurred during the current pregnancy and one that occurred before the current pregnancy, particularly for women with possible Zika virus exposure before the current pregnancy. These limitations should be considered when counseling pregnant women about the risks and benefits of testing for Zika virus infection during pregnancy. This updated guidance emphasizes a shared decision-making model for testing and screening pregnant women, one in which patients and providers work together to make decisions about testing and care plans based on patient preferences and values, clinical judgment, and a balanced assessment of risks and expected outcomes.

For these recommendations, the definition of possible Zika virus exposure has not changed and includes travel to, or residence in an area with risk for mosquito-borne Zika virus transmission or sex with a partner who has traveled to or resides in an area with risk for mosquito-borne Zika virus transmission. These areas can be found on the CDC “Zika Travel Information” webpage.*

Key recommendations include the following:

1) All pregnant women in the United States and U.S. territories should be asked about possible Zika virus exposure before and during the current pregnancy, at every prenatal care visit. CDC recommends that pregnant women not travel to any area with risk for Zika virus transmission. It is also recommended that pregnant women with a sex partner who has traveled to or lives in an area with risk for Zika virus transmission use condoms or abstain from sex for the duration of the pregnancy.

2) Pregnant women with possible Zika virus exposure and symptoms of Zika virus disease should be tested to diagnose the cause of their symptoms. The updated recommendations include concurrent Zika virus nucleic acid test (NAT) and serologic testing as soon as possible through 12 weeks after symptom onset.

3) Asymptomatic pregnant women with ongoing possible Zika virus exposure should be offered Zika virus NAT testing three times during pregnancy. IgM antibody testing is no longer routinely recommended because IgM can persist for months after infection; therefore, IgM results cannot reliably determine whether an infection occurred during the current pregnancy. The optimal timing and frequency of testing of asymptomatic pregnant women with NAT alone is unknown. For pregnant women who have received a diagnosis of laboratory-confirmed Zika virus infection (by either NAT or serology) positive/equivocal Zika virus or dengue virus IgM and Zika virus plaque neutralization test (PRNT) ≥10 and dengue virus PRNT <10 results) any time before or during the current pregnancy, additional Zika virus testing is not recommended. For pregnant women without a prior laboratory-confirmed diagnosis of Zika virus, NAT testing should be offered at the initiation of prenatal care, and if Zika virus RNA is not detected on clinical specimens, two additional tests should be offered during the course of the pregnancy coinciding with prenatal visits.

4) Asymptomatic pregnant women who have recent possible Zika virus exposure (i.e., through travel or sexual exposure)

but without ongoing possible exposure are not routinely recommended to have Zika virus testing. Testing should be considered using a shared patient-provider decision-making model, one in which patients and providers work together to make decisions about testing and care plans based on patient preferences and values, clinical judgment, a balanced assessment of risks and expected outcomes, and the jurisdiction’s recommendations. Based on the epidemiology of Zika virus transmission and other epidemiologic considerations (e.g., seasonality), jurisdictions might recommend testing of asymptomatic pregnant women, either for clinical care or as part of Zika virus surveillance. With the decline in the prevalence of Zika virus disease, the updated recommendations for the evaluation and testing of pregnant women with recent possible Zika virus exposure but without ongoing possible exposure are now the same for all areas with any risk for Zika virus transmission.

5) Pregnant women who have recent possible Zika virus exposure and who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome should receive Zika virus testing to assist in establishing the etiology of the birth defects. Testing should include both NAT and IgM tests.

6) The comprehensive approach to testing placental and fetal tissues has been updated. Testing placental and fetal tissue specimens can be performed for diagnostic purposes in certain scenarios (e.g., women without a diagnosis of laboratory-confirmed Zika virus infection and who have a fetus or infant with possible Zika virus-associated birth defects**). However, testing of placental tissues for Zika virus infection is not routinely recommended for asymptomatic pregnant women who have recent possible Zika virus exposure but without ongoing possible exposure and who have a live born infant without evidence of possible Zika virus–associated birth defects.

7) Zika virus IgM testing as part of preconception counseling to establish baseline IgM results for nonpregnant women with ongoing possible Zika virus exposure is not warranted because Zika virus IgM testing is no longer routinely recommended for asymptomatic pregnant women with ongoing possible Zika virus exposure.

CDC continues to evaluate all available evidence and will update recommendations as new information becomes available.

** Possible Zika virus–associated birth defects that meet the CDC surveillance case definition include the following: brain abnormalities and/or microcephaly, intracranial calcifications, ventriculomegaly, neural tube defects and other early brain malformations, eye abnormalities, or other consequences of central nervous system dysfunction including arthrogryposis (joint contractures), congenital hip dysplasia, and congenital deafness) (https://www.cdc.gov/zika/geo/pregnancy-outcomes.html). In all cases, infants or fetuses with possible Zika virus–associated birth defects should also be evaluated for other etiologies of congenital anomalies.

Zika Virus Infection

Zika virus is a mosquito-borne flavivirus that is closely related to dengue, West Nile, Japanese encephalitis, and yellow fever viruses (1). During 2015–2016, Zika virus spread rapidly and caused outbreaks across the Americas; 47 countries and territories in the Americas reported Zika virus outbreaks. However, since early 2017, the reported incidence of Zika virus disease in the region has declined (2).

The World Health Organization uses a country classification scheme that describes the epidemiology of Zika virus transmission to aid in geographic risk assessment. Some areas (e.g., American Samoa) have been reclassified to indicate that Zika virus transmission has been interrupted (3,4), which is reflective of the declining trends in the prevalence of Zika virus disease. As of July 23, 2017, 95 countries and territories have been designated by CDC as areas with any possible risk for Zika virus transmission.

Although the understanding of the consequences of Zika virus infection is improving, diagnosing Zika virus infection accurately continues to present challenges. First, Zika virus is present in body fluids only transiently, which makes confirming the presence of the virus difficult. Second, serologic testing, based on the immunologic response, cannot always reliably determine when infection occurred. Finally, serologic tests are prone to false-positive results and cross-reactivity with other flaviviruses (5). With declining prevalence of Zika virus disease (2), the probability of false-positive test results increases (6). The changing epidemiology further limits the diagnostic capability of currently available Zika virus tests. In this context, CDC has updated the interim guidance for health care providers caring for pregnant women with possible Zika virus exposure to provide new information and highlight current testing limitations.

Persistence of Zika Virus Nucleic Acid and Immune Response

Data from outbreaks before 2015 indicated that Zika virus RNA was detected in serum for up to 7 days after symptom onset (1,7). However, in some persons, Zika virus RNA can be detected in body fluids longer than has been documented previously. The Zika Virus Persistence (ZiPer) Study of persons with NAT-confirmed Zika virus disease, recently reported detection of viral RNA in serum 8–15 days after symptom onset in 36% (10 of 28) of participants, 16–30 days after symptom onset in 21% (27 of 129), and >60 days after symptom onset in 4% (three of 79) (8). Prolonged detection of Zika virus RNA in serum obtained from pregnant women was also reported; three of the five pregnant women included
in the ZiPer study had detectable RNA 46 days after symptom onset, and one had detectable RNA 80 days after symptom onset. This finding is consistent with other small case series (<20 pregnant women in total) that have demonstrated detection of Zika virus RNA for longer than had been previously reported, up to 107 days after symptom onset and 53 days after last exposure (9–15).

Zika virus IgM antibodies typically become detectable within the first 2 weeks after symptom onset (1,8,16). Published data on the duration of detection of IgM antibodies following Zika virus infection are limited. In the ongoing ZiPer study, IgM antibodies were detected in 34% (17 of 50) of participants at 0–7 days after symptom onset, 100% (28 of 28) at 8–15 days after symptom onset, and 87% (52 of 60) >60 days after symptom onset (8). In addition, consistent with what is known about other flaviviruses (17), unpublished preliminary data from this study indicate a median of 4 months (122 days, range = 8–210 days) to the first negative Zika virus IgM result (18). Thus, detection of IgM antibodies might not indicate an infection that occurred during the current pregnancy. Inability to determine the timing of infection through IgM testing is a major challenge for pregnant women and their health care providers, making it difficult for health care providers to counsel pregnant women about the risk for congenital Zika virus infection.

Neutralizing antibodies develop shortly after IgM antibodies and likely persist for many years (19). Based on experience with other flaviviruses, previous Zika virus infection is likely to confer prolonged, possibly lifelong, immunity (20). Testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (positive/equivocal Zika virus or dengue virus IgM and Zika virus PRNT ≥10 and dengue virus PRNT <10 results). However, in light of the limitations of serologic testing (e.g., cross-reactivity and false-positive test results), for pregnant women without a previous diagnosis of laboratory-confirmed Zika virus infection, including those with laboratory evidence of flavivirus infection or laboratory evidence of presumptive Zika virus or flavivirus infection (Table 1), decisions about testing during a subsequent pregnancy should be made using a shared patient-provider decision-making model. If the decision is made to test, only NAT testing is recommended, because IgM antibody testing might not be able to determine the timing of infection among pregnant women who have had exposure to Zika virus before the current pregnancy.

**Zika Virus Diagnostic Testing**

Diagnostic testing for Zika virus infection can be accomplished using molecular and serologic methods; several NAT and serology assays have received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) for use on nontissue clinical specimens.\(^{11,55}\) Zika virus NAT is used to identify viral RNA in clinical or pathologic specimens, and for most persons with suspected Zika virus disease, a positive NAT result confirms acute Zika virus infection. However, despite the high specificity of NAT, false-positive results can occur (1,8,16). In addition, because Zika virus RNA is cleared from blood and other body fluids and tissues, a negative NAT result does not exclude acute Zika virus infection.

Several assays can be used to detect Zika virus IgM antibodies in serum or cerebrospinal fluid. Zika virus IgM tests can be difficult to interpret because of false-positives and cross-reactivity with other flaviviruses, especially in persons who were previously infected with or vaccinated against a related flavivirus (5,21). Additionally, a negative IgM test result does not rule out Zika virus infection when an IgM test is performed before the development of IgM antibodies or after the antibodies have waned.

PRNT measures virus-specific neutralizing antibody titers and should be performed for Zika and dengue viruses in NAT-negative, IgM-nonnegative (i.e., positive, equivocal, presumptive positive, or possible\(^{55}\)) specimens (21). In primary flavivirus infections (i.e., a person’s first flavivirus infection), PRNT can often identify the infecting virus (21). PRNT can also assist in identifying false-positive IgM. However, PRNT might not discriminate between anti-Zika virus antibodies and cross-reacting antibodies in persons who have been previously infected with or vaccinated against a related flavivirus (i.e., secondary flavivirus infection) (22,23). In addition, if areas with risk for Zika virus transmission experience increasing levels of dengue virus transmission, the difficulty in differentiating between cross-reactive Zika virus and dengue virus antibodies will further complicate interpretation of test results and diagnosis of Zika virus infection. This is especially concerning at this time, as epidemiologic trends suggest a reduced likelihood of Zika virus transmission in the Americas, compared with 2016 (2,24).

Efforts to develop and validate Zika virus serologic assays with improved specificity for Zika virus infection and the ability to distinguish a recent infection from a previous infection are ongoing. CDC is currently working with multiple manufacturers to validate tests in development and will update testing recommendations as new information becomes available.

\(^{11}\) https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika
\(^{55}\) Terms listed here are only examples of assay interpretation terminology because nonnegative serology terminology varies by assay. For explanation of a specific interpretation, refer to the instructions for use for the specific assay performed. Information on each assay can be found at https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika under the “Labeling” tab for the specific assay.
### TABLE 1. Interpretation*† of results of nucleic acid and antibody testing§¶ for suspected Zika virus infection — United States (including U.S. territories), July 2017

<table>
<thead>
<tr>
<th>Zika virus NAT (serum)**</th>
<th>Zika virus NAT (urine) **</th>
<th>Zika virus IgM††</th>
<th>Zika virus PRNT</th>
<th>Dengue virus PRNT</th>
<th>Interpretation and recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Any result</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Acute Zika virus infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Acute Zika virus infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Acute Zika virus infection</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative or not performed</td>
<td>Positive</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Presumptive Zika virus infection; timing of infection cannot be determined***</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative or not performed</td>
<td>Negative</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Presumptive Zika virus infection; specific virus cannot be identified; timing of infection cannot be determined***</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative or not performed</td>
<td>Any nonnegative result§§</td>
<td>≥10</td>
<td>&lt;10</td>
<td>Zika virus infection; timing of infection cannot be determined***</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative or not performed</td>
<td>Positive</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Presumptive flavivirus infection; specific virus cannot be identified; timing of infection cannot be determined***</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative or not performed</td>
<td>Any nonnegative result§§</td>
<td>&lt;10</td>
<td>Any result</td>
<td>No evidence of Zika virus infection</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative or not performed</td>
<td>Any nonnegative result§§</td>
<td>≥10</td>
<td>≥10</td>
<td>No laboratory evidence of Zika virus infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative or not performed</td>
<td>Positive for Zika virus AND negative for dengue virus</td>
<td>Not performed because PRNT is not recommended</td>
<td>Presumptive Zika virus infection; timing of infection cannot be determined***</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Negative or not performed</td>
<td>Positive for Zika virus AND positive for dengue virus</td>
<td>Not performed because PRNT is not recommended</td>
<td>Presumptive flavivirus infection; specific virus cannot be identified; timing of infection cannot be determined***</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Negative or not performed</td>
<td>Equivocal (either or both assays)</td>
<td>Not performed because PRNT is not recommended</td>
<td>Insufficient information for interpretation</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Negative or not performed</td>
<td>Negative on both assays</td>
<td>Not performed because PRNT is not recommended</td>
<td>Consider repeat testing</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.

* Final interpretations of results of Zika virus tests should be performed after all testing is completed.
† Serology test results that indicate flavivirus infection should be interpreted in the context of circulating flaviviruses.
§ Dengue virus IgM testing is recommended for symptomatic pregnant women as well as for asymptomatic pregnant women residing in areas where PRNT is not recommended.
¶ Currently, PRNT confirmation is not routinely recommended for persons living in Puerto Rico.
** Serum must be submitted for all persons tested for Zika virus infection; a urine specimen for Zika virus NAT testing should always be submitted concurrently with a serum specimen.
†† For laboratory interpretation in the presence of dengue virus IgM results refer to https://www.cdc.gov/dengue/clinicallab/laboratory.html.
* Positive results include “positive,” “presumptive Zika virus positive,” or “possible Zika virus positive.” These are examples of assay interpretations that might accompany test results; positive serology terminology varies by assay. For explanation of a specific interpretation, refer to the instructions for use for the specific assay performed. Information on each assay can be found at https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#Zika under the “Labeling” for the specific assay.
§§ Nonnegative results include “positive,” “equivocal,” “presumptive positive,” or “possible positive.” These are examples of assay interpretations that might accompany test results; nonnegative serology terminology varies by assay. For explanation of a specific interpretation, refer to the instructions for use for the specific assay performed. Information on each assay can be found at https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#Zika under “Labeling” for the specific assay.
*** Zika virus IgM positive result is reported as “presumptive positive or flavivirus infection” to denote the need to perform confirmatory PRNT titers against Zika virus, dengue virus, and other flaviviruses to which the person might have been exposed to resolve potential false-positive results that might have been caused by cross-reactivity or nonspecific reactivity. In addition, ambiguous test results (e.g., inconclusive, equivocal, and indeterminate) that are not resolved by retesting also should have PRNT titers performed to rule out a false-positive result. However, PRNT confirmation is currently not routinely recommended for persons living in Puerto Rico.
Updated Interim Guidance for Laboratory Testing of Pregnant Women with Exposure to Areas with Risk for Zika Virus Transmission

As many areas in the Americas move into a subsequent (e.g., a second or third) mosquito season after introduction of Zika virus, testing becomes more complex. Given the evolving situation and the many uncertainties, the updated testing algorithms for symptomatic and asymptomatic pregnant women (Figure 1) (Figure 2) emphasize a shared patient-provider decision-making model. Counseling is recommended before and after testing, and Zika virus test results should be interpreted in the context of several limitations (Box). To address new and emerging data, the laboratory interpretations of Zika virus testing (Table 1) have also been updated.

Health care providers should continue to ask pregnant women at each prenatal visit about possible Zika virus exposure (e.g., travel to, or residence in an area with risk for mosquito-borne Zika virus transmission or sex with a partner who has traveled to or resides in an area with risk for mosquito-borne Zika virus transmission), specifically before and during the current pregnancy. Health care providers should ask about presence of symptoms of Zika virus disease (e.g., fever, rash, arthralgia, and conjunctivitis) and place, duration, and type of travel to assess a woman's potential for Zika virus exposure. Data from other mosquito-borne illnesses indicate that intensity of transmission, duration of travel, and type of travel influence the likelihood of infection (25,26); these factors might also affect the likelihood of Zika virus acquisition. Knowledge of a pregnant woman's possible exposure to Zika virus before and during pregnancy is critical contextual information that should be used to tailor pretest and posttest counseling and interpretation of test results (Box). Zika virus IgM test results might be difficult to interpret for pregnant women who have had exposure to any area with risk for Zika virus transmission before the current pregnancy, and this difficulty underscores the importance of shared patient-provider decision-making.

Pregnant women with recent possible Zika virus exposure and symptoms of Zika virus disease. Testing for Zika virus infection is still recommended for pregnant women with symptoms of Zika virus disease and possible Zika virus exposure, with the main goal of establishing a diagnosis that accounts for their symptoms, or ruling out Zika virus infection so that an alternative diagnosis can be considered. Negative test results should prompt evaluation for other causes, which might include dengue virus or chikungunya virus infection, depending on the symptoms and epidemiology of circulating viruses.

Concurrent NAT (serum and urine) and serologic testing (serum) is recommended for pregnant women as soon as possible, through 12 weeks after symptom onset (Figure 1). Reports of prolonged detection of Zika virus RNA in symptomatic pregnant women support longer time frames for the performance of molecular diagnostic testing (8–11,13–15). However, the proportion of pregnant women with this finding is unknown. Expanding the time frame for NAT testing through 12 weeks after symptom onset allows for a longer period in which to make a NAT-confirmed diagnosis of Zika virus infection in some pregnant women. However, because of the potential for false-positive NAT results (6,27), updated recommendations include NAT testing of both serum and urine and concurrent Zika virus IgM antibody testing to confirm the diagnosis of acute Zika virus infection with more than one test (Table 1).

For women who seek care >12 weeks after symptom onset, Zika virus IgM testing might be considered; however, a negative result does not rule out an infection during pregnancy because IgM levels decline over time. A positive result should be interpreted within the context of the known limitations of serologic testing.

Asymptomatic pregnant women with ongoing possible Zika virus exposure. For asymptomatic pregnant women with ongoing exposure to Zika virus, testing for Zika virus infection should be offered as part of routine obstetric care because it might identify acute infection during pregnancy (Figure 2). Previous guidance recommended IgM testing with reflex NAT once during the first and second trimester of pregnancy for women with ongoing possible Zika virus exposure (28). IgM testing is no longer routinely recommended because of the limitations of IgM tests and the difficulty in interpreting results.

The optimal timing and frequency for testing asymptomatic pregnant women with NAT alone is unknown; NAT for asymptomatic pregnant women should be informed by jurisdictional trends in Zika virus transmission, the duration of ongoing possible exposure during pregnancy, and data on the duration of Zika virus RNA detection in body fluids. For pregnant women who have received a diagnosis of laboratory-confirmed Zika virus infection any time before or during the current pregnancy, additional Zika virus testing is not recommended. For women without a prior laboratory-confirmed diagnosis of Zika virus, NAT should be offered at the initiation of prenatal care, and if Zika virus RNA is not detected on clinical specimens, two additional NAT tests should be offered during the course of the pregnancy coinciding with prenatal visits. The proportion of fetuses and infants with Zika virus–associated birth defects is highest among women with first and early second trimester infections (29); therefore, conducting all NAT during the first and second trimesters might

---

FIGURE 1. Updated interim testing recommendations*†§|| and interpretation of results***—United States (including U.S. territories), July 2017

ASK pregnant women about

Travel to or residence in areas with risk for Zika virus transmission before and during current pregnancy
Possible sexual exposure before and during current pregnancy
A diagnosis of laboratory-confirmed Zika virus infection before current pregnancy
Symptoms of Zika virus disease during current pregnancy (e.g., fever, rash, conjunctivitis, and arthralgia)
If no symptoms reported, refer to asymptomatic algorithm

Before testing, discuss testing limitations and potential risks for misinterpretation of test results

WHOM to test?
Pregnant women reporting possible exposure during current pregnancy and symptoms of Zika virus disease

WHEN to test?
As soon as possible, through 12 weeks after symptom onset

WHICH tests?

RESULTS and ADDITIONAL tests

Positive Zika virus NAT
If Zika virus IgM result negative, further testing may be warranted

Negative Zika virus NAT
AND Zika virus IgM serology

Negative Zika virus NAT
AND nonnegative Zika virus IgM

Plaque reduction neutralization test (PRNT)

Zika virus PRNT ≥10
AND dengue virus PRNT <10

Zika virus PRNT ≥10
AND dengue virus PRNT ≥10

Zika virus PRNT <10

INTERPRETATION

Acute Zika virus infection

Zika virus infection; timing of infection cannot be determined
For pregnant women without Zika virus exposure before the current pregnancy, positive IgM represents recent Zika virus infection

Flavivirus infection; specific virus and timing of infection cannot be determined
For pregnant women without Zika virus exposure before the current pregnancy, positive IgM represents recent unspecified flavivirus infection

No evidence of Zika virus infection

Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.

* Ask about type and duration of Zika virus exposure before and during current pregnancy. Exposure before the current pregnancy might limit interpretation of Zika virus IgM results; pretest counseling can help inform testing decisions. Some patients may choose not to receive Zika virus IgM testing.

† Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (positive/equivocal Zika virus or dengue virus IgM and Zika virus PRNT ≥10 and dengue virus PRNT <10 results).

§ This algorithm also applies to pregnant women with possible Zika virus exposure who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome.

‖ The duration of detectable Zika virus RNA in pregnant women following infection is not known. Preliminary data suggest that NAT might remain positive for several weeks after symptom onset in some pregnant women. Zika virus IgM antibodies are most likely to be detected within 12 weeks after infection; however, IgM antibodies might be detected for months after infection, limiting the ability to determine whether infection occurred before or during the current pregnancy.

** Dengue virus IgM antibody testing is recommended for symptomatic pregnant women. For laboratory interpretation in the presence of dengue virus IgM results, refer to https://www.cdc.gov/dengue/clinical/lab/laboratory.html. Nonnegative results include “positive,” “equivocal,” “presumptive positive,” or “possible positive.” These are examples of assay interpretation that might accompany test results; nonnegative serology terminology varies by assay. For explanation of a specific interpretation, refer to the instructions for use for the specific assay performed. Information on each assay can be found at https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.html#zika under the “Labeling” tab for the specific assay.


§§ Despite the high specificity of NAT, false-positive NAT results have been reported. If both serum and urine specimens are NAT-negative, regardless of IgM antibody results, results should be interpreted as evidence of acute Zika virus infection. If either serum or urine specimen is NAT-positive in conjunction with a positive Zika virus IgM result, results should be interpreted as evidence of acute Zika virus infection. If NAT is only positive on serum or urine and IgM testing is negative, repeat testing on the original NAT-positive specimen. If repeat NAT is positive, results should be interpreted as evidence of acute Zika virus infection. If repeat NAT testing is negative, results are indeterminate and health care providers should repeat Zika virus IgM antibody testing on a serum specimen collected ≥2 weeks after symptom onset. If subsequent IgM antibody test is positive, interpret as evidence of acute Zika virus infection, but if negative, interpret as no evidence of Zika virus infection.

*** Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://wwwnc.cdc.gov/travel/page/zika-travel-information) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period]), or sex without a condom during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.

††† For the purposes of this guidance, recent possible Zika virus exposure or Zika virus/flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.
FIGURE 2. Updated interim testing recommendations*†§ and interpretation of results¶** for asymptomatic pregnant women with possible Zika virus exposure††§§¶¶ — United States (including U.S. territories), July 2017

[Diagram with decision tree for testing]

ASK pregnant women about

- Travel to or residence in areas with risk for Zika virus transmission before and during pregnancy
- Possible sexual exposure before and during current pregnancy
- A diagnosis of laboratory-confirmed Zika virus infection before current pregnancy
- Symptoms of Zika virus disease during current pregnancy (e.g., fever, rash, conjunctivitis, and arthralgia)

Before testing, discuss testing limitations and potential risks for misinterpretation of test results

WHOM to test?

Asymptomatic pregnant women with ongoing possible Zika virus exposure

WHEN to test?

Three times during pregnancy
First test at initiation of prenatal care

WHICH tests?

Zika virus NAT (serum and urine)

RESULTS

Positive Zika virus NAT
Negative Zika virus NAT

INTERPRETATION

Acute Zika virus Infection
No Zika virus RNA detected (Zika virus infection during pregnancy cannot be ruled out)

Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.

* Ask about type and duration of Zika virus exposure before and during the current pregnancy. Exposure before the current pregnancy might limit interpretation of Zika virus IgM results; pretest counseling can help inform testing decisions.

† Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (positive/equivocal Zika virus or dengue virus IgM and Zika virus PRNT ≥10 and dengue virus PRNT <10 results).

§ The interval for Zika virus NAT testing during pregnancy is unknown. Preliminary data suggest that NAT might remain positive for several weeks after infection in some pregnant women. For women without a prior laboratory-confirmed diagnosis of Zika virus, NAT testing should be offered at the initiation of prenatal care, and if Zika virus RNA is not detected on clinical specimens, two additional tests should be offered during the course of the pregnancy coinciding with prenatal visits. The proportion of fetuses and infants with Zika virus–associated birth defects is highest among women with first and early second trimester infections; therefore, conducting all NAT testing during the first and second trimesters might be considered to help identify infections early in pregnancy. However, adverse outcomes have been associated with infection diagnosed in the third trimester; therefore, testing every trimester might be considered.

¶ Despite the high specificity of NAT, false-positive NAT results have been reported. If both serum and urine specimens are NAT-positive, interpretation should be acute Zika virus infection. If NAT is only positive on serum or urine, testing should be repeated on the original NAT-positive specimen. If repeat NAT is positive, results should be interpreted as evidence of acute Zika virus infection. If repeat NAT testing is negative, results are indeterminate and health care providers should perform IgM testing on a specimen collected ≥2 weeks after initial specimen collection. For laboratory interpretation, refer to https://www.cdc.gov/zika/pdfs/lab-table.pdf.

** A negative Zika virus NAT result does not exclude infection during pregnancy because it represents a single point in time. Zika virus RNA levels decline over time, and the duration of the presence of Zika virus RNA in serum and urine following infection varies among pregnant women. Despite Zika virus IgM antibody test limitations (e.g., cross-reactivity with other flaviviruses and prolonged detection for months, presenting challenges in determining the timing of infection), which should be discussed as part of pretest counseling, patients may still choose to receive Zika virus IgM testing.

†† Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://wwwnc.cdc.gov/travel/page/zika-travel-information) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period]), or sex without a condom, during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.

§§ Persons with ongoing possible Zika virus exposure include those who reside in or frequently travel (e.g., daily or weekly) to an area with risk for Zika virus transmission.

¶¶ For the purposes of this guidance, recent possible Zika virus exposure or Zika virus/flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.
BOX. Key information needed for deciding whether to test and how to interpret serology results

- Pregnant women with possible Zika virus exposure should be asked about their risk for exposure both before and during the current pregnancy. Health care providers should ask about the presence of symptoms of Zika virus disease (e.g., fever, rash, arthralgia, and conjunctivitis), and place, duration, and type of travel to assess a woman's potential for exposure to Zika virus and other flaviviruses (e.g., dengue or West Nile viruses).
- It is important to ascertain whether a woman had exposure to Zika virus before the current pregnancy because Zika virus immunoglobulin M (IgM) antibodies can be detected for months after an infection. A positive Zika virus IgM result could indicate antibodies from infection before the current pregnancy, thus limiting the ability to distinguish between an infection that occurred before the current pregnancy and one that occurred during the current pregnancy.
- It is important to ascertain whether a woman had exposure to flaviviruses other than Zika virus before the current pregnancy because a positive IgM result might have been caused by cross-reactivity from a previous flavivirus exposure.
- Health care providers and counselors should provide appropriate pretest counseling to inform decisions on whether to test; Zika virus test results should be interpreted within the context of known limitations.
- A negative Zika virus IgM test result, if performed during the recommended time frame, in the setting of a negative Zika virus nucleic acid test (NAT) result, provides some reassurance of absence of Zika virus infection during the current pregnancy. However, a negative Zika virus IgM test result should be interpreted within the context of the limitations of the assay.
- When plaque reduction neutralization testing (PRNT) is indicated and performed during the recommended time frame, a negative PRNT result in the setting of a negative NAT result indicates that there is no laboratory evidence of Zika virus infection.

be considered to help identify infections early in pregnancy. However, adverse outcomes have been associated with infection diagnosed in the third trimester (28); therefore testing every trimester might also be considered.

Serologic testing is not routinely recommended for asymptomatic pregnant women with ongoing possible Zika virus exposure because of the potential for prolonged detection of Zika virus IgM, which poses challenges in determining whether the infection and therefore the risk of congenital Zika virus infection, occurred during the current pregnancy. In addition, in areas with ongoing dengue virus transmission, a positive Zika virus IgM result might occur because of serologic cross-reactivity. Despite these limitations, which should be discussed as part of pretest counseling, patients may still choose to receive Zika virus IgM testing (Table 1).

Although a recommendation to consider Zika virus IgM testing as part of preconception counseling to establish baseline IgM results for nonpregnant women with ongoing possible Zika virus exposure was previously issued, Zika virus IgM is no longer routinely recommended for asymptomatic pregnant women with ongoing possible Zika virus exposure, and therefore baseline preconception testing is not warranted. Zika virus testing is not recommended to determine timing of conception or pregnancy for couples in which one or both partners has had possible Zika virus exposure. Zika virus testing for this purpose is of uncertain value because: 1) IgM testing has diagnostic limitations; 2) Zika virus NAT testing of serum does not reflect persistence in other body fluids (e.g., semen). The current understanding of Zika virus shedding in genital secretions is limited (30); testing semen and vaginal fluids for Zika virus is not currently available outside research settings.

Asymptomatic pregnant women with recent possible Zika virus exposure (i.e., through travel or sex) but without ongoing possible exposure. For asymptomatic pregnant women with recent possible Zika virus exposure (i.e., through travel or sex), but without ongoing possible exposure, testing for Zika virus infection is not routinely recommended. However, testing should be considered using a shared decision-making model, one in which patients and providers work together to make decisions about testing and care plans based on patient preferences and values, clinical judgment, a balanced assessment of risks and expected outcomes, and the jurisdiction's recommendations. Health care providers should consider potential exposure risk factors when deciding whether to advise testing. These include symptoms, type and length of possible exposure, Zika virus transmission trends at location of possible exposure and the use of prevention measures (e.g., insect repellant, appropriate clothing, and condom use). Jurisdictional recommendations may take into account the epidemiology of Zika virus transmission and other epidemiologic considerations (e.g., seasonality and mosquito surveillance and control factors) in areas with risk for Zika virus transmission and, therefore, might include a routine recommendation to test asymptomatic pregnant women either for clinical care or as part of Zika virus infection surveillance.

Although preliminary data indicate that the risk for Zika virus–associated birth defects does not differ by maternal symptom status, testing is not routinely recommended for asymptomatic pregnant women with recent possible Zika virus exposure but
without ongoing possible exposure to address the increased probability of false positive results in the setting of the declining prevalence of Zika virus disease (28, 29). The limitations of currently available tests and the lack of a vaccine or an effective therapy to prevent congenital infection or mitigate sequelae of Zika virus infection during pregnancy, or in the neonate, underscore the importance of shared patient-provider decision-making. The decision about Zika virus testing should take into account the patient’s unique circumstances and should allow pregnant women to make an informed decision about the utility of testing. If testing is conducted for asymptomatic pregnant women with recent possible Zika virus exposure, but without ongoing possible exposure, the testing algorithm for symptomatic pregnant women with possible Zika virus exposure (Figure 1) should be used, applying time frames from last possible Zika virus exposure.

Pregnant women with possible Zika virus exposure who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome. Maternal Zika virus NAT and IgM testing should be performed. Consideration of amniocentesis should be individualized because data about its usefulness in diagnosing congenital Zika virus infection are limited. If amniocentesis is performed as part of clinical care, NAT testing should be performed on amniocentesis specimens. A recent study reported that detection of Zika virus RNA in amniocentesis specimens from pregnancies with a fetus with Zika virus–associated birth defects indicate fetal infection. However, data also suggested that detection of Zika virus RNA in amniotic fluid could be transient and that Zika virus RNA might not always be detectable in amniotic fluid after fetal infection (13).

Updated Interim Guidance for Prenatal Management of Pregnant Women with Laboratory Evidence of Possible Zika Virus Infection†††

For pregnant women with laboratory evidence of possible Zika virus infection, serial fetal ultrasounds (every 3–4 weeks) should be considered to assess fetal anatomy, particularly fetal neuroanatomy, and to monitor growth. A study of 17 pregnancies in symptomatic women with laboratory-confirmed Zika virus infection and adverse fetal outcomes in Colombia and a summary of eight published studies of 37 pregnancies reported a median of 18 weeks from symptom onset to prenatal diagnosis of microcephaly (31). This finding is consistent with other reports about prenatal diagnosis of microcephaly. Among 37 pregnancies with confirmed or suspected Zika virus infection, a median of 21 weeks (range = 3–29 weeks) from maternal symptom onset to prenatal diagnosis of microcephaly was observed (31). Given the length of time for the detection of prenatal microcephaly, prenatal ultrasounds should carefully evaluate the fetal anatomy, particularly the neuroanatomy, to identify brain or structural abnormalities that might occur before microcephaly.

Decisions about performing amniocentesis should be individualized because there is a paucity of data regarding the usefulness of amniocentesis in diagnosing congenital Zika virus infection. 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. The optimal time to perform amniocentesis to diagnose congenital Zika virus infection is not known; health care providers should discuss the risks and benefits of amniocentesis with their patients.

This guidance also applies to pregnant women with laboratory evidence of presumptive Zika virus or flavivirus infection; timing of infection cannot be determined (Table 1).

Updated Interim Guidance for the Evaluation of Placental and Fetal Tissue Specimens for Zika Virus Infection

Detection of Zika virus RNA has been reported in placental tissues and in fetal and infant brain tissue 15–210 days (mean = 81 days) and 119–238 days (mean = 163 days), respectively, from maternal symptom onset (32). Among 546 live births with travel-associated possible maternal Zika virus exposure in the 50 U.S. states and the District of Columbia in 2016 for which placental specimens were submitted to CDC, 60 (11%) were positive for Zika virus RNA (33). When restricted to live births without a laboratory-confirmed Zika virus infection based on maternal or infant Zika virus testing of serum or urine, 47 of 482 (10%) were positive for Zika virus RNA (33). Although, the proportion of live births with positive placental reverse-transcription polymerase chain reaction (RT-PCR) results was relatively low, these results provided definitive evidence of maternal Zika virus infection during that pregnancy. As with serologic and NAT testing of serum and urine, the proportion of pregnancies with a positive Zika virus RT-PCR on tissue specimens is expected to decrease in the setting of declining prevalence of Zika virus disease in the Americas.

††† Laboratory evidence of possible Zika virus infection during pregnancy is defined as 1) Zika virus infection detected by a Zika virus RNA nucleic acid test (NAT) on any maternal, placental, or fetal specimen (referred to as NAT-confirmed) or 2) diagnosis of Zika virus infection, timing of infection cannot be determined or unspecified flavivirus infection, timing of infection cannot be determined by serologic tests on a maternal specimen (i.e., positive/equivocal Zika virus immunoglobulin M [IgM] and Zika virus plaque reduction neutralization test [PRNT] titer ≥10, regardless of dengue virus PRNT value; or negative Zika virus IgM, and positive or equivocal dengue virus IgM, and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT titer). The use of PRNT for confirmation of Zika virus infection, including in pregnant women and infants, is not routinely recommended in Puerto Rico (https://www.cdc.gov/zika/laboratories/lab-guidance.html).
Testing placental tissue specimens from pregnancies with possible Zika virus exposure that result in live births can be considered for diagnostic purposes in certain scenarios. It may be considered for symptomatic pregnant women and women with infants with possible Zika virus–associated birth defects, without a definitive diagnosis of laboratory-confirmed Zika virus infection during pregnancy (Table 2). Similar to the updated testing recommendations for asymptomatic pregnant women who have recent possible Zika virus exposure but without ongoing possible exposure, testing of placental tissues is not routinely recommended; however, it should be considered for women who have a fetus or infant with possible Zika virus–associated birth defects.

Finally, testing of placental and fetal tissues may be considered in selected scenarios for pregnancies resulting in a miscarriage or fetal loss/stillbirth (and testing of autopsy tissues in the event of an infant death) to provide insight into the potential etiology of the fetal loss or infant death (Table 2), which could inform a woman’s future pregnancy planning. Additional information is available at https://www.cdc.gov/zika/laboratories/test-specimens-tissues.html.

**Implications of Updated Interim Guidance for Laboratory Testing of Pregnant Women with Possible Zika Virus Exposure for the Evaluation and Care of Infants with Possible Congenital Zika Virus Exposure**

Interim guidance for the evaluation of infants with congenital Zika virus exposure has been previously published; infants who meet one or more of the published criteria for testing for congenital Zika virus infection should be tested and evaluated in accordance with the updated CDC interim guidance for the evaluation and management of infants with possible Zika virus infection (34). However, in light of the updated recommendations that will likely reduce routine Zika virus testing of asymptomatic pregnant women with recent possible Zika virus exposure but without ongoing possible exposure, it is critical that pediatric health care providers inquire about possible maternal and congenital Zika virus exposure for every newborn. Infants born to mothers with possible Zika virus exposure during pregnancy but who did not receive testing, including asymptomatic pregnant women with recent possible Zika virus exposure but without ongoing possible exposure, should receive a comprehensive physical examination, including standardized measurement of head circumference and newborn hearing screen, as part of routine pediatric care. In addition, based on the level of possible Zika virus exposure (e.g., duration and type of exposure, use of prevention measures, intensity of Zika virus transmission at the location of travel), the provider should consider whether further evaluation of the newborn for possible congenital Zika virus infection is warranted, in which case, a head ultrasound, and ophthalmologic assessment should be considered. Based on results of the evaluation, testing of the infant for Zika virus infection could be considered.

This guidance also applies to infants born to mothers with negative maternal testing in the setting of ongoing possible Zika virus exposure or a possible Zika virus exposure that occurred more than 12 weeks before maternal testing (https://www.cdc.gov/zika/hc-providers/infants-children/evaluation-testing.html). Recommendations for outpatient management during the first 12 months of life include monitoring of head circumference and development and are provided in the updated CDC interim guidance for the evaluation and management of infants with possible Zika virus infection (34).

**Prevention of Zika Virus Infection**

CDC recommends that pregnant women avoid travel to any area with risk for Zika virus transmission. To prevent Zika virus infection during pregnancy, all pregnant women and their partners should receive counseling on prevention measures including strategies to prevent mosquito bites and sexual transmission of Zika virus (35). If pregnant women must travel, CDC recommends strict adherence to strategies to prevent mosquito bites and sexual transmission. Pregnant women living in areas with risk for Zika virus transmission should also follow these strategies. Couples wishing to conceive should receive preconception counseling about how to minimize risks for Zika virus infection (30). Other persons at risk for Zika virus exposure should receive information on travel and strategies to prevent mosquito bites and sexual transmission.§§§§§§

## TABLE 2. Interim guidance for Zika virus testing of formalin-fixed, paraffin-embedded placental, fetal, or infant autopsy tissues for completed pregnancies with possible Zika virus exposure during pregnancy — United States (including U.S. territories), July 2017

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Maternal Zika virus test results on nonissue clinical specimens (e.g., serum, urine)</th>
<th>Testing of placental tissues</th>
<th>Testing of placental and fetal tissues</th>
<th>Testing of placental and infant autopsy tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal Zika virus infection**</td>
<td>Zika virus infection; timing of infection cannot be determined††</td>
<td>Flavivirus infection; timing of infection cannot be determined</td>
<td>&gt;12 weeks after symptom onset or exposure,** with either negative maternal Zika virus IgM, or no maternal testing conducted</td>
</tr>
<tr>
<td>Live birth, possible Zika virus–associated birth defects***</td>
<td>Not indicated†††</td>
<td>Should be considered to aid in maternal diagnosis</td>
<td>Not indicated***</td>
<td>Not indicated***</td>
</tr>
<tr>
<td>Live birth, no obvious Zika virus–associated birth defects at birth</td>
<td>Not indicated</td>
<td>May be considered to aid in maternal diagnosis on a case-by-case and jurisdictional basis. Not routinely recommended for asymptomatic women with possible Zika virus exposure but without ongoing possible exposure</td>
<td>Not indicated***</td>
<td>Not indicated***</td>
</tr>
</tbody>
</table>

** Testing of placental tissues

††† Testing of placental and fetal tissues

Testing of placental and infant autopsy tissues

Abbreviations: IHC = immunohistochemistry; NAT = nucleic acid test; RT-PCR = reverse-transcription polymerase chain reaction.

** Zika virus testing on formalin-fixed, paraffin-embedded tissue specimens is conducted at CDC’s Infectious Diseases Pathology Branch (IDPB) and includes Zika virus RT-PCR on placental and fetal/infant tissues. Zika virus IHC may be performed on placental tissues into the second trimester, fetal tissues from any gestational age, and infant autopsy tissues.

*** Placental tissues include placental disc, umbilical cord, and fetal membranes. Zika virus RNA can be focal within placental tissues, and testing of three sections of placenta, one section of umbilical cord, and one section of fetal membrane is recommended (https://www.cdc.gov/zika/laboratories/test-specimens-tissues.html). For pregnancy losses and infants deaths, submission of placental tissues in addition to fetal or infant autopsy tissues, if available, is preferred, but if not available will not preclude placental testing.

††† Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://www.cdc.gov/zika/geo/index.html) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period]), or sex without a condom, during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.

Zika virus testing is not routinely recommended for asymptomatic pregnant women with recent possible Zika virus exposure but without ongoing exposure and who have a fetus or infant without Zika virus–associated birth defects.

** In the event of a confirmed maternal acute Zika virus infection or confirmed congenital Zika virus infection in the infant (e.g., a positive NAT), placental testing from live births is not indicated. Currently, placental testing does not routinely provide additional diagnostic information in the setting of a maternal or infant diagnosis of acute or congenital Zika virus infection, respectively.

††† For women with no possible Zika virus exposure before the current pregnancy, a positive IgM result likely represents acute Zika virus infection, and placental testing is not indicated.

** All or part of possible maternal Zika virus exposure, or symptom onset occurred >12 weeks before maternal serum specimen was collected.

*** Includes pregnant women with negative Zika virus NAT and negative Zika virus IgM ≤12 weeks after symptom onset or exposure.

*** Possible Zika virus–associated birth defects that meet the CDC surveillance case definition include the following: brain abnormalities and/or microcephaly, intracranial calcifications, ventriculomegaly, neural tube defects and other early brain malformations, eye abnormalities, or other consequences of central nervous system dysfunction including arthrogryposis (joint contractures), congenital hip dysplasia, and congenital deafness (https://www.cdc.gov/zika/geo/pregnancy-outcomes.html). In all cases, infants or fetuses with possible Zika virus–associated birth defects should also be evaluated for other etiologies of congenital anomalies.

††† May be considered to aid in infant and maternal diagnosis.
And Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Kelley VanMaldeghem, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Kimberly Newsome, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Konrad E. Hayashi, MD, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, CDC; Marson E. Rice, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Madelyn Baez-Santiago, PhD, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Megan R. Reynolds, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Rebecca Free, MD, Division of Emergency Operations, Office of Public Health Preparedness and Response, CDC; Myles Johnson, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Shannon Fleck-Derderian, MPH, Office of the Director, National Center on Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, CDC; Meghan Raycraft, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Kim Woodruff, MPH, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC; Shannon Fleck-Derderian, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Madelyn Baez-Santiago, PhD, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Konrad E. Hayashi, MD, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, CDC; Marson E. Rice, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Madelyn Baez-Santiago, PhD, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Meghan Raycraft, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Rebecca Free, MD, Division of Emergency Operations, Office of Public Health Preparedness and Response, CDC; Myles Johnson, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Regina M. Simeone, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Shannon Fleck-Derderian, MPH, Office of the Director, National Center for Emerging and Zoonotic Infectious Diseases, CDC; Somaia Khan, MPH, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; Tonya R. Williams, PhD, Division of Human Development and Disability, National Center on Birth Defects and Developmental Disabilities, CDC.

Conflict of Interest

No conflicts of interest were reported.

1Zika Virus Response Team, CDC.

Corresponding author: Titilope Oduyebo, Zikamch@cdc.gov; 770-488-7100.

References


Announcements

World Hepatitis Day — June 28, 2017

July 28, 2017 is World Hepatitis Day, an annual day of observance established by the World Health Organization to promote awareness and understanding of viral hepatitis. An estimated 325 million persons are infected with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) worldwide (1), and an estimated 1.3 million persons die from related causes annually (2). In June 2016, the World Health Assembly endorsed the Global Health Sector Strategy on Viral Hepatitis 2016–2021, which sets goals for the elimination of HBV and HCV as global health threats by 2030 and outlines the global actions needed to reach these goals (2). The theme of this year’s World Hepatitis Day is “Eliminate Hepatitis.”

This issue of MMWR includes a report on progress toward achieving HCV elimination in the nation of Georgia, which in April 2015, became the first country in the world to launch such a program. Georgia has set an ambitious goal of 90% reduction in HCV prevalence by 2020. Documenting Georgia’s progress, challenges, and strategies to address the challenges can inform global HCV elimination actions. Additional information and resources are available at https://www.cdc.gov/hepatitis.

References


Monitoring Selected National HIV Prevention and Care Objectives

CDC monitors progress on selected national human immunodeficiency virus (HIV) prevention and care objectives using surveillance data (1) and has released two HIV care continuums for 2014: a diagnosis-based continuum and a prevalence-based continuum (2,3). A diagnosis-based HIV continuum monitors key steps needed for a person living with diagnosed HIV infection to reach viral suppression, which leads to improved health outcomes and reduced risk for transmission to others. To determine a diagnosis-based HIV continuum, CDC uses the number of persons living with diagnosed HIV infection as the denominator. CDC monitors engagement in medical care and viral suppression in 38 jurisdictions that have complete reporting of CD4 and viral load laboratory results. Among persons living with diagnosed HIV infection at year-end 2014 in 38 jurisdictions, 73% received HIV medical care in 2014, 57% were retained in continuous care, and 58% were virally suppressed (1).

Because the first step in entering HIV care is receiving a diagnosis, CDC has also estimated an HIV prevalence-based continuum, which uses the estimated number of all persons living with diagnosed or undiagnosed HIV infection as the denominator. Among the estimated 1.1 million persons living with HIV infection in the United States in 2014, 85% had received a diagnosis (1). Extrapolating from 38 jurisdictions with complete reporting, an estimated 62% of persons living with HIV infection received HIV medical care in 2014, 48% were retained in continuous care, and 49% were virally suppressed (2).

More information is available in the Division of HIV/AIDS Prevention report and accompanying fact sheet and slide set (1–3).

References

Erratum

Vol. 66, No. 18

In the report “State HCV Incidence and Policies Related to HCV Preventive and Treatment Services for Persons Who Inject Drugs — United States, 2015–2016,” on page 466, the second sentence of the second paragraph should have read “HCV incidence rates increased by 167% nationally from 0.3 cases per 100,000 U.S. population in 2010 to 0.8 in 2015 (4).”

In the cover box “Hepatitis Awareness Month and Testing Day — May 2017,” on page 465, the last sentence of the second paragraph should have read ”During 2010–2015, HCV incidence rates increased by 167% with the highest rates among young persons who inject drugs (PWID).†”
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Age-Adjusted Percentage* of Adults Aged ≥18 Years Who Were Never in Pain, in Pain Some Days, or in Pain Most Days or Every Day in the Past 6 Months,†
by Employment Status§ — National Health Interview Survey,¶
United States, 2016

* With 95% confidence intervals indicated by error bars. Percentages were age-adjusted to the projected 2000 U.S. population as the standard population, using five age groups: 18–29, 30–39, 40–49, 50–59, and ≥60 years.
† Based on responses to the question “In the past 6 months, how often did you have pain? Would you say never, some days, most days, or every day?” For this figure, response categories “most days” and “every day” are combined.
§ Based on responses to the following questions: “What was [person]/were you doing last week?” and “Have you ever held a job or worked at a business?” Based on the first question, adults who were “working for pay at a job or business,” “with a job or business but not at work,” “working, but not for pay, at a family-owned job or business” were classified as “currently employed.” Adults who were “looking for work and not looking for work” based on the first question and who subsequently answered “yes” to the second question were classified as “previously employed.” Adults who were “looking for work or not working at a job or business and not looking for work” based on the first question and who subsequently answered “no” to the second question were classified as “never employed.”
¶ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population aged ≥18 years and are derived from the National Health Interview Survey sample adult component.

In 2016, 37.7% of adults aged ≥18 years never had pain, 42.8% had pain on some days, and 19.6% had pain most days or every day in the past 6 months. A higher percentage of adults who were previously employed (30.4%) had pain most days or every day compared with never employed adults (19.4%) and currently employed adults (15.1%). Never employed adults (42.0%) and currently employed adults (39.9%) were more likely to report never having had pain than previously employed adults (30.7%).

Reported by: Carla E. Zelaya, PhD, CZelaya@cdc.gov, 301-458-4164; James M. Dahlhamer, PhD; Jacqueline W. Lucas, MPH.