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Opioid Use Disorder Documented at Delivery Hospitalization — United States, 1999–2014

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Opioid use by pregnant women represents a significant public health concern given the association of opioid exposure and adverse maternal and neonatal outcomes, including preterm labor, stillbirth, neonatal abstinence syndrome, and maternal mortality (*1*,*2*). State-level actions are critical to curbing the opioid epidemic through programs and policies to reduce use of prescription opioids and illegal opioids including heroin and illicitly manufactured fentanyl, both of which contribute to the epidemic (*3*). Hospital discharge data from the 1999–2014 Healthcare Cost and Utilization Project (HCUP) were analyzed to describe U.S. national and state-specific trends in opioid use disorder documented at delivery hospitalization. Nationally, the prevalence of opioid use disorder more than quadrupled during 1999–2014 (from 1.5 per 1,000 delivery hospitalizations to 6.5; p<0.05). Increasing trends over time were observed in all 28 states with available data (p<0.05). In 2014, prevalence ranged from 0.7 in the District of Columbia (DC) to 48.6 in Vermont. Continued national, state, and provider efforts to prevent, monitor, and treat opioid use disorder among reproductive-aged and pregnant women are needed. Efforts might include improved access to data in Prescription Drug Monitoring Programs, increased substance abuse screening, use of medication-assisted therapy, and substance abuse treatment referrals.

Data were analyzed from the National Inpatient Sample (NIS; 1999–2014) and the State Inpatient Databases (SID; 1999–2014) of HCUP, Agency for Healthcare Research and Quality (*4*). NIS approximates a 20% stratified sample of all U.S. community hospital discharges participating in HCUP and is weighted to be nationally representative. Survey-specific analysis techniques were used to account for clustering, stratification, and weighting in NIS analyses (*4*). The SID contain state-specific data on hospital inpatient stays, regardless of payer; 30 states and DC had publically available data (Table).

The annual number of in-hospital delivery discharges were identified from the 1999–2014 NIS and SID files using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic and procedure codes pertaining to obstetric delivery (*2*). Cases of opioid use disorder were identified from diagnoses of opioid dependence (ICD-9-CM 304.00–304.03, 304.70–304.73) and nondependent opioid abuse (ICD-9-CM 305.50–305.53), aligning with *Diagnostic and Statistical Manual-5* criteria.* Annual prevalence of opioid use disorder per 1,000 delivery hospitalizations during 1999–2014 was calculated nationally using NIS. Opioid

* https://pcssnow.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf.

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use disorder prevalence was calculated using the SID for all 30 states and DC. For the 28 states with at least 3 consecutive years of data,[†] linear trends were assessed using logistic regression. For states with significant trends (p-values <0.05), average annual rate changes were estimated from the beta coefficient for year and the national or state-specific intercept. A sensitivity analysis was performed to assess whether results differed in a resident-only sample.

During 1999–2014, the national prevalence of opioid use disorder increased 333%, from 1.5 cases per 1,000 delivery hospitalizations to 6.5 (Figure 1), an average annual increase of 0.4 per 1,000 delivery hospitalizations per year (p<0.05). State data were available for 30 states and DC; however, availability by year ranged from 14 states in 1999 to 28 states in 2011 (Table). In 1999, the prevalence of opioid use disorder ranged from 0.1 per 1,000 delivery hospitalizations in Iowa to 8.2 in Maryland, and in 2014, prevalence ranged from 0.7 in DC to 48.6 in Vermont; prevalence exceeded 30 per 1,000 delivery hospitalizations in Vermont and West Virginia (Figure 2). During 1999–2014, all 28 states experienced significant increasing linear trends (p<0.05) (Table). Over the study period, the average annual rate increase was lowest in California (0.01 per 1,000 delivery hospitalizations per year), whereas the highest average annual rate increases occurred in Maine, New Mexico, Vermont, and West Virginia, ranging from 2.5 to 5.4 opioid use disorder diagnoses per 1,000 delivery hospitalizations per year. The sensitivity analysis revealed no large differences between state residents and nonresidents.

[†] Arizona, Arkansas, California, Colorado, Florida, Georgia, Hawaii, Iowa, Kentucky, Maine, Maryland, Massachusetts, Michigan, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, Oregon, Rhode Island, South Carolina, South Dakota, Utah, Vermont, Washington, West Virginia, and Wisconsin.

Discussion

Nationally, rates of opioid use disorder at delivery hospitalization more than quadrupled during 1999–2014. These findings are consistent with previously documented national trends in opioid use disorder at delivery hospitalization during 1998–2011 (*2*) and increased national incidence of neonatal abstinence syndrome during 1999–2013 (*1*). Among 25 states and DC with 2014 data, the prevalence in Vermont and West Virginia was >3%. Although no previous multistate analyses of opioid use disorder at delivery hospitalization exist, these trends are mostly consistent with state neonatal abstinence syndrome estimates during 1999–2013 (*5*). Increasing trends might represent actual increases in prevalence or improved screening and diagnosis (*6*). Diagnostic procedures differ by state, and states with enhanced procedures for identifying infants with neonatal abstinence syndrome might ascertain more cases of maternal opioid use disorder.

These estimates also correlate with state opioid prescribing rates in the general population. West Virginia, for example, had a prescribing rate estimated at 138 opioid prescriptions per 100 persons in 2012, suggesting that individual persons might receive more than one opioid prescription per year (*7*).

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TABLE. National and state-specific prevalence of opioid use disorder per 1,000 delivery hospitalizations* — National Inpatient Sample (NIS)† and State Inpatient Database,§ Healthcare Cost and Utilization Project (HCUP), 1999–2014

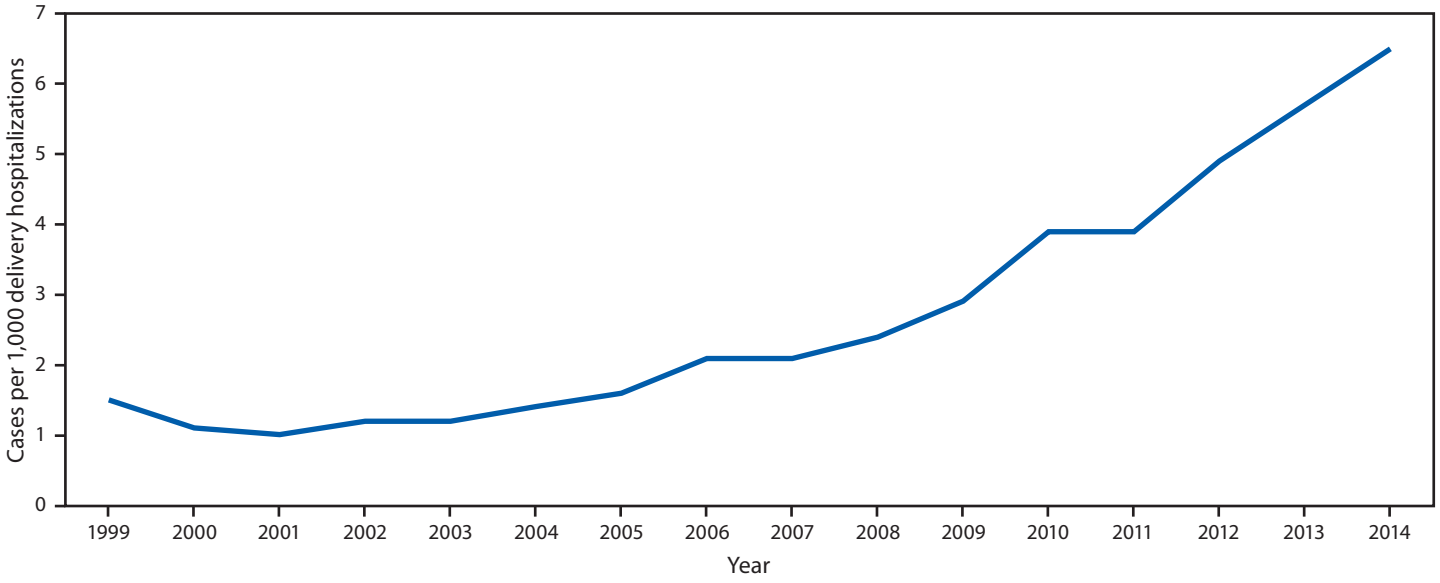
State	Year																Average annual rate change¶
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	
National	1.5	1.1	1.0	1.2	1.2	1.4	1.6	2.1	2.1	2.4	2.9	3.9	3.9	4.9	5.7	6.5	0.39
Arizona	1.1	1.0	1.3	1.1	1.2	1.1	1.5	1.1	1.4	1.2	1.9	2.1	3.0	3.5	4.7	5.2	0.28
Arkansas	—	—	—	—	—	0.4	0.6	0.8	0.7	1.1	1.2	1.0	1.6	1.9	2.6	2.5	0.25
California	1.2	1.0	1.2	—	1.1	1.1	1.0	1.1	1.0	1.1	1.2	1.3	1.6	—	—	—	0.01
Colorado	0.4	0.5	0.6	0.6	0.7	0.7	0.7	0.8	1.0	1.1	1.2	1.6	1.8	2.1	2.9	3.6	0.20
District of Columbia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.6	0.7	—**
Florida	0.5	0.5	0.5	0.6	0.7	0.9	1.0	1.2	1.6	2.1	3.0	4.1	5.1	5.6	6.3	6.6	0.58
Georgia	—	—	—	—	—	—	—	—	—	—	—	—	—	2.0	2.4	2.7	0.39
Hawaii	—	0.6	0.6	0.5	0.5	0.5	0.3	1.0	0.4	0.8	0.7	0.5	0.9	1.1	1.3	2.4	0.09
Iowa	0.1	0.2	0.0	0.0	0.1	0.2	0.2	0.2	0.2	0.4	0.5	0.6	0.8	1.2	1.4	1.3	0.10
Kentucky	—	0.4	0.9	1.6	2.4	2.5	3.1	3.9	4.0	5.1	6.1	7.2	9.5	14	15.7	19.3	1.55
Maine	0.7	0.6	1.5	2.3	4.0	—	—	9.4	10.7	13.5	21.7	26.2	27.8	34.1	—	—	4.13
Maryland	8.2	6.7	7.6	7.4	7.5	7.5	7.6	7.6	7.1	6.9	7.7	8.8	9.1	10.9	11.8	11.7	0.27
Massachusetts	2.0	2.7	2.4	2.6	2.9	3.7	4.6	4.9	6.5	6.9	8.3	8.8	9.6	12.2	13.1	—	0.90
Michigan	—	1.0	0.9	1.1	1.1	1.3	1.6	1.7	2.3	2.9	3.3	4.2	5.1	5.4	6.2	7.7	0.55
Minnesota	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.4	—**
Mississippi	—	—	—	—	—	—	—	—	—	—	—	1.9	1.6	—	—	—	—**
Nebraska	—	—	0.2	0.1	0.1	0.4	0.4	0.2	0.2	0.4	0.3	0.2	0.3	1.1	0.9	1.2	0.08
Nevada	—	—	—	0.6	0.6	1.2	1.1	1.1	1.0	1.3	1.7	2.0	2.3	3.1	3.4	4.5	0.33
New Jersey	4.1	4.3	4.0	3.8	4.0	3.4	4.0	3.3	3.5	3.6	4.1	4.5	4.5	5.0	5.3	5.6	0.08
New Mexico	—	—	—	—	—	—	—	—	—	3.8	3.9	5.5	7.6	10.6	13.6	14.8	2.47
New York	1.6	1.5	1.4	1.5	1.6	1.6	1.4	1.6	1.7	1.9	2.1	2.3	3.0	3.1	4.2	4.9	0.20
North Carolina	—	0.2	0.3	0.6	0.7	0.7	1.1	1.3	1.3	1.8	2.5	2.8	3.7	4.9	6.4	7.8	0.64
Oregon	1.2	0.9	1.5	1.7	1.4	1.8	2.1	2.5	2.1	2.7	3.8	4.4	4.4	5.7	6.9	8.4	0.49
Rhode Island	—	—	—	4.1	3.3	4.3	4.3	3.1	4.0	3.8	4.9	6.1	7.4	7.2	8.0	10.2	0.51
South Carolina	0.4	0.3	0.3	0.2	0.4	0.5	1.0	1.1	1.2	1.3	1.9	2.2	2.8	3.3	4.4	—	0.34
South Dakota	—	—	—	—	—	—	—	—	0.1	0.3	0.0	0.5	0.8	0.8	1.2	1.5	0.29
Utah	—	0.4	0.4	0.5	0.6	0.8	0.9	1.3	1.1	1.4	2.0	2.3	2.0	2.6	2.7	3.7	0.25
Vermont	—	—	0.5	2.4	3.7	4.0	7.6	12.9	14.6	19.0	28.5	27.1	33.8	43.7	51.1	48.6	5.37
Washington	1.2	0.9	1.1	1.3	1.7	1.9	2.4	2.8	2.6	3.4	4.2	5.3	6.9	7.1	8.5	10.8	0.71
West Virginia	—	0.6	1.0	1.6	2.3	3.0	4.2	6.8	7.1	8.2	10.1	11.2	15.3	21.3	29.8	32.1	2.83
Wisconsin	0.3	0.5	0.3	0.5	0.5	0.7	1.0	1.1	1.4	2.0	2.8	3.5	4.6	5.6	6.9	7.6	0.65

* Prevalence numerator consisted of cases of opioid type dependence and nondependent opioid abuse based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes (304.00–304.03, 304.70–304.73, 305.50–305.53), and denominator consisted of national and state delivery hospitalization discharges.
† Includes data from all states participating in HCUP each year (https://www.hcup-us.ahrq.gov/partners.jsp?NIS), weighted to produce national estimates. Rates through 2011 are weighted with trend weights, and rates 2012 and after are weighted using original NIS discharge weights to account for the change in NIS design in 2012.
§ Includes 30 states and the District of Columbia with publically available data. Availability of data ranged from 14 states in 1999 to 28 states in 2011.
¶ Estimated average annual change in the prevalence rate of opioid use disorder diagnoses per 1,000 delivery hospitalizations; all estimates were significant ($p<0.05$).
** Insufficient data (<3 years) to assess linear trend.

Excessive prescribing and challenges in accessing nonopioid treatments to control pain contribute to the rise in opioid use disorder. In an attempt to address prescribing rates, CDC supports maximizing and enhancing Prescription Drug Monitoring Programs, state-based databases that collect, monitor, and analyze controlled substance dispensing to detect risky prescribing practices and patient behaviors, such as multiple sources of prescriptions (*7*).

The 2016 CDC *Guideline for Prescribing Opioids for Chronic Pain* recommends that providers take an active role in combatting the opioid epidemic by considering opioid therapy for chronic pain only if expected benefits for pain and function are anticipated to outweigh risks (*8*). CDC and the American College of Obstetricians and Gynecologists (ACOG) guidelines recommend that before prescribing opioids for chronic pain, clinicians should ensure they are appropriate, review the Prescription Drug Monitoring Program, provide contraception counseling, and discuss risks of opioid use in pregnancy (*8*,*9*). ACOG recommends universal substance use screening at the first prenatal visit to manage opioid use disorder (*9*). If a patient has opioid use disorder, clinicians should prescribe medication-assisted therapy when possible and appropriate (*8*,*9*). Pregnant

FIGURE 1. National prevalence of opioid use disorder per 1,000 delivery hospitalizations* — National Inpatient Sample (NIS),† Healthcare Cost and Utilization Project (HCUP), United States, 1999–2014



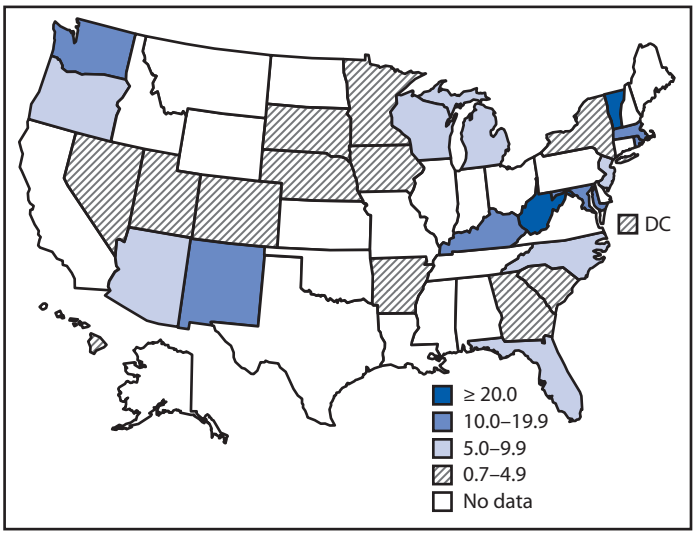
* Prevalence numerator consisted of cases of opioid type dependence and nondependent opioid abuse based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes (304.00–304.03, 304.70–304.73, 305.50–305.53), and denominator consisted of delivery hospitalization discharges.
† Includes data from all states participating in HCUP each year (https://www.hcup-us.ahrq.gov/partners.jsp?NIS), weighted to produce national estimates. Rates before 2012 are weighted with trend weights, and rates after 2012 are weighted using original NIS discharge weights to account for the change in NIS design in 2012.

women with opioid use disorder involving heroin might require referral to harm reduction services (e.g., comprehensive syringe services). Arranging for pregnant patients with opioid use disorder to deliver at facilities prepared to monitor and care for infants with neonatal abstinence syndrome can facilitate access to appropriate care (*8*,*9*). After delivery, women might need referrals to postpartum psychosocial support services, substance-use treatment, and relapse-prevention programs (*8*).

Differing state policies might contribute to the state-to-state variability in opioid use disorder diagnosis. As of July 2018, eight states require health care professionals to test for prenatal drug exposure if it is suspected, and 24 states and DC require the reporting of suspected use (*10*). In addition, 23 states and DC consider substance use during pregnancy to be child abuse under child-welfare statutes, and three consider it grounds for civil commitment, which might result in women concealing substance use from their providers (*10*). However, data on the impact of these policies are scarce.

The findings in this report are subject to at least five limitations. First, not all states provide data to the public-use SID database. Within the data provided, not all hospitals participated; however, at least 80% of births reported to CDC's National Center for Health Statistics are represented for each state.§ For the NIS, 2014 data were sampled from 45 states

FIGURE 2. Prevalence of opioid use disorder per 1,000 delivery hospitalizations* — State Inpatient Database, Healthcare Cost and Utilization Project, 28 states, 2013–2014†



* Prevalence numerator consisted of opioid type dependence and nondependent opioid abuse based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes (304.00–304.03, 304.70–304.73, 305.50–305.53), and denominator consisted of state delivery hospitalization discharges.
† Prevalence reported are for 2014, except for two states (Massachusetts and South Carolina) for which 2014 data were not available; 2013 data are reported for these states.

§ https://wonder.cdc.gov/natality.html.

Summary

What is already known about this topic?

National rates of opioid use disorder are increasing among reproductive-aged and pregnant women, and opioid use during pregnancy is associated with adverse maternal and neonatal outcomes.

What is added by this report?

National opioid use disorder rates at delivery more than quadrupled during 1999–2014. Rates significantly increased in all 28 states with 3 years of data. Rate increases in Maine, New Mexico, Vermont, and West Virginia exceeded 2.5 per 1,000 deliveries per year. In 2014, rates ranged from 0.7 (District of Columbia) to 48.6 (Vermont).

What are the implications for public health practice?

National, state, and provider efforts are needed to prevent, monitor, and treat opioid use disorder among reproductive-aged and pregnant women.

that include 94% of U.S. community hospital discharges. Second, analysis includes all hospital deliveries, regardless of the mother's state of residency. Thus, results can only be interpreted for delivery hospitalizations in each state, which might not reflect trends among residents, although the sensitivity analysis revealed no large differences in rates by resident status. Third, results might not be generalizable to births that occurred outside of a hospital; these represent only 1.5% of all births.[¶] Fourth, opioid use disorder might be underreported in this analysis; documentation of opioid use disorder at delivery hospitalization might not reflect diagnoses at other points in the pregnancy. Although universal verbal screening for substance use is recommended by ACOG (*9*), it is often not standard practice, which can lead to underestimates. Fifth, these data are ICD-code–dependent, limiting the ability to differentiate the source of opioid use disorder. The accuracy of codes might vary by hospital and state, leading to misreporting of opioid use disorder.

This first multistate analysis of opioid use disorder among delivery hospitalizations can be used by states to monitor the prevalence of opioid use disorder at delivery hospitalizations. There is continued need for national, state, and provider efforts to prevent, monitor, and treat opioid use disorder among reproductive-aged and pregnant women.

[¶] https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_12.pdf.

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Conflict of Interest

No conflicts of interest were reported.

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Naloxone Administration Frequency During Emergency Medical Service Events — United States, 2012–2016

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As the opioid epidemic in the United States has continued since the early 2000s (*1*,*2*), most descriptions have focused on misuse and deaths. Increased cooperation with state and local partners has enabled more rapid and comprehensive surveillance of nonfatal opioid overdoses (*3*).* Naloxone administrations obtained from emergency medical services (EMS) patient care records have served as a useful proxy for overdose surveillance in individual communities and might be a previously unused data source to describe the opioid epidemic, including fatal and nonfatal events, on a national level (*4*–*6*). Using data from the National Emergency Medical Services Information System (NEMSIS),† the trend in rate of EMS naloxone administration events from 2012 to 2016 was compared with opioid overdose mortality rates from National Vital Statistics System multiple cause-of-death mortality files. During 2012–2016, the rate of EMS naloxone administration events increased 75.1%, from 573.6 to 1004.4 administrations per 100,000 EMS events, mirroring the 79.7% increase in opioid overdose mortality from 7.4 deaths per 100,000 persons to 13.3. A bimodal age distribution of patients receiving naloxone from EMS parallels a similar age distribution of deaths, with persons aged 25–34 years and 45–54 years most affected. However, an accurate estimate of the complete injury burden of the opioid epidemic requires assessing nonfatal overdoses in addition to deaths. Evaluating and monitoring nonfatal overdose events via the novel approach of using EMS data might assist in the development of timely interventions to address the evolving opioid crisis.

NEMSIS Public Release Research data sets from 2012 through 2016 were used for this analysis. Approximately 10,000 EMS agencies and 49 U.S. states and territories contribute data to the NEMSIS National EMS Database, resulting in a national convenience sample of EMS events (*7*). EMS naloxone administration events were defined as the administration of at least 1 naloxone dose during EMS patient care. EMS events for this evaluation included 9-1-1 responses, responses during special event coverage, and provision of care by EMS crew in an ambulance intercept§ or during mutual aid to another ambulance response.¶ Those events in which opioid analgesics were administered by EMS, where no patient was found by the responding EMS crew, or where the event was a medical transport or interfacility transfer were excluded. Because the focus of this evaluation was on rates of naloxone administration events as a proxy to opioid overdoses, rather than severity of overdoses, multiple naloxone dosing was not considered. Administration of naloxone by EMS is the standard of care for many EMS systems in the prehospital setting for patients in cardiac arrest and those who are unconscious. Thus, recognizing that not all naloxone administrations by EMS represent actual opioid overdoses, a subanalysis of suspected overdoses, defined as the subset of EMS events with naloxone administration and documented evidence of drug ingestion/poisoning,** was conducted to obtain the potential range of actual opioid overdoses treated by EMS. The primary outcome examined was the annual rate of naloxone administration per 100,000 EMS events with a secondary analysis of trends in patient characteristics. Chi-squared tests of linear trend were used to compare data across the 5 yearly time points (2012 to 2016) along with the percent increase over this period.

The estimated rate of EMS naloxone administration was compared with opioid overdose mortality rates reported in CDC's National Vital Statistics System multiple cause-of-death mortality files during 2012–2016.†† Following the methodology used in past work used to describe drug overdose mortality (*2*), opioid-involved deaths during the study period, with

* https://www.cdc.gov/drugoverdose/foa/state-opioid-mm.html.
† https://nemsis.org/.
§ Ambulance intercepts occur when one EMS provider meets a transporting EMS unit with the intent of receiving a patient or providing a higher level of care. https://nemsis.org/media/nemsis_v2/documents/Data_Managers_Council_-_Data_Definitions_Project_Final_Ve..pdf.

¶ All EMS events in the NEMSIS Public Release Research Dataset for the years 2012 through 2016 were included in the study population. Naloxone administration was ascertained by "Medication Given (NEMSIS data element E18_03) = Naloxone or Naloxone Hydrochloride." EMS patients who were administered an opioid analgesic (morphine, morphine sulfate, fentanyl, hydromorphone, or hydromorphone hydrochloride) by EMS and subsequently administered naloxone were not included. Events were included if the variable "Type of Service Requested (E02_04)" was "9-1-1 Response," and response options were the following: "Scene (field value = 30)," "Intercept (35)," "Mutual Aid (50)," and "Standby (55)," excluding events with "Interfacility Transfer (40)" or "Medical Transport (45)." Events with "Incident/Patient Disposition (E20_10)" field values of "Cancelled (4815)" or "No Patient Found (4825)" and those that occurred in the U.S. territories of Guam (66) and the U.S. Virgin Islands (78) identified under "EMS Agency State (D01_03)," were also excluded from the study population.
** EMS records were included if any of the following were documented as drug ingestion, poisoning, or overdose: "complaint reported by dispatch (E03_01, field value = 510)," "EMS provider's primary impression (E09_15, 1690)," "EMS provider's secondary impression (E09_16, 1825)," and "cause of injury (E10_01, 9530)."
†† https://wonder.cdc.gov/.

underlying causes of death related to poisoning with a multiple cause of death involving opioids, were queried by year.[§§]

From 2012 to 2016, a stepwise increase occurred in the number of EMS events with naloxone administration (Table 1). The increase persisted in the subset of suspected overdoses, EMS naloxone administrations with documented evidence of a drug ingestion/poisoning (Table 2). During 2012–2016, the rate of naloxone administration events overall increased 75.1%, from 573.6 to 1,004.4 administrations per 100,000 EMS events (Table 2), and the rate of naloxone administration in suspected overdoses increased 119.0%, from 230.6 to 505.2. Concomitant with the increase in naloxone administration rates was a 79.7% increase in age-adjusted opioid mortality rate, from 7.4 deaths per 100,000 persons in 2012 to 13.3 in 2016 (Table 2).

A bimodal distribution was observed in the age groups of patients who received naloxone during EMS events, with modes at ages 25–34 years and 45–54 years (Table 1) (Figure). In 2012, a larger proportion of naloxone administration events occurred among persons aged 45–54 years (19.8%, 18,049) than among persons aged 25–34 years (17.2%, 15,686, p<0.001). By 2016, this finding had reversed, and a larger proportion of naloxone administration events occurred among persons aged 25–34 years (21.2%, 35,179) than among persons aged 45–54 years (17.7%, 29,491, p<0.001). A similar bimodal age distribution was also identified in opioid overdose deaths from 2012 to 2016, mirroring the two modes observed in EMS data (Figure).

[§§] To obtain estimates of opioid-involved deaths from the Multiple Cause of Death Data (https://wonder.cdc.gov), the *International Classification of Disease, Tenth Revision* (ICD-10) codes of X40–X44, X60–X64, X85, and Y10–Y14 were used for underlying cause of death and ICD-10 codes of T40.0, T40.1, T40.2, T40.3, T40.4, and T40.6 were used for multiple cause of death.

Discussion

This cross-sectional evaluation of the large NEMSIS Public Release Research data sets from 2012 to 2016 demonstrated that the increase in the rate of all naloxone administration by EMS parallels the increase in rate of fatal opioid overdoses. As proposed, examining naloxone administrations by EMS professionals might be a useful and timely tool to gauge the comprehensive prevalence of opioid overdoses, including those that do not end in a fatal event. EMS data regarding naloxone administration can be used by health care organizations and communities to benchmark the performance of interventions over time and compare with national averages, as well as assist in the development of timely interventions.

This analysis also demonstrated a bimodal age distribution in both naloxone administrations by EMS and opioid overdose deaths. Further, a trend of increasing naloxone administrations and deaths in younger persons (aged 25–34 years) was observed. The reasons for these findings are difficult to discern from these data. Whereas efforts have been increased to control access to and misuse of prescription opioid pain relievers, use of

TABLE 1. Patient demographics for emergency medical services (EMS) event records with documented administration of naloxone — United States, 2012– 2016

Characteristic	Year, no. (%) 2012 (N = 91,853)	2013 (N = 108,957)	2014 (N = 123,400)	2015 (N = 167,182)	2016 (N = 207,584)	P–value*
Suspected overdose[†]	36,933 (40.2)	45,002 (41.3)	53,601 (43.4)	79,611 (47.6)	104,412 (50.3)	<0.001
Age group (yrs)						
0–14	628 (0.7)	605 (0.6)	718 (0.6)	859 (0.5)	1,080 (0.5)	<0.001
15–24	11,715 (12.8)	13,159 (12.1)	14,350 (11.7)	19,759 (11.9)	23,135 (11.2)	
25–34	15,686 (17.2)	18,955 (17.5)	22,947 (18.7)	35,179 (21.2)	47,411 (23.0)	
35–44	13,910 (15.2)	16,190 (14.9)	18,325 (14.9)	25,929 (15.6)	33,979 (16.5)	
45–54	18,049 (19.8)	20,815 (19.2)	22,812 (18.6)	29,491 (17.7)	36,333 (17.6)	
55–64	14,014 (15.3)	17,557 (16.2)	19,930 (16.2)	26,366 (15.9)	32,439 (15.7)	
65–74	7,808 (8.5)	9,856 (9.1)	11,380 (9.3)	14,271 (8.6)	16,431 (8.0)	
≥75	9,575 (10.5)	11,341 (10.5)	12,344 (10.1)	14,463 (8.7)	15,684 (7.6)	
Male	49,343 (54.0)	59,492 (54.9)	69,564 (56.7)	97,542 (58.6)	126,600 (61.3)	<0.001
Race						
White	57,438 (78.0)	65,786 (76.2)	73,257 (75.6)	96,625 (75.0)	112,277 (72.0)	<0.001
Black	11,062 (15.0)	14,639 (17.0)	17,018 (17.6)	23,660 (18.4)	33,338 (21.4)	
Other[§]	5,182 (7.0)	5,871 (6.8)	6,680 (6.9)	8,618 (6.7)	10,370 (6.7)	

Source: National Emergency Medical Services Information System (https://nemsis.org/), 2012–2016.
* Nonparametric test of trend.
[†] EMS records were included if any of the following were documented as drug ingestion, poisoning, or overdose: complaint reported by dispatch (E03_01, field value 510), EMS provider's primary impression (E09_15, field value 1690), EMS provider's secondary impression (E09_16, field value 1825), and cause of injury (E10_01, field value 9530).
[§] American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, other/unknown.

TABLE 2. Rates of emergency medical services (EMS) naloxone administration events and opioid overdose deaths — National EMS Information System (NEMSIS) and CDC National Vital Statistics System, United States, 2012–2016*

Year	NEMSIS† EMS naloxone administration events rate (95% CI)		CDC¶ opioid-involved death rate (95% CI)
	Overall	Suspected opioid§	
2012	573.6 (569.9–577.3)	230.6 (228.3–233.0)	7.4 (7.3–7.5)
2013	666.0 (662.0–669.9)	275.1 (272.5–277.6)	7.9 (7.8–8.0)
2014	691.3 (687.4–695.1)	300.3 (297.7–302.8)	9.0 (8.9–9.1)
2015	805.1 (801.3–809.0)	383.4 (380.7–386.1)	10.4 (10.3–10.5)
2016	1,004.4 (1,000.1–1,008.7)	505.2 (502.1–508.3)	13.3 (13.2–13.4)
% Change**	75.1	119.0	79.7

Abbreviation: CI = confidence interval.

* Naloxone administration event rate expressed as rate per 100,000 EMS events; age-adjusted mortality rate expressed per 100,000 persons.

† Per 100,000 EMS events. Data from NEMSIS (https://nemsis.org/), 2012–2016.

§ EMS records were included if any of the following were documented as drug ingestion, poisoning, or overdose: complaint reported by dispatch (E03_01, field value 510), EMS provider's primary impression (E09_15, field value 1690), EMS provider's secondary impression (E09_16, field value 1825), and cause of injury (E10_01, field value 9530).

¶ Per 100,000 population. Data from CDC's National Vital Statistics System, Multiple Cause of Death Data, 2012–2016; CDC WONDER (https://wonder.cdc.gov). To obtain estimates of opioid-involved deaths from the Multiple Cause of Death Data see https://wonder.cdc.gov; *International Classification of Disease, Tenth Revision* (ICD-10) codes X40–X44, X60–X64, X85, and Y10–Y14 were used for underlying cause of death and ICD-10 codes T40.0, T40.1, T40.2, T40.3, T40.4, and T40.6 were used for multiple cause of death.

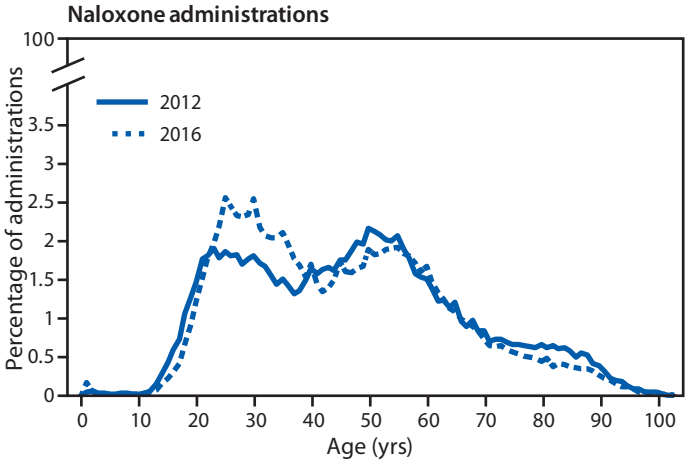
** Percent change calculated from 2012 to 2016.

illicit opioids such as fentanyl is increasing (*8*,*9*). Use of heroin and illicitly manufactured fentanyl is associated with younger age groups (*9*,*10*). This change from misuse of prescription opioid pain relievers to highly potent illicit opioids offers a plausible explanation for the increased prevalence of naloxone administration by EMS and deaths in the younger age group. However, rates of drug overdose deaths have increased in all age groups, with convergence of these rates for those aged 25–34, 35–44, and 45–54 years.¶¶ As this prevalence of disease changes, there is a potential impact on years of life lost caused by opioid overdose in the United States.

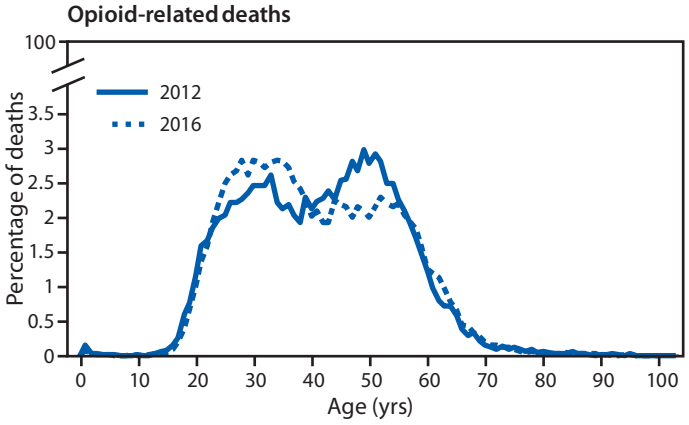
The novel use of EMS naloxone administration data to examine nonfatal overdoses, in conjunction with mortality and emergency department data (*3*), provides a more robust picture of the burden of injury for opioid overdose epidemic. The overall rate of naloxone administration increased by 75.1% from 2012 to 2016. In the subgroup analysis of suspected overdose events, the increase was even higher (119.0%), suggesting that EMS providers are increasingly more likely to administer naloxone in borderline cases. Because these patients represent a population still at risk for overdose and death, more work is needed to understand nonfatal overdose events.

¶¶ https://www.cdc.gov/nchs/products/databriefs/db294.htm.

FIGURE. Percentage of emergency medical services naloxone administrations and percentage of opioid-related deaths, by age — United States, 2012 and 2016



Source: National Emergency Medical Services Information System, 2012 and 2016.



Source: Multiple Cause of Death Data, 2016, National Vital Statistics System, CDC.

The findings in this report are subject to at least five limitations. First, this analysis focused on naloxone administered by EMS personnel in a large convenience sample of EMS records. The accuracy and completeness of data entered into the NEMSIS Public Release Research data set are dependent on correct and thorough entries by EMS personnel. The accuracy of these data are unknown, limiting the ability to assess the rate of naloxone use by laypersons and non-EMS personnel. Second, naloxone use by laypersons or other first responders, including law enforcement, without activation of the EMS system is not reflected in these data sets. Third, variations in EMS record documentation submitted to the NEMSIS National EMS Database might present a potential misclassification bias. Fourth, because these data were deidentified, it was not possible to assess naloxone administration over repeated events. Although the increased use of potent illicit opioids has

Summary

What is already known about this topic?

Naloxone administration data from emergency medical services (EMS) records have been used for surveillance for opioid overdoses on a local level.

What is added by this report?

Analysis of a national database of EMS events found that from 2012 to 2016, the rate of naloxone administrations increased 75.1%, from 573.6 to 1004.4 per 100,000 EMS events, mirroring a 79.7% increase in the age-adjusted opioid mortality rate.

What are the implications for public health practice?

Monitoring nonfatal overdose events using EMS records provides a more complete evaluation of the potential injury burden and a means of benchmarking for communities and EMS agencies to better address the evolving opioid epidemic.

resulted in multiple naloxone administrations during many EMS events (*6*), multiple naloxone administrations and dosages of naloxone given by EMS were not assessed. Finally, because this was a secondary analysis of cross-sectional data, causality cannot be inferred.

Evaluating and monitoring nonfatal overdose events might assist in the development of more timely emergency response interventions, more naloxone administrations in suspected drug overdose cases, and referral to treatment and care coordination. EMS agencies and their communities can also compare naloxone administrations with national benchmarks to evaluate the effectiveness of interventions. EMS data are useful for identifying populations at risk, such as those surviving an opioid overdose, and could assist in meeting the challenge of decreasing the mortality impact of the opioid epidemic. Further, these results support widening the scope of discussion concerning opioid epidemic overdoses and demonstrate the importance of EMS providers in providing a more complete evaluation of opioid overdose injury burden in the United States.

Conflict of Interest

No conflicts of interest were reported.

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Extrapulmonary Nontuberculous Mycobacterial Disease Surveillance — Oregon, 2014–2016

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Nontuberculous mycobacteria (NTM), ubiquitous in soil and water, usually infect immunocompromised persons. However, even healthy persons are susceptible to infection through percutaneous inoculation. Although 77% of NTM diseases manifest as primarily pulmonary illnesses (*1*), NTM also infect skin, bones, joints, the lymphatic system, and soft tissue. NTM infections can have incubation periods that exceed 5 years (*2*), often require prolonged treatment, and can lead to sepsis and death. Extrapulmonary NTM outbreaks have been reported in association with contaminated surgical gentian violet (*3*), nail salon pedicures (*4*), and tattoos received at tattoo parlors (*5*), although few surveillance data have been available for estimating the public health burden of NTM.* On January 1, 2014, the Oregon Health Authority designated extrapulmonary NTM disease a reportable condition. To characterize extrapulmonary NTM infection, estimate resources required for surveillance, and assess the usefulness of surveillance in outbreak detection and investigation, 2014–2016 extrapulmonary NTM surveillance data were reviewed, and interviews with stakeholders were conducted. During 2014–2016, 134 extrapulmonary NTM cases (11 per 1 million persons per year) were reported in Oregon. The age distribution was bimodal, with highest incidence among persons aged <10 years (20 per 1 million persons per year) and persons aged 60–69 years (18 per 1 million persons per year). The most frequently reported predisposing factors (occurring within 14–70 days of symptom onset) were soil exposure (41/98; 42%), immunocompromised condition (42/124; 34%), and surgery (32/120; 27%). Overall, 43 (33%) patients were hospitalized, 18 (15%) developed sepsis, and one (0.7%) died. Surveillance detected or helped to control two outbreaks at low cost. Jurisdictions interested in implementing extrapulmonary NTM surveillance can use the Council of State and Territorial Epidemiologists (CSTE) standardized case definition (*6*) for extrapulmonary NTM reporting or investigative guidelines maintained by the Oregon Health Authority (*7*).

In Oregon, electronic laboratory reports of reportable diseases are uploaded daily to the statewide communicable disease database, the Oregon Public Health Epidemiologists' User System (Orpheus). Staff members from the patients' local public health jurisdiction investigate extrapulmonary NTM cases by collecting clinical data and information on any predisposing factors occurring during the 14–70 days preceding symptom onset from medical charts and patient interviews, then enter the data into Orpheus. An epidemiologist reviews case data for quality and completeness and generates annual state infectious disease epidemiology reports. The Oregon Health Authority does not require laboratories to retain extrapulmonary NTM isolates.

For this analysis, a case of extrapulmonary NTM was defined (according to Oregon Health Authority investigative guidelines at the time) as a culture-confirmed extrapulmonary NTM infection involving skin or soft tissue from a wound or abscess, lymphatic tissue, urine, or other normally sterile site (e.g., blood or spinal fluid), in an Oregon resident, with the first specimen collected during January 1, 2014–December 31, 2016, and extrapulmonary NTM symptom onset after December 31, 2012. Cultures that were positive only for *Mycobacterium gordonae*, a common environmental contaminant, were excluded. Patient demographics and predisposing factors (prespecified by literature review and expert opinion) were described, and incidence was calculated using 2014–2016 Oregon population estimates from the Portland State University Population Research Center. Resource requirement estimates were developed through interviews with stakeholders, including the Oregon Health Authority epidemiologist whose assignments include extrapulmonary NTM surveillance, the informatics programmer, and three local public health nurses who estimated public health personnel time to perform extrapulmonary NTM surveillance. The utility assessment consisted of a review of how extrapulmonary NTM surveillance data were used to identify or investigate outbreaks.

Characteristics of Extrapulmonary NTM Cases

During 2014–2016, a total of 134 extrapulmonary NTM cases were reported in Oregon (11 per 1 million persons per year). Patients ranged in age from 10 months to 92 years (median age = 50.8 years). Seventy (52%) patients were female, 96 (72%) were white, 43 (33%) were hospitalized, 18 (15%) developed sepsis, and one (1%) died. Among patients for whom exposure risk factors were reported, the most frequently reported predisposing factors were soil exposure (41/98; 42%), immunocompromised condition (42/124; 34%), and surgery (32/120; 27%). Approximately two thirds of patients (68%) reported more than one predisposing factor (Table 1).

* https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.201611-860OC.

TABLE 1. Characteristics, clinical outcomes, and predisposing factors for 134 cases of extrapulmonary nontuberculous mycobacteria (NTM) infections — Oregon, 2014–2016

Characteristic	No. (%)
Total cases 2014–2016	**134 (100)**
2014	45 (34)
2015	44 (33)
2016	45 (34)
Sex	
Female	70 (52)
Male	64 (48)
Race	
White	96 (72)
Asian/Pacific Islander	9 (7)
Other or multiple	6 (4)
Black	2 (1)
American Indian/Alaska Native	1 (1)
Unknown	20 (15)
Ethnicity	
Non-Hispanic	96 (72)
Hispanic	12 (9)
Unknown	26 (19)
Outcome	
Hospitalized (130)	43 (33)
Sepsis (123)	18 (15)
NTM-related death	1 (1)
Predisposing factor*	
Worked with potting soil (98)	41 (42)
Immunocompromised (124)	42 (34)
Surgery (120)	32 (27)
Outpatient infusions or injections (110)	24 (22)
Skin trauma (107)	21 (20)
Immunosuppressive therapy (120)	23 (19)
Hot tub or spa use (104)	16 (15)
Acupuncture (106)	13 (12)
Fish tank maintenance (104)	9 (9)
Nail salon visit (103)	7 (7)
Fish handling (105)	6 (6)
Tattoo receipt (108)	2 (2)
>1 Predisposing factor† (124)	84 (68)

* 14–70 days before symptom onset.
† Denominator for >1 predisposing factor row is the total number of patients who responded to at least two questions.

A bimodal age distribution was observed, with highest number of cases and the highest incidence among persons aged 0–9 years (20 per 1 million persons per year) and persons aged 60–69 years (18 per 1 million persons per year) (Table 2). Among 29 infections in patients aged 0–9 years, 25 (86%) were caused by *Mycobacterium avium* complex. Among 26 infections in patients aged 60–69 years, six (23%) were caused by *Mycobacterium avium* complex. The remainder of cases in this age group primarily was caused by either *M. chelonae* or *M. abscessus* (nine; 35%) or *M. fortuitum* (six; 23%) (Figure).

Among persons aged 0–9 years, 76% had infected lymph nodes, compared with 4% among persons aged 60–69 years. The latter age group's most common specimen sources were tissue (31%) (not further specified), wounds (19%), blood (12%), and joints (12%).

TABLE 2. Number of extrapulmonary nontuberculous mycobacteria (NTM) cases and incidence, by year and age groups — Oregon, 2014–2016

Year/Age group	No. of cases	Cases per 1 million persons per year
Overall	**134**	**11**
Year		
2014	45	11
2015	44	11
2016	45	11
Age group (yrs)		
0–9	29	20
10–19	2	1
20–29	3	2
30–39	10	6
40–49	21	13
50–59	26	16
60–69	26	18
70–79	13	16
80–99	4	8

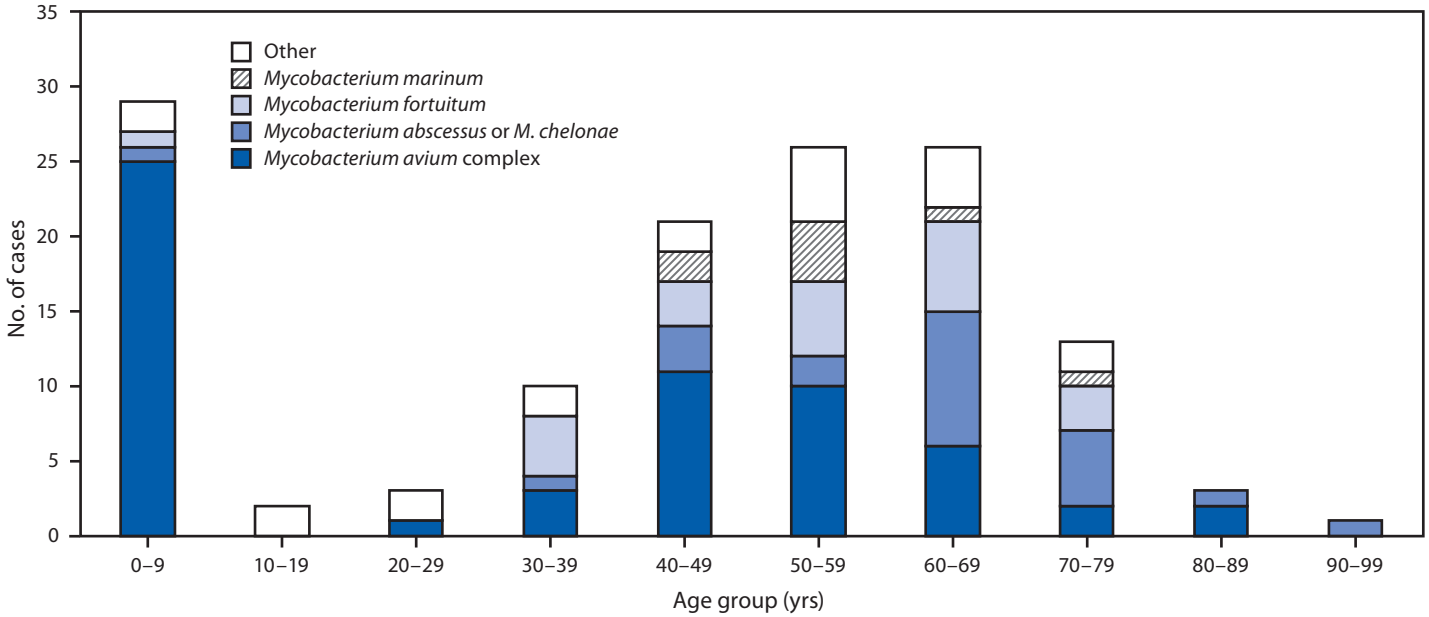
Detection and Management of Extrapulmonary NTM Outbreaks

An outbreak of seven *M. fortuitum* infections in two small neighboring counties was initially reported by hospital staff members after the outbreak had begun in July 2013 and before mandatory reporting had commenced in January 2014. The outbreak was associated with knee and hip replacement procedures during 2013–2014, a single device manufacturer, and multiple hospitals and operating room staff members. The investigation began 102 days after the second confirmed laboratory report became available. Intraoperative risks identified included suboptimal surgical infection control practices. The presence of a single device manufacturer representative† at six of the seven surgical procedures was associated with NTM surgical site infection. Oregon Health Authority received no reports of cases of *M. fortuitum* infections among joint replacement patients beyond the two counties. Public health officials recommended that all operating room staff members adhere to the Association of Perioperative Registered Nurses infection control guidelines.

During 2015, two *M. haemophilum* infections were reported to a local health department; both involved receipt of tattoos at the same tattoo parlor. The outbreak investigation began 33 days after the second confirmed laboratory report became available. The tattoo artist used water from a cooler to dilute ink and wipe tattoos during their placement. After public health officials recommended using sterile water, no additional extrapulmonary NTM infections were associated with the parlor.

† Because of prosthetic joints' complexity, device manufacturer representatives commonly attend and advise the surgeon during joint replacement surgeries.

FIGURE. Nontuberculous mycobacteria (NTM) species identified in cases with extrapulmonary NTM infections, by age group — Oregon, 2014–2016



Costs of Establishment and Maintenance of Extrapulmonary NTM Surveillance

All estimated costs related to extrapulmonary NTM surveillance were for salaries. Local health department nurses reported spending approximately 90 minutes investigating each case. Incremental direct costs to add extrapulmonary NTM to public health notifiable disease surveillance were approximately $6,000 for implementation and approximately $10,000 in annual operating costs.

Discussion

During 2005–2006, an analysis of Oregon laboratory data reported an annual extrapulmonary NTM infection prevalence of 16 cases per 1 million persons (*1*); however, clinical data were insufficient to characterize disease burden, and the authors reported only prevalence, not incidence data. In January 2014, extrapulmonary NTM infections became reportable in Oregon. Although extrapulmonary NTM infections are rare, they can be associated with substantial severity, including hospitalization, sepsis, and death. Costs to set up and maintain the surveillance system were minimal. Limited time was needed to investigate each case, case counts were few, and existing electronic reporting infrastructure minimized laboratory reporting costs.

In Oregon, extrapulmonary NTM surveillance detected outbreaks, augmented case finding, and guided subsequent control measures. Surveillance aided the outbreak investigation among joint replacement patients; the lack of cases reported elsewhere in the state argued against widespread product contamination during manufacturing. That is, because NTM was reportable in Oregon, surveillance would have identified extrapulmonary NTM infections among joint replacement patients in other counties if a production site contaminated the products. Surveillance for extrapulmonary NTM infections also detected the outbreak among tattoo parlor patrons who lacked a common health care provider who might have recognized a pattern and reported the outbreak. Time to investigation of the tattoo parlor–associated outbreak was 69 days shorter than the time to investigate the previous outbreak that began before mandatory extrapulmonary NTM reporting. If the outbreak among joint replacement patients had occurred when reporting and surveillance procedures were established, the investigation might have begun sooner.

Detection of extrapulmonary NTM outbreaks can be delayed if the condition is not reportable. For example, NTM is not reportable in Georgia. Investigation of an outbreak of extrapulmonary *M. abscessus* infections after dental pulpotomy in Georgia commenced approximately 1 year after the second case was diagnosed; 20 cases among children were ultimately identified (*8*) (Melissa Tobin-D'Angelo, Georgia Department of Public Health, personal communication, June 2018).

It is important for clinicians to be aware of the possibility of an NTM outbreak because they can help identify extrapulmonary NTM outbreaks. In 2013, a clinician reporting two extrapulmonary NTM cases among medical tourists led to detection of an NTM outbreak traced to cosmetic surgery centers in the Dominican Republic; subsequent case finding identified outbreak cases from four other states (*9*,*10*). Extrapulmonary

Summary

What is already known about this topic?

Nontuberculous mycobacteria (NTM) infections can cause serious morbidity, especially in health care–associated infections and outbreaks.

What is added by this report?

Oregon instituted mandatory extrapulmonary NTM reporting in January 2014. During 2014–2016, 134 cases were reported (11 cases per 1 million persons per year), including 43 hospitalizations, 18 patients with sepsis, and one death. The surveillance system helped detect or control two outbreaks at low cost.

What are the implications for public health practice?

Publicly available resources (e.g., the Council of State and Territorial Epidemiologists case definition, Oregon's investigative guidelines, and the Oregon case report form) offer states and territories adaptable tools to implement surveillance for extrapulmonary NTM infections.

NTM surveillance could enhance detection and identification of the source of multijurisdictional outbreaks. Contaminated cardiopulmonary bypass heater-cooler devices have caused a large, ongoing international outbreak of *M. chimaera* infections among cardiac surgery patients (*2*). Long incubation periods complicated detection of this outbreak. Systematic extrapulmonary NTM surveillance in other states and countries might have led to earlier detection.

The findings in this report are subject to at least three limitations. First, the routinely asked predisposing factor questions did not specify whether a particular factor (e.g., surgery) involved the infection site, which could have resulted in overestimates of that factor's impact. In January 2018, the case report form was revised to address this issue. Second, sensitivity of extrapulmonary NTM surveillance might be limited because clinicians might not suspect extrapulmonary NTM infection and, consequently, might not order cultures for mycobacteria. Finally, these data only represent cases diagnosed in Oregon during 2014–2016 and are not generalizable to other states because of different population characteristics, predisposing factor rates, and adoption of electronic laboratory reporting.

To promote nationwide extrapulmonary NTM surveillance, CSTE developed a standardized case definition for extrapulmonary NTM surveillance (*6*). State and territorial public health authorities can use this case definition to ensure compatible surveillance across jurisdictions. In addition, the Oregon Health Authority improved its investigative guidelines and case report form by making the predisposing factor questions body-site specific. Forms are publicly available for states and territories to adapt for extrapulmonary NTM surveillance implementation (*7*). NTM surveillance is ongoing in Oregon.

Extrapulmonary NTM infections cause considerable morbidity, sometimes resulting in hospitalization or sepsis, in Oregon. Systematic reporting of these infections has led to detection and control of outbreaks at relatively low cost. Publicly available resources (e.g., the CSTE case definition, Oregon's investigative guidelines, and the Oregon case report form) offer states and territories adaptable tools to implement extrapulmonary NTM surveillance.

Conflict of Interest

No conflicts of interest were reported.

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Vital Signs: Zika-Associated Birth Defects and Neurodevelopmental Abnormalities Possibly Associated with Congenital Zika Virus Infection — U.S. Territories and Freely Associated States, 2018

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Abstract

Introduction: Zika virus infection during pregnancy causes serious birth defects and might be associated with neurodevelopmental abnormalities in children. Early identification of and intervention for neurodevelopmental problems can improve cognitive, social, and behavioral functioning.

Methods: Pregnancies with laboratory evidence of confirmed or possible Zika virus infection and infants resulting from these pregnancies are included in the U.S. Zika Pregnancy and Infant Registry (USZPIR) and followed through active surveillance methods. This report includes data on children aged ≥1 year born in U.S. territories and freely associated states. Receipt of reported follow-up care was assessed, and data were reviewed to identify Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection.

Results: Among 1,450 children of mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy and with reported follow-up care, 76% had developmental screening or evaluation, 60% had postnatal neuroimaging, 48% had automated auditory brainstem response-based hearing screen or evaluation, and 36% had an ophthalmologic evaluation. Among evaluated children, 6% had at least one Zika-associated birth defect identified, 9% had at least one neurodevelopmental abnormality possibly associated with congenital Zika virus infection identified, and 1% had both.

Conclusion: One in seven evaluated children had a Zika-associated birth defect, a neurodevelopmental abnormality possibly associated with congenital Zika virus infection, or both reported to the USZPIR. Given that most children did not have evidence of all recommended evaluations, additional anomalies might not have been identified. Careful monitoring and evaluation of children born to mothers with evidence of Zika virus infection during pregnancy is essential for ensuring early detection of possible disabilities and early referral to intervention services.

Introduction

Zika virus infection during pregnancy can cause serious birth defects, including structural abnormalities of the brain and eye (*1*–*7*). As infants with congenital Zika virus infection get older, problems such as epilepsy, vision loss, and developmental delays have been increasingly recognized (*8*). Early identification of and intervention for adverse neurodevelopmental outcomes have been determined to improve cognitive, social, and behavioral functioning and to be cost effective to society in general (*9*–*12*).

The most critical time to intervene and promote optimal brain development is during the first 3 years of life (*9*). To facilitate early identification and intervention, CDC released clinical guidance for the evaluation and management of infants with possible congenital Zika virus infection in January 2016 (*13*). The guidance was based largely on existing guidelines for pediatric health promotion and care (*14*); expert opinion was incorporated from clinicians and researchers with knowledge of congenital infections and of clinical care of infants

with birth defects as described in early reports (*15*–*18*). Recommendations for the care and management of infants with possible congenital Zika virus exposure and infants with one or more clinical findings consistent with congenital Zika virus syndrome have remained largely unchanged through subsequent updates (*19*). Standard evaluation* at birth and during each well-child visit is recommended for all infants and young children with possible prenatal Zika virus exposure (*13*,*19*). Laboratory testing for Zika virus is recommended for infants born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy and for infants with one or more clinical findings consistent with congenital Zika syndrome born to mothers with possible Zika virus exposure, regardless of maternal testing results. In addition to a standard evaluation, infants born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy should have a cranial ultrasound or other brain imaging and a comprehensive ophthalmologic evaluation performed by age 1 month to detect subclinical brain and eye findings (*19*).

To better understand the effects of Zika virus infection during pregnancy on mothers and children from a national surveillance perspective, CDC collaborated with state, territorial, and local health departments on the U.S. Zika Pregnancy and Infant Registry (USZPIR)† to monitor pregnancy and infant/child outcomes among pregnancies with laboratory evidence of confirmed or possible Zika virus infection (www.cdc.gov/pregnancy/zika/research/registry.html). The USZPIR currently monitors outcomes of approximately 7,300 pregnancies, over 4,800 of which are reported from the U.S. territories and freely associated states§ (https://www.cdc.gov/pregnancy/zika/data/pregwomen-uscases.html). This report is the first to provide data on Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection identified during infancy and early childhood among children aged ≥1 year who were born in the U.S. territories and freely associated states.§

Methods

Pregnancies with laboratory evidence of confirmed or possible Zika virus infection¶ and infants resulting from these pregnancies are included in the USZPIR and followed through active surveillance methods (*6*). Data on birth defects and neurodevelopmental outcomes were abstracted from prenatal, birth hospitalization, pediatric, and specialty care medical records using standardized methods and reported to the USZPIR. CDC provided technical assistance to all U.S. territories and freely associated states that reported cases to the USZPIR through the Zika Local Health Department Initiative (https://www.cdc.gov/pregnancy/zika/research/lhdi.html) and the Epidemiology and Laboratory Capacity for Infectious Diseases Cooperative Agreement (https://www.cdc.gov/ncezid/dpei/epidemiology-laboratory-capacity.html). This report includes children who, among pregnancies reported to the USZPIR, 1) were born in U.S. territories or freely associated states; 2) had a date of birth on or before February 1, 2017, and reached age 1 year on or before February 1, 2018; and 3) had follow-up care reported to the USZPIR by June 1, 2018. For the purpose of this analysis, follow-up care was defined as clinical care at age >14 days reported to the USZPIR. Children from multiple gestation pregnancies were counted separately; infants who died during the first year of life were excluded.

Among children who met the definition for reported follow-up care, the percentages who were reported to have received each of the following types of clinical care or evaluations,

* Standard evaluation includes a comprehensive physical exam, including growth parameters; newborn hearing screen, preferably with automated auditory brainstem response (ABR); developmental monitoring and screening using validated screening tools recommended by the American Academy of Pediatrics (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Screening/Pages/Screening-Tools.aspx); and vision screening as recommended by the American Academy of Pediatrics Policy Statement "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians" (http://pediatrics.aappublications.org/content/137/1/e20153596). Infants should be referred for automated ABR by age 1 month if the newborn hearing screen was passed using only otoacoustic emissions methodology.

† The U.S. Zika Pregnancy and Infant Registry (USZPIR) refers to the Zika Pregnancy and Infant Registries implemented in all U.S. states, the District of Columbia, all U.S. territories, and U.S. freely associated states. The USZPIR is an enhanced surveillance system that collects data on pregnancy and infant/child outcomes in pregnancies with laboratory evidence of confirmed or possible Zika virus infection. In Puerto Rico, the USZPIR is also known as the Zika Active Pregnancy Surveillance System (ZAPSS). Children are followed through age 36 months in Puerto Rico and through age 24 months in other U.S. territories, freely associated states, and U.S. states.

§ U.S. territories and freely associated states reporting cases included American Samoa, Federated States of Micronesia, Marshall Islands, Puerto Rico, and the U.S. Virgin Islands.

¶ Maternal laboratory evidence of confirmed or possible Zika virus infection was defined as 1) Zika virus infection detected by a Zika virus RNA nucleic acid test (NAT) (e.g., reverse transcription–polymerase chain reaction [RT-PCR]) on any maternal, placental, fetal, or infant specimen (referred to as NAT-confirmed) or 2) detection of recent Zika virus infection or recent unspecified flavivirus infection by serologic tests on a maternal, fetal, or infant specimen (i.e., either positive or 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). Infants with positive or equivocal Zika virus IgM are included, provided a confirmatory PRNT has been performed on a maternal or infant specimen. The use of PRNT for confirmation of Zika virus infection, including in pregnant women and infants, is not routinely recommended in Puerto Rico; dengue virus is endemic and cross-reactivity is likely to occur in most cases (https://www.cdc.gov/zika/laboratories/lab-guidance.html). In Puerto Rico, detection of a positive Zika IgM result in a pregnant woman, fetus, or infant (within 48 hours after delivery) was considered sufficient to indicate possible Zika virus infection.

recommended in CDC clinical guidance, were calculated: 1) neuroimaging (cranial ultrasound, computed tomography, or magnetic resonance imaging) any time after birth; 2) hearing screen by automated auditory brainstem response (ABR) or audiologic evaluation by diagnostic ABR (ABR-based hearing screen or evaluation) any time after birth; 3) ophthalmologic evaluation any time after birth; 4) developmental screening or evaluation at age >14 days; and 5) physical examination, as indicated by reported growth parameters (head circumference, length, or weight) at age >14 days.

Data were reviewed by clinical subject matter experts to identify Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection (Box). Data for each child were reviewed by at least two reviewers; discrepant review findings were discussed among clinical subject matter experts to reach agreement. Although the category of neural tube defects and other early brain malformations was initially included in the surveillance case definition for Zika-associated birth defects, it was excluded in this report because of growing evidence suggesting a lack of association of these defects with congenital Zika virus infection (*6*,*20*). Postnatal-onset microcephaly detected during follow-up care is distinct from microcephaly detected at birth and is included among neurodevelopmental abnormalities possibly associated with congenital Zika virus infection (Box). Neurodevelopmental findings such as hearing loss, seizures, or swallowing abnormalities consistently documented in reports of infants with possible congenital Zika virus infection were specifically selected for inclusion; however, the broad range of neurodevelopmental abnormalities possibly associated with congenital Zika virus infection necessitates inclusion of less specific but more prevalent categories, such as possible developmental delay. The percentages of these adverse outcomes were calculated among all children born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy with reported follow-up care, as well as among the subset of children born to mothers with nucleic acid testing (NAT)–confirmed infection during pregnancy, with reported follow-up care.

A sensitivity analysis to address the concern about possible misclassification of microcephaly at birth** was performed by excluding infants with a birth head circumference measurement indicating microcephaly and no other Zika-associated birth defects, who subsequently had normal neuroimaging and at least two postnatal measurements with a head circumference above the tenth percentile for the infant's age and sex. Among infants tested after birth for Zika virus with either NAT or serologic tests (immunoglobulin M [IgM]) in serum, urine, or cerebrospinal fluid, the percent positivity is reported.

Results

The U.S. territories and freely associated states reported 4,816 pregnancies with laboratory evidence of confirmed or possible Zika virus infection by June 1, 2018, including 4,320 (90%) completed on or before February 1, 2018; 4,165 (96%) pregnancies resulted in 4,199 live-born infants, and 155 (4%) resulted in a pregnancy loss (Figure 1). Seven infants were excluded who would have reached age 1 year on or before February 1, 2018 and were reported to have died, including three who died during the first 14 days of life. By February 1, 2018, a total of 2,141 (51%) children were aged ≥1 year, 1,450 (68%) of whom had some follow-up care reported to the USZPIR after age 14 days.

Among these 1,450 children 1,376 (95%) had at least one physical examination reported after 14 days of life, 1,106 (76%) had at least one developmental screening or evaluation, 864 (60%) had postnatal neuroimaging, and 695 (48%) had at least one ABR-based hearing screen or evaluation. An ophthalmologic evaluation was reported for 522 (36%) children (Figure 2).

Among all 1,450 children with reported follow-up care, 203 (14%) had a Zika-associated birth defect, neurodevelopmental abnormality possibly associated with congenital Zika virus infection identified, or both: 87 (6%) had at least one Zika-associated birth defect, 136 (9%) had at least one neurodevelopmental abnormality possibly associated with congenital Zika virus infection, and 20 (1%) had both (Table). Among the 1,386 (96%) children who did not have microcephaly detected at birth, 822 (59%) received neuroimaging, including 14 (2%) who had at least one brain anomaly identified. In addition, among the 494 (36%) children who received an ophthalmologic evaluation, 12 (2%) had at least one eye anomaly identified. Thus, had these infants not received neuroimaging or ophthalmologic evaluation, 26 brain or eye anomalies in 23 children might have gone undetected.

The sensitivity analysis to assess possible misclassification of microcephaly at birth identified 84 (6%) children with microcephaly among the 1,450 children who had follow-up care reported: five infants had microcephaly at birth with brain or eye anomalies identified at birth; 59 had microcephaly at birth with no brain or eye anomalies identified at birth; and 20 infants did not have microcephaly identified at birth but had postnatal identification of microcephaly. The 59 infants with only microcephaly at birth included 15 who had no other Zika-associated birth defects identified during follow-up care, had normal neuroimaging, and had

** Microcephaly was defined as head circumference at delivery <3rd percentile for infant sex and gestational age, regardless of birth weight. When multiple head circumference measurements were available, the majority of those measurements had to be <3rd percentile for a designation of microcephaly. A clinical diagnosis of microcephaly or mention of microcephaly or small head in the medical record was not required. (https://www.cdc.gov/pregnancy/zika/data/pregnancy-outcomes.html).

BOX. Surveillance case classification — children, neonate to 2 years of age, born to mothers with any evidence of Zika virus infection during pregnancy

Zika-associated birth defects: Selected structural anomalies of the brain or eyes present at birth (congenital) and detected from birth to age 2 years. Microcephaly at birth, with or without low birthweight, was included as a structural anomaly.

- **Selected congenital brain anomalies:** intracranial calcifications; cerebral atrophy; abnormal cortical formation (e.g., polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia); corpus callosum abnormalities; cerebellar abnormalities; porencephaly; hydranencephaly; ventriculomegaly/hydrocephaly.
- **Selected congenital eye anomalies:** microphthalmia or anophthalmia; coloboma; cataract; intraocular calcifications; chorioretinal anomalies involving the macula (e.g., chorioretinal atrophy and scarring, macular pallor, and gross pigmentary mottling), excluding retinopathy of prematurity; optic nerve atrophy, pallor, and other optic nerve abnormalities.
- **Microcephaly at birth:** birth head circumference <3rd percentile for infant sex and gestational age based on INTERGROWTH-21st online percentile calculator (http://intergrowth21.ndog.ox.ac.uk/).

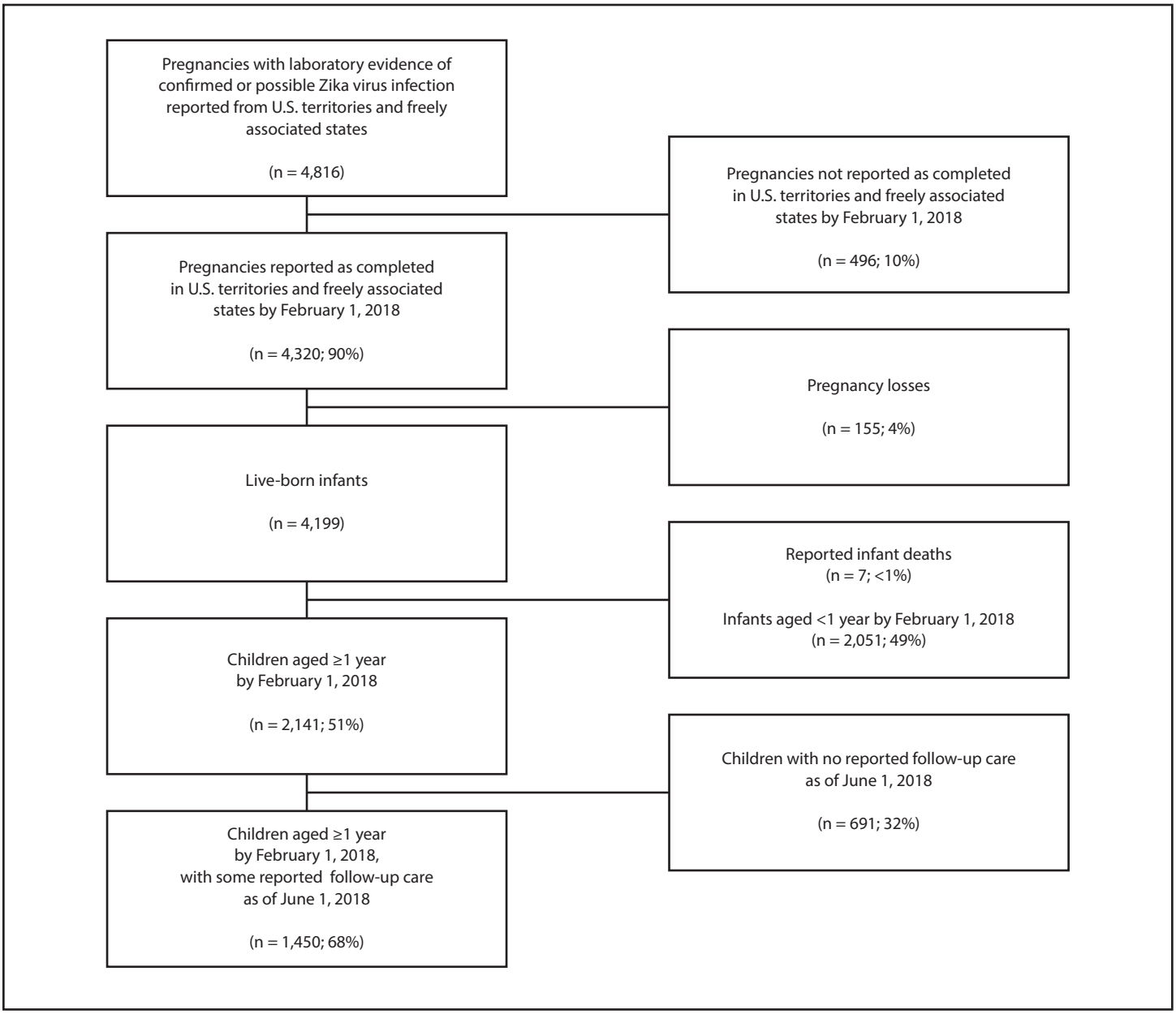
Neurodevelopmental abnormalities possibly associated with congenital Zika virus infection: Consequences of neurologic dysfunction detected from birth (congenital) to age 2 years. Postnatal-onset microcephaly was included as a neurodevelopmental abnormality.

- **Hearing abnormalities**: Hearing loss or deafness documented by testing, most frequently auditory brainstem response (ABR). Includes sensorineural hearing loss, mixed hearing loss, and hearing loss not otherwise specified. Failed newborn hearing screen is not sufficient for diagnosis.
- **Congenital contractures:** Multiple contractures (arthrogryposis) and isolated clubfoot documented at birth. Brain anomalies must be documented for isolated clubfoot, but not for arthrogryposis.
- **Seizures:** Documented by electroencephalogram or physician report. Includes epilepsy or seizures not otherwise specified; excludes febrile seizures.
- **Body tone abnormalities:** Hypertonia or hypotonia documented at any age in conjunction with 1) a failed screen or assessment for gross motor function; 2) suspicion or diagnosis of cerebral palsy from age 1 year to age 2 years; or 3) assessment by a physician or other medical professional, such as a physical therapist.
- **Movement abnormalities:** Dyskinesia or dystonia at any age; suspicion or diagnosis of cerebral palsy from age 1 year to age 2 years.
- **Swallowing abnormalities:** Documented by instrumented or noninstrumented evaluation, presence of a gastrostomy tube, or physician report.
- **Possible developmental delay:** Abnormal result from most recent developmental screening (i.e., failed screen for gross motor domain or failed screen for ≥2 developmental domains at the same time point or age); developmental evaluation; or assessment review by developmental pediatrician. Results from developmental evaluation are considered the gold standard if available.
- **Possible visual impairment:** Includes strabismus (esotropia or exotropia), nystagmus, failure to fix and follow at age <1 year; diagnosis of visual impairment at age ≥1 year.
- **Postnatal-onset microcephaly:** Two most recent head circumference measurements reported from follow-up care <3rd percentile for child's sex and age based on World Health Organization child growth standards; downward trajectory of head circumference percentiles with most recent measurement <3rd percentile. Age at measurement was adjusted for gestational age in infants born at <40 weeks' gestational age through age 24 months chronological age.

at least two postnatal measurements with a head circumference above the tenth percentile for the infant's sex and age. Excluding these 15 infants from the 87 with Zika-associated birth defects results in a decrease in the estimated percentage of affected children from 6% to 5%.

Among the 1,450 children whose mothers had laboratory evidence of confirmed or possible Zika virus infection during pregnancy and who had follow-up care reported, 136 (9%) had neurodevelopmental abnormalities possibly associated with congenital Zika virus infection identified (Table). One hundred sixteen (8%) had one or more neurodevelopmental abnormalities possibly associated with congenital Zika virus infection identified, but no Zika-associated birth defects; of these 116 children, 58 (50%) had only possible developmental delay

FIGURE 1. Children born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy — U.S. Zika Pregnancy and Infant Registry, U.S. territories and freely associated states, February 1, 2017–June 1, 2018*,†,§,¶,**



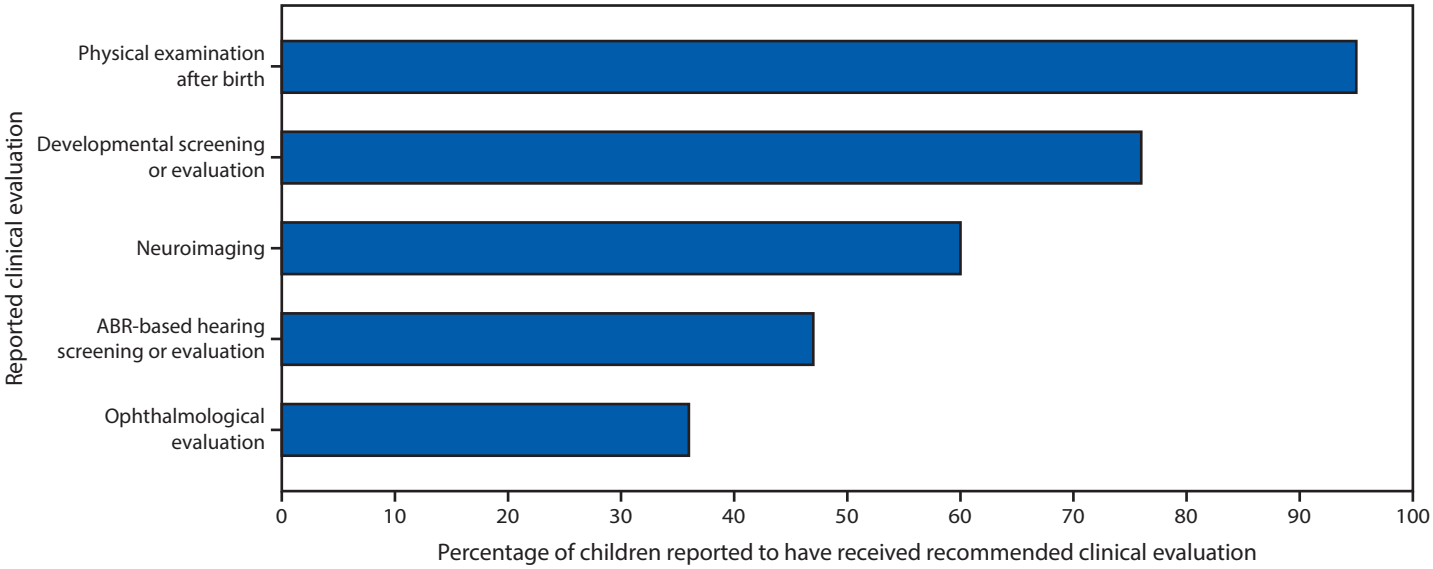
* Percentages might not sum to 100 because of rounding.
† Date and location of pregnancy completion were required to document a completed pregnancy in U.S. territories and freely associated states.
§ Live-born infants include 4,199 infants from 4,165 pregnancies (includes 34 multiple gestation pregnancies).
¶ Of the 691 children with no reported follow-up care as of June 1, 2018, 99 were reported to have moved out of U.S. territories and freely associated states.
** Of the 1,450 children aged ≥1 year by February 1, 2018, with some reported follow-up care by June 1, 2018, 154 were reported to have moved out of U.S. territories and freely associated states.

identified, and 25 (22%) had possible developmental delay with at least one other neurodevelopmental abnormality possibly associated with congenital Zika virus infection identified.

Among 943 pregnancies with NAT-confirmed Zika virus infection, 144 (15%) had a Zika-associated birth defect, neurodevelopmental abnormality possibly associated with congenital Zika virus infection identified, or both: 62 (7%) had at least one Zika-associated birth defect identified. Ninety-nine (10%) had at least one neurodevelopmental abnormality possibly associated with congenital Zika virus infection identified, and 17 (2%) had both.

Among the 1,450 children in this analysis, 607 (42%) did not receive testing for Zika virus infection in serum, urine, or cerebrospinal fluid. Among the 843 (58%) who did receive testing, 32

FIGURE 2. Percentage of children aged ≥1 year born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy reported to have received recommended clinical evaluations*,†,§,¶, among children with reported follow-up care†† (n = 1,450) — U.S. Zika Pregnancy and Infant Registry (USZPIR), U.S. territories and freely associated states, February 1, 2017–June 1, 2018**



Abbreviation: ABR = auditory brainstem response.

* Physical examination after birth denotes at least one physical examination, indicated by length, weight, or head circumference measurements and date of measurements, at age >14 days reported to the USZPIR.

† Developmental screening or evaluation denotes at least one developmental screening or evaluation result at age >14 days reported to the USZPIR.

§ Neuroimaging denotes at least one postnatal imaging of the infant head (cranial ultrasound, computed tomography, or magnetic resonance imaging) result reported to the USZPIR.

¶ ABR-based hearing screening or evaluation denotes at least one ABR-based hearing screen or evaluation result reported to the USZPIR. Of 1,450 children with reported follow-up care, 96% had at least one hearing screen or evaluation of any kind reported to the USZPIR.

** Ophthalmological evaluation denotes at least one ophthalmological evaluation result reported to the USZPIR.

†† Any clinical care at age >14 days reported to the USZPIR.

(4%) tested positive by either NAT or IgM (four of 69 tested by NAT only; zero of 18 tested by IgM only; and 28 of 756 tested by both NAT and IgM tested positive by either NAT or IgM). Zika-associated birth defects or neurodevelopmental abnormalities possibly associated with congenital Zika virus infection were identified in children with positive Zika virus IgM or NAT, negative IgM and NAT, and in those who did not receive testing.

Conclusion and Comments

A total of 1,450 children aged ≥1 year were born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy in the U.S. territories and freely associated states and were reported to the USZPIR. Among these children, approximately one in seven (14%) were identified during infancy or early childhood as having either a Zika-associated birth defect, a neurodevelopmental abnormality possibly associated with congenital Zika virus infection, or both.

The 6% with Zika-associated birth defects in this report can be viewed in the context of the previously published baseline frequency of brain and eye abnormalities potentially related to Zika virus infection. Before the introduction of Zika in the Region of the Americas the baseline frequency of brain and eye abnormalities potentially related to Zika virus infection among live-born infants was approximately 0.16% (*21*), suggesting a more than 30-fold increase over baseline.

Among all children aged ≥1 year by February 1, 2018, 68% had some follow-up care reported to the USZPIR. Of these children, 95% had at least a physical examination, 76% had developmental screening or evaluation, and 60% had neuroimaging. Approximately one half of the children (48%) had an ABR-based hearing screen or evaluation, and approximately one third of the children (36%) had an ophthalmologic evaluation reported to the USZPIR. Because the full spectrum of adverse outcomes related to congenital Zika virus infection is not yet known, careful monitoring and evaluation of children born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy is essential for ensuring early detection of possible disabilities and early referral to intervention services that might improve outcomes. For example, with early identification of vision problems, a prescription for corrective eyeglasses might be beneficial to a child's development (*12*). Among children without microcephaly detected at birth, brain or eye anomalies might have gone undetected without neuroimaging or ophthalmologic evaluation.

TABLE. Outcomes among children aged ≥1 year from pregnancies with any laboratory evidence of confirmed or possible Zika virus infection (n = 1,450) and with nucleic acid test–confirmed Zika virus infection (n = 943) and with reported follow-up care* — U.S. Zika Pregnancy and Infant Registry (USZPIR), U.S. territories and freely associated states, February 1, 2017–June 1, 2018

Zika-related outcomes	Any laboratory evidence of confirmed or possible Zika virus infection during pregnancy (n = 1,450)† No. (%)	Pregnancies with nucleic acid test–confirmed Zika virus infection (n = 943)§ No. (%)
Zika-associated birth defect¶	87 (6)	62 (7)
Neurodevelopmental abnormality possibly associated with congenital Zika virus infection**	136 (9)	99 (10)
Zika-associated birth defect and neurodevelopmental abnormality possibly associated with congenital Zika virus infection	20 (1)	17 (2)
Total with Zika-associated birth defect, neurodevelopmental abnormality possibly associated with congenital Zika virus infection, or both	**203 (14)**	**144 (15)**
Microcephaly		
Microcephaly at birth††	64 (4)	44 (5)
Postnatal-onset microcephaly only§§	20 (1)	12 (1)
Total with microcephaly	**84 (6)**	**56 (6)**

* Any clinical care at age >14 days reported to the USZPIR.

† Includes maternal, placental, or infant laboratory evidence of confirmed or possible Zika virus infection during pregnancy based on presence of Zika virus RNA by a positive nucleic acid test (e.g., reverse transcription–polymerase chain reaction [RT-PCR]), serologic evidence of a Zika virus infection, or serologic evidence of an unspecified flavivirus infection.

§ Includes maternal, placental, or infant laboratory evidence of confirmed Zika virus infection during pregnancy based on presence of Zika virus RNA by a positive nucleic acid test (e.g., RT-PCR).

¶ Includes Zika-associated birth defect detected from birth to age 2 years with or without neurodevelopmental abnormality possibly associated with congenital Zika virus infection. Zika-associated birth defects include selected congenital brain anomalies (intracranial calcifications; cerebral atrophy; abnormal cortical formation; corpus callosum abnormalities; cerebellar abnormalities; porencephaly; hydranencephaly; ventriculomegaly/hydrocephaly); selected congenital eye anomalies (microphthalmia or anophthalmia; coloboma; cataract; intraocular calcifications; chorioretinal anomalies involving the macula, excluding retinopathy of prematurity; and optic nerve atrophy, pallor, and other optic nerve abnormalities); and/or microcephaly at birth (birth head circumference <3rd percentile for infant sex and gestational age based on INTERGROWTH-21st online percentile calculator [http://intergrowth21.ndog.ox.ac.uk/]).

** Includes neurodevelopmental abnormality possibly associated with congenital Zika virus infection detected from birth to age 2 years, with or without Zika-associated birth defect. Neurodevelopmental abnormalities possibly associated with congenital Zika virus infection include hearing abnormalities; congenital contractures; seizures; body tone abnormalities; movement abnormalities; swallowing abnormalities; possible developmental delay; possible visual impairment; and/or postnatal-onset microcephaly (two most recent head circumference measurements reported from follow-up care <3rd percentile for child's sex and age based on World Health Organization child growth standards; downward trajectory of head circumference percentiles with most recent <3rd percentile. Age at measurement was adjusted for gestational age in infants born at <40 weeks' gestational age, through age 24 months chronological age).

†† Microcephaly at birth is a subset of Zika-associated birth defects and was defined as birth head circumference <3rd percentile for infant sex and gestational age based on INTERGROWTH-21st online percentile calculator (http://intergrowth21.ndog.ox.ac.uk/).

§§ Postnatal-onset microcephaly is a subset of neurodevelopmental abnormalities possibly associated with congenital Zika virus infection and was defined as two most recent head circumference measurements reported from follow-up care <3rd percentile for child's sex and age based on World Health Organization child growth standards; downward trajectory of head circumference percentiles with most recent <3rd percentile. Age at measurement was adjusted for gestational age in infants born at <40 weeks' gestational age, through age 24 months chronological age.

Many infants did not have Zika virus testing results reported. This could be because of changing recommendations for laboratory testing of infants born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy (*19*). Among infants with testing reported, only 4% tested positive for Zika virus infection by IgM or NAT. In addition, limitations of laboratory testing for Zika virus have been previously described (*19*); Zika virus RNA is only transiently present in body fluids; thus, a negative NAT result does not rule out infection. Zika virus-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection also were identified in children with negative Zika virus NAT or IgM test results. These finding are consistent with other reports of infants with clinical findings suggestive of possible congenital Zika syndrome but with negative laboratory results (*2*,*20*,*22*).

Microcephaly is challenging to monitor accurately as an outcome because it is difficult to reliably measure head circumference in a newborn, it can be affected by inaccuracies in estimated gestational age, and it does not distinguish between a small head size related to underlying pathology and one that will subsequently exhibit typical brain development (*3*). The sensitivity analysis suggests that the number of infants with Zika-associated birth defects could be a modest overestimate.

This is the first analysis assessing neurodevelopmental abnormalities possibly associated with congenital Zika virus infection in addition to Zika-associated birth defects among children born to mothers in the U.S. territories and freely associated states with laboratory evidence of confirmed or possible Zika virus infection during pregnancy. Although there are large cohort studies monitoring pregnancies with and without Zika virus infection in several countries, the data in this report come from the largest cohort of children born to mothers with laboratory evidence of confirmed or possible Zika virus

Summary

What is already known about this topic?

Zika virus infection during pregnancy can cause serious birth defects and might be associated with neurodevelopmental abnormalities.

What is added by this report?

Among children aged ≥1 year born in U.S. territories and freely associated states to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy and who had follow-up care reported, 6% had a Zika-associated birth defect, 9% had ≥1 neurodevelopmental abnormality possibly associated with congenital Zika virus infection, and 1% had both.

What are the implications for public health practice?

Given the potential benefits from interventions during early critical periods of infant development, health care providers should share information on maternal Zika virus exposure and closely monitor child health and development.

infection during pregnancy in the world who are currently being monitored as part of an enhanced surveillance system.

Whereas the cohort size is a strength of this analysis, the findings in this report are subject to at least five limitations. First, the data are limited to evaluations and clinical care received and reported to the USZPIR. The recommended services might not have been available to all children, and among those with reported follow-up care, information was limited for some children. In addition, data are limited to clinical records reported to the USZPIR; collecting these data are challenging because children might be seen in various outpatient settings and by multiple providers. To alleviate this barrier, territorial and state jurisdictions made extensive efforts to actively follow up, abstract, and report available data; CDC also provided substantial technical assistance. Second, it is possible that children with recognized health problems might have received follow-up care more frequently than did those without identified health problems, which might lead to an overestimate of the percentage of children with Zika-related health problems. Third, estimates of the baseline frequencies of neurodevelopmental abnormalities among very young children are available only for a few of the specific abnormalities; the lack of an appropriate comparison group limits assessment of whether the prevalence of reported neurodevelopmental abnormalities in the U.S. territories and freely associated states among children born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy is an increase over baseline levels. Fourth, given the potential persistence, cross-reactivity, or nonspecific reactivity of IgM, some mothers included in the USZPIR might not have been infected with Zika virus during their pregnancy. For this reason, an analysis of child outcomes restricted to pregnancies with NAT-confirmed Zika virus infection was included, and similar percentages of children with a Zika-associated birth defect, a neurodevelopmental abnormality possibly associated with congenital Zika virus infection, or both were found. Finally, it might be difficult to distinguish between birth defects and neurodevelopmental abnormalities that might be causally linked to congenital Zika virus infection and those that might be attributable to unrelated causes; thus, this report describes occurrences without attributing causation.

Despite the limitations, this report extends understanding about the impact of congenital Zika virus infection. Whereas approximately 6% of children with congenital Zika virus exposure have Zika-associated birth defects, more children have neurodevelopmental abnormalities possibly associated with congenital Zika virus infection, identified during follow-up care, albeit without an appropriate comparison group on the baseline prevalence of these neurodevelopmental abnormalities among very young children. Given that most children did not have evidence of all recommended evaluations according to data reported to the USZPIR, additional unidentified anomalies might exist in this population. Furthermore, it is recognized that there were substantial disruptions to the provision of clinical care in Puerto Rico and the U.S. Virgin Islands related to hurricanes in 2017 (*23*); many families also were internally displaced or left the affected territories, potentially resulting in fewer follow-up care data reported to the USZPIR. Children who were most affected by Zika virus infection during pregnancy might have been either more or less likely to be displaced after hurricanes; there is no specific information on the impact of this displacement in these estimates. However, jurisdictional staff members attempted to find families and link them to the USZPIR in their new jurisdiction.

It is essential that health care providers who care for children have access to information regarding maternal exposure to Zika virus infection during pregnancy. This will improve the identification of children born to mothers with laboratory evidence of confirmed or possible Zika virus infection during pregnancy so that they can receive recommended postnatal evaluations. Zika virus transmission is far less prevalent in the Americas in 2018 than during 2015–2017 (https://www.cdc.gov/zika/reporting/case-counts.html); however, information about this cohort of children can inform and guide future responses to outbreaks of Zika virus that will inevitably occur among susceptible populations and disproportionately affect pregnant women and their children.

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Conflict of Interest

No conflicts of interest were reported.

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Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Men with Possible Zika Virus Exposure — United States, August 2018

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On August 7, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

Zika virus infection can occur as a result of mosquitoborne or sexual transmission of the virus. Infection during pregnancy is a cause of fetal brain abnormalities and other serious birth defects (*1*,*2*). CDC has updated the interim guidance for men with possible Zika virus exposure who 1) are planning to conceive with their partner, or 2) want to prevent sexual transmission of Zika virus at any time (*3*). CDC now recommends that men with possible Zika virus exposure who are planning to conceive with their partner wait for at least 3 months after symptom onset (if symptomatic) or their last possible Zika virus exposure (if asymptomatic) before engaging in unprotected sex. CDC now also recommends that for couples who are not trying to conceive, men can consider using condoms or abstaining from sex for at least 3 months after symptom onset (if symptomatic) or their last possible Zika virus exposure (if asymptomatic) to minimize their risk for sexual transmission of Zika virus. All other guidance for Zika virus remains unchanged. The definition of possible Zika virus exposure remains unchanged and includes travel to or residence in an area with risk for Zika virus transmission (https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika) or sex without a condom with a partner who traveled to or lives in an area with risk for Zika virus transmission. CDC will continue to update recommendations as new information becomes available.

Review of Evidence

Primarily transmitted through the bite of an infected *Aedes aegypti* mosquito, Zika virus can also be transmitted through unprotected sex (i.e., without correct and consistent use of a condom) with an infected partner. As of July 3, 2018, 52 cases of confirmed sexual transmission of Zika virus infection have been reported in the United States since 2015 (https://www.cdc.gov/zika/reporting/case-counts.html). Most documented reports of sexual transmission have involved transmission from a man to a woman (*4*); however, transmission also has been reported from a man to another man (*5*) and from a woman to a man (*6*).

Despite their limited generalizability to humans, preliminary data from animal studies suggest that sexual transmission of Zika virus during pregnancy might pose a higher risk to the fetus than mosquitoborne transmission. In female rhesus macaques, vaginal inoculation (as a model for sexual transmission) of Zika virus appeared to enhance viral dissemination to the female reproductive tract, compared with subcutaneous inoculation (*7*). In an immunodeficient mouse model, poorer maternal outcomes and higher fetal viral titers were observed when exposure was through sexual transmission rather than subcutaneous or intravaginal infection (*8*). Prevention of sexual transmission of Zika virus during pregnancy can reduce the risk for maternal infection and the potential for congenital Zika syndrome.

The risk for congenital Zika syndrome associated with maternal Zika virus infection during the periconceptional period is not known. Maternal infection with other viruses (e.g., rubella) during the periconceptional period have been associated with infection in the fetus and adverse pregnancy outcomes; although in some cases, the timing of infection relative to conception was uncertain (*9*–*13*). To date, there are no published data definitively linking Zika virus infection around the time of conception to adverse pregnancy outcomes.

Since the last update of this guidance on October 7, 2016 (*3*), additional evidence relevant to the assessment of risk for sexual transmission of Zika virus infection has been reported. A literature search of PubMed was performed to identify new human studies and data published in English since October 2016. References for included articles were also screened. Specific search terms used included "sexual transmission" or "semen" or "seminal fluid" and "Zika." The search yielded 15 publications, including case reports, case series, and nine cohort studies, which were reviewed for new, primary data.

Among the currently available reports of sexual transmission of Zika virus, the longest period from symptom onset in the index case to potential sexual transmission to a partner was between 32–41 days (*14*); most reports indicate much shorter intervals (*4*). The longest period after symptom onset at which replication-competent (i.e., potentially infectious) virus has been detected in semen by culture or cytopathic effect was 69 days (*15*). No other studies reported potentially infectious Zika virus in semen specimens obtained ≥40 days after symptom onset (*16*–*33*).

Numerous publications have reported on the detection of Zika virus RNA in semen (*4*,*15*–*41*), although this might not indicate the presence of infectious virus at the time of sampling

or correlate with the potential for sexual transmission of infectious virus. In the largest published cohort study to date, involving 184 men with confirmed symptomatic Zika virus infection from whom a baseline specimen and serial semen specimens were collected at 2-week intervals, Zika virus RNA shedding in semen declined during the 3 months after symptom onset (*28*). Overall, Zika virus RNA was detected in semen in 61% (22 of 36); 43% (48 of 112); and 21% (28 of 131) of participants from whom specimens were collected within 30, 31–60, and 61–90 days of illness onset, respectively. At >90 days after illness onset, semen of ≤7% of participants had detectable Zika virus RNA. The estimated mean time to clearance of Zika virus RNA from semen was 54 days (*28*). Another large cohort study conducted in Puerto Rico followed 117 men, 89 of whom provided semen specimens and reported similar results: at >90 days after illness onset 11% (8 of 74) of men had detectable RNA in semen (Gabriela Paz-Bailey, Division of Vectorborne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC; personal communication, 2018) (*32*). Similar findings have been observed in smaller cohort studies (*16*,*17*,*23*,*25*,*29*,*37*,*39*). Zika virus RNA has been detected in semen for as long as 370 days after symptom onset (*17*); however, detection for long periods is rare. Limited data suggest the incidence of Zika virus RNA shedding in semen and its persistence after infection are likely similar for symptomatic and asymptomatic men infected with Zika virus (*40*–*42*).

Guidance for Preconception Counseling and Prevention of Sexual Transmission

CDC's last interim guidance released in October 2016 was based on the maximum duration of detection of Zika virus RNA in semen. In the last interim guidance, CDC recommended that men with possible Zika virus exposure wait at least 6 months after symptom onset (if symptomatic) or their last possible Zika virus exposure (if asymptomatic) before trying to conceive with their partner (*3*). New data published since then support an update to that interim guidance. CDC now recommends that men with possible Zika virus exposure who are planning to conceive with their partner wait for at least 3 months after symptom onset (if symptomatic) or their last possible Zika virus exposure (if asymptomatic) before engaging in unprotected sex. CDC now also recommends that for couples who are not trying to conceive, men can consider using condoms or abstaining from sex for at least 3 months after symptom onset (if symptomatic) or their last possible Zika virus exposure (if asymptomatic) to minimize their risk for sexual transmission of Zika virus. Recommendations for men with possible Zika virus exposure whose partner is pregnant remain unchanged; these couples should be advised to consistently and correctly use condoms during sex or abstain from sex for the duration of the pregnancy (Table).

CDC continues to recommend shared patient-provider decision making, in which couples and health care providers work together to make decisions about timeframes to wait before trying to conceive after possible Zika virus exposure. Some couples might choose to wait shorter or longer periods after possible Zika virus exposure, based on individual circumstances (e.g., age, fertility, or details of possible exposure), clinical judgment, and a balanced assessment of risks and expected outcomes. Other guidance for preconception counseling and prevention of sexual transmission of Zika virus after possible Zika virus exposure remains unchanged (*3*).

TABLE. CDC recommendations for preconception counseling and prevention of sexual transmission of Zika virus among persons with possible Zika virus exposure — United States, August 2018

Exposure scenario	Recommendations (update status)
Only the male partner travels to an area with risk for Zika virus transmission and couple planning to conceive	The couple should use condoms or abstain from sex for at least 3 months after the male partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). **(Updated recommendation)**
Only the female partner travels to an area with risk for Zika virus transmission and couple planning to conceive	The couple should use condoms or abstain from sex for at least 2 months after the female partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). **(No change in recommendation)***
Both partners travel to an area with risk for Zika virus transmission and couple planning to conceive	The couple should use condoms or abstain from sex for at least 3 months from the male partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). **(Updated recommendation)**
One or both partners have ongoing exposure (i.e., live in or frequently travel to an area with risk for Zika virus transmission) and couple planning to conceive	The couple should talk with their health care provider about their plans for pregnancy, their risk for Zika virus infection, the possible health effects of Zika virus infection on a baby, and ways to protect themselves from Zika. If either partner develops symptoms of Zika virus infection or tests positive for Zika virus infection, the couple should follow the suggested timeframes listed above before trying to conceive. **(No change in recommendation)***
Men with possible Zika virus exposure whose partner is pregnant	The couple should use condoms or abstain from sex for the duration of the pregnancy. **(No change in recommendation)***

* Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure—United States, September 2016. MMWR Morb Mortal Wkly Rep 2016;65:1077–81.

Summary

What is already known about this topic?

Zika virus infection during pregnancy is a cause of serious birth defects. CDC previously released interim guidance on preconception counseling and prevention of sexual transmission of Zika virus in October 2016.

What is added by this report?

CDC now recommends that men with possible Zika virus exposure who are planning to conceive with their partner wait at least 3 months after symptom onset or their last possible Zika virus exposure before engaging in unprotected sex. This updated timeframe also applies to prevent sexual transmission of Zika virus.

What are the implications for public health practice?

These recommendations provide couples planning pregnancy with updated timeframes expected to reduce the risk for fetal Zika virus infection.

Conflict of Interest

No conflicts of interest were reported.

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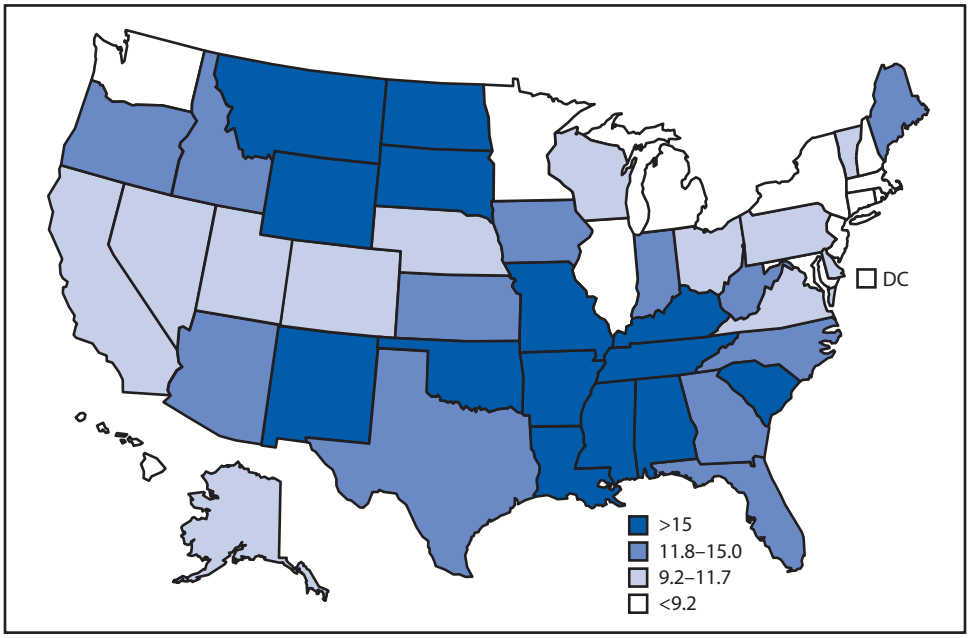
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Age-Adjusted Death Rates* for Motor Vehicle Traffic Injury† — United States, 2016



Abbreviation: DC = District of Columbia.
* Rates are deaths per 100,000 standard population.
† Motor vehicle traffic injuries are identified with *International Classification of Disease, Tenth Revision* (ICD–10) codes V02–V04[.1,.9],V09.2,V12–V14[.3–.9],V19[.4–.6],V20–V28[.3–.9],V29–V79[.4–.9],V80[.3–.5],V81.1,V82.1,V83– V86[.0–.3],V87[.0–.8],V89.2).

In 2016, the death rate in the United States for motor vehicle traffic injury was 11.7 per 100,000 standard population. The three states with the highest age-adjusted death rates were Mississippi (25.4), Alabama (23.3), and South Carolina (20.9). New York (5.3), Rhode Island (5.0), and the District of Columbia (4.5) had the lowest rates.

Source: National Vital Statistics System. Underlying cause of death data, 2016. https://wonder.cdc.gov/ucd-icd10.html.

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For more information on this topic, CDC recommends the following link: https://www.cdc.gov/motorvehiclesafety/states/index.html.

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