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Antidepressant Prescription Claims Among Reproductive-Aged Women With Private Employer-Sponsored Insurance — United States 2008–2013

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Antidepressant medication use during pregnancy has been increasing in the United States (*1*). Many women require antidepressants on an ongoing basis, and a clear consensus on the safest medication options for both the mother and her fetus does not exist (*2*). Given that half of all U.S. pregnancies are unplanned (*3*), antidepressant use will occur during the first weeks of pregnancy, a critical period for fetal development. To understand trends among women of reproductive age, CDC used Truven Health's MarketScan Commercial Claims and Encounters data* to estimate the number of antidepressant prescriptions filled by women aged 15–44 years with private employer-sponsored insurance. During 2008–2013, an average of 15.4% of women aged 15–44 years filled at least one prescription for an antidepressant in a single year. The most frequently filled antidepressants included sertraline, bupropion, and citalopram. Prescribing of antidepressants is common, and research on antidepressant safety during pregnancy needs to be accelerated to provide evidence-based information to health care providers and women about the potential risks for antidepressant exposure before and during pregnancy and between pregnancies.

CDC used Truven Health's 2008–2013 MarketScan Commercial Claims and Encounters databases, a large convenience sample of employed persons and their dependents with private employer-sponsored insurance, to assess outpatient prescription drug claims for antidepressants. Demographic information is available for all persons enrolled in these private health insurance plans, regardless of whether or not the beneficiary seeks health care during a given year. In addition, all inpatient admissions, outpatient services, and outpatient pharmacy claims are available for each health care encounter.

CDC analyzed data on women aged 15–44 years who had ≥11 months of enrollment per calendar year in a private health insurance plan that included prescription drug coverage. Outpatient pharmacy claims were searched for antidepressant medications using national drug codes to determine whether women filled an antidepressant prescription during a given calendar year, regardless of the indication for use. The annual number, annual proportion, and overall average proportion of reproductive-aged women who filled an antidepressant prescription from an outpatient pharmacy were analyzed by

* Proprietary data on inpatient services, outpatient services, and pharmacy claims provided by a convenience sample of commercial insurance providers (http://truvenhealth.com).

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specific antidepressant medication and medication class, age group, and U.S. geographic region.

An average of 5.8 million privately insured reproductive-aged women (range = 4.6–6.8 million) were included in the analytic sample each year during 2008–2013. During 2008–2013, on average, 15.4% of reproductive-aged women (range = 15.3%–15.6%) filled a prescription for an antidepressant from an outpatient pharmacy each year; 76.0% filled prescriptions for only one type of antidepressant (Table). The most commonly filled antidepressant prescriptions by reproductive-aged women each year were for sertraline (filled by an average of 3.3% of reproductive-aged women each year), bupropion (2.7%), citalopram (2.6%), escitalopram (2.5%), and fluoxetine (2.3%) (Table). Overall, the percentage of reproductive-aged women with antidepressant claims remained relatively stable during 2008–2013; however, prescription claims for some antidepressants showed modest variability (Figure 1).

Variation in antidepressant claims by geographic region and age group was detected. A larger percentage of reproductive-aged women in the North Central and South regions of the United States filled an antidepressant prescription compared with women in the Northeast and West regions. By age group, the percentage of reproductive-aged women who filled a prescription for an antidepressant ranged from an average of 8.3% among women aged 15–19 years to 20.9% among women aged 40–44 years (Table). However, among reproductive-aged women who filled prescriptions for common antidepressants (those filled by at least 0.5% of reproductive-aged women), the age distribution varied. Women aged 15–24 years represented 12.5% of women filling prescriptions for duloxetine but 24.0% of women filling prescriptions for fluoxetine. There was less variation in the proportion of women filling an antidepressant who were aged 25–34 years, ranging from 26.8% (for trazodone) to 32.9% (for sertraline). Women aged 35–44 years accounted for the largest proportion of reproductive-aged women filling prescriptions for all common antidepressant types, including 44.0% who filled prescriptions for sertraline and 60.3% who filled prescriptions for duloxetine (Figure 2).

Discussion

Approximately 15.4% of this convenience sample of reproductive-aged women with private employer-sponsored insurance filled a prescription for an antidepressant during 2008–2013. This relative frequency of dispensing of antidepressant prescriptions to this population raises public health concerns, given the high proportion of unplanned pregnancies, the lack of adequate information on the safety or risk of antidepressant use during pregnancy, and the reported possible association between the use of some antidepressants during early pregnancy and the occurrence of some major birth defects (*1*). There is some evidence of associations between early pregnancy use of paroxetine and five specific birth defects (anencephaly, gastroschisis, omphalocele, and selected cardiac defects, including atrial septal defects and right ventricular outflow tract obstruction defects), as well as two defects associated with fluoxetine use (right ventricular outflow tract obstruction defects and craniosynostosis) (*1*).

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TABLE. Number and percentage of reproductive-aged women* who filled a prescription for an antidepressant, by demographic characteristics and medication type — Truven Health MarketScan Commercial Claims and Encounters data, United States, 2008–2013

	2008	2009	2010	2011	2012	2013	Average 2008–2013
Characteristic	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**%**
Total women†	**4,631,109 (100)**	**5,266,704 (100)**	**5,671,940 (100)**	**6,476,309 (100)**	**6,811,114 (100)**	**5,695,016 (100)**	**NA§**
Any antidepressant prescription filled	708,924 (15.3)	813,078 (15.4)	873,951 (15.4)	1,009,566 (15.6)	1,056,901 (15.5)	874,755 (15.4)	15.4
Age group (yrs)							
15–19	59,945 (7.5)	69,743 (7.7)	77,625 (7.8)	93,468 (8.3)	103,604 (8.9)	91,937 (9.4)	8.3
20–24	62,177 (11.1)	71,742 (11.3)	77,658 (11.2)	112,143 (11.5)	130,986 (11.7)	117,070 (11.8)	11.5
25–29	90,767 (14.0)	106,020 (14.1)	109,521 (13.9)	120,299 (14.0)	124,089 (13.7)	94,456 (13.3)	13.8
30–34	126,257 (16.6)	147,319 (16.8)	159,369 (16.7)	179,429 (17.0)	185,085 (16.7)	147,854 (16.1)	16.7
35–39	172,042 (19.2)	196,682 (19.4)	211,170 (19.4)	229,468 (19.7)	228,472 (19.5)	186,058 (19.0)	19.4
40–44	197,736 (20.5)	221,572 (20.5)	238,608 (20.5)	274,759 (21.2)	284,665 (21.3)	237,380 (21.2)	20.9
Region							
Northeast	66,128 (13.8)	79,069 (13.1)	107,847 (14.1)	147,961 (14.7)	163,054 (14.9)	134,460 (14.0)	14.2
North Central	188,443 (16.2)	244,541 (16.6)	241,848 (16.5)	258,061 (16.7)	272,684 (16.6)	213,174 (17.4)	16.7
South	339,799 (15.9)	367,782 (16.0)	372,593 (16.2)	422,960 (16.3)	420,343 (16.2)	331,520 (16.1)	16.1
West	111,424 (13.4)	120,218 (13.6)	148,987 (13.2)	157,329 (13.1)	184,872 (13.3)	167,196 (13.0)	13.3
Missing	3,130 (12.8)	1,468 (11.1)	2,676 (13.3)	23,255 (18.1)	15,948 (18.0)	28,405 (17.2)	17.0
Specific antidepressants¶							
Any SSRI	487,162 (10.5)	559,285 (10.6)	603,423 (10.6)	702,701 (10.9)	736,732 (10.8)	612,758 (10.8)	10.7
Citalopram	90,439 (2.0)	121,572 (2.3)	148,932 (2.6)	195,292 (3.0)	196,904 (2.9)	144,590 (2.5)	2.6
Escitalopram	139,915 (3.0)	146,292 (2.8)	141,053 (2.5)	142,047 (2.2)	155,965 (2.3)	149,225 (2.6)	2.5
Fluoxetine	108,672 (2.4)	121,163 (2.3)	129,746 (2.3)	151,481 (2.3)	158,899 (2.3)	132,496 (2.3)	2.3
Fluvoxamine	2,824 (0.1)	3,474 (0.1)	3,929 (0.1)	4,657 (0.1)	4,882 (0.1)	4,302 (0.1)	0.1
Paroxetine	46,584 (1.0)	48,676 (0.9)	47,324 (0.8)	50,212 (0.8)	49,611 (0.7)	38,364 (0.7)	0.8
Sertraline	142,052 (3.1)	168,946 (3.2)	187,223 (3.3)	222,186 (3.4)	235,716 (3.5)	196,352 (3.5)	3.3
Any SNRI	136,578 (3.0)	157,010 (3.0)	163,630 (2.9)	181,154 (2.8)	180,029 (2.6)	141,301 (2.5)	2.8
Desvenlafaxine	7,863 (0.2)	25,540 (0.5)	32,041 (0.6)	33,993 (0.5)	30,103 (0.4)	20,742 (0.4)	0.4
Duloxetine	62,725 (1.4)	68,022 (1.3)	68,162 (1.2)	74,796 (1.2)	73,802 (1.1)	56,073 (1.0)	1.2
Milnacipran	NA**	3,091 (0.1)	5,677 (0.1)	6,089 (0.1)	5,127 (0.1)	3,392 (0.1)	0.1
Venlafaxine	72,469 (1.6)	69,873 (1.3)	66,960 (1.2)	75,967 (1.2)	80,054 (1.2)	67,893 (1.2)	1.3
Any Tricyclic	63,336 (1.4)	74,558 (1.4)	80,365 (1.4)	95,100 (1.5)	100,704 (1.5)	82,764 (1.5)	1.4
Amitriptyline	40,277 (0.9)	47,253 (0.9)	50,993 (0.9)	59,056 (0.9)	63,134 (0.9)	51,202 (0.9)	0.9
Any MAOI	420 (0)	422 (0)	435 (0)	484 (0)	470 (0)	419 (0)	0
Any Other	172,295 (3.7)	197,719 (3.8)	216,320 (3.8)	252,159 (3.9)	272,318 (4.0)	230,147 (4.0)	3.9
Bupropion	126,812 (2.7)	145,163 (2.8)	153,627 (2.7)	174,711 (2.7)	181,636 (2.7)	151,873 (2.7)	2.7
Trazodone	47,901 (1.0)	55,641 (1.1)	66,639 (1.2)	79,737 (1.2)	87,589 (1.3)	75,494 (1.3)	1.2
Filled only one prescription for an antidepressant	127,619 (2.8)	145,864 (2.8)	154,523 (2.7)	174,900 (2.7)	182,358 (2.7)	145,278 (2.6)	2.7
Filled prescription(s) for only one type of antidepressant††	541,820 (11.7)	617,605 (11.7)	662,792 (11.7)	764,441 (11.8)	799,599 (11.7)	662,501 (11.6)	11.7
Filled prescriptions for multiple antidepressant types§§	167,104 (3.6)	195,473 (3.7)	211,159 (3.7)	245,125 (3.8)	257,302 (3.8)	212,254 (3.7)	3.7

Abbreviations: MAOI = monoamine oxidase inhibitor; NA = not applicable; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

* Women aged 15–44 years, who were enrolled for ≥11 months of the year in a private health plan with prescription drug coverage.

† The same woman might have been included in multiple years of data.

§ Average percentage during the study period is not a relevant calculation when looking at the total population.

¶ Not mutually exclusive.

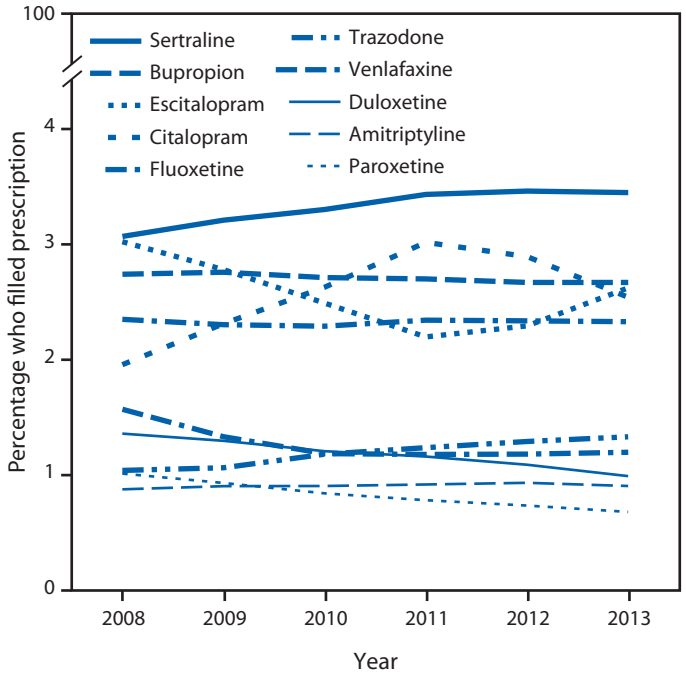
** Milnacipran was not approved by the U.S. Food and Drug Administration until 2009.

†† Includes women with claims for only one specific type of antidepressant during the calendar year.

§§ Includes medications filled concurrently or separately during the same calendar year.

Approximately 30% of reproductive-aged women had current depression or had ever received a clinical diagnosis of a depressive or anxiety disorder, based on 2006 data from the Behavioral Risk Factor Surveillance System, and these conditions often went untreated (*4*). Although rates of self-reported depression were similar among white and nonwhite women, the rates of clinical diagnosis and treatment were lower among nonwhite women (*4*). Depressed women have higher rates of smoking, binge or heavy drinking, obesity, and physical inactivity, which might also pose risks to a developing fetus during pregnancy (*5*). It is important for all women to be screened for depression, including pregnant women and women who have recently given birth (*6*). Ideally, women and their health care providers should discuss treatment options for depression in advance of pregnancy and choose the treatment course that is best for both the mother

FIGURE 1. Proportion of reproductive-aged women* who filled a prescription† for one of the most common antidepressant types,§ by year — Truven Health MarketScan Commercial Claims and Encounters data, 2008–2013



* Women aged 15–44 years who were enrolled in a private health plan that included prescription drug coverage for ≥11 months of the year.
† Women could have filled prescriptions for more than one medication type.
§ Selective serotonin reuptake inhibitors include sertraline, escitalopram, citalopram, fluoxetine, and paroxetine. Serotonin and norepinephrine reuptake inhibitors include venlafaxine and duloxetine. Amitriptyline is a tricyclic antidepressant. Other antidepressants include bupropion and trazodone.

Summary

What is already known on this topic?

Antidepressant use is relatively common among women of reproductive age, and the use of certain antidepressants during early pregnancy are possibly associated with the occurrence of some major birth defects. Multiple treatment options can be considered for reproductive-aged women with depression and related disorders. Given that half of all U.S. pregnancies are unplanned, use of antidepressants will occur during the first weeks of pregnancy, a critical period for fetal development.

What is added by this report?

During 2008–2013, approximately 15% of a convenience sample of reproductive-aged women (aged 15–44 years) with employer-sponsored insurance filled a prescription for antidepressants. The most commonly filled antidepressants were sertraline, bupropion, and citalopram. Women aged 35–44 years accounted for the largest proportion of reproductive-aged women filling prescriptions for all common antidepressant types.

What are the implications for public health practice?

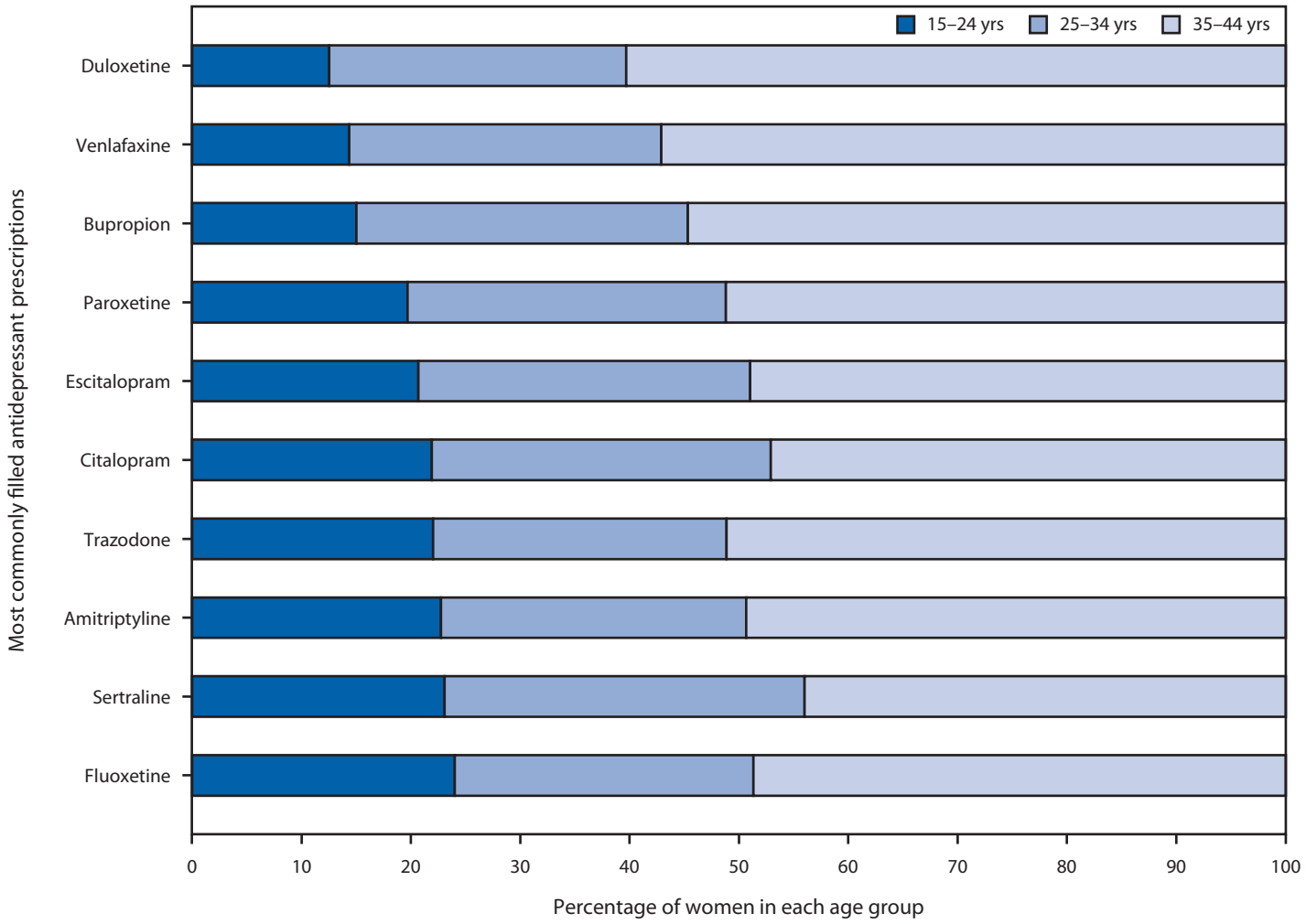
Antidepressant use is common among women of reproductive age, and research on antidepressant safety during pregnancy needs to be accelerated to provide evidence-based information for health care providers so they can effectively weigh the risks and benefits of treatment options in reproductive-aged women who are planning to or could become pregnant.

and the baby, which could include medication, but could also include other types of treatment such as counseling.

Published studies examining antidepressant use specifically among women of reproductive age are limited, and none describe antidepressant use in the same interval as the current study (i.e., use in a given year). Analysis of nationally representative data from the 2005–2008 National Health and Nutrition Examination Survey determined that 9% of women aged 18–39 years reported taking an antidepressant medication during the preceding month, and that antidepressant use increased significantly with increasing age (*7*). Other studies have used health insurance claims data to assess antidepressant use among pregnant women (*8,9*). These studies have also provided estimates of prepregnancy use, which might provide a basis for comparison with the estimate in this report. Antidepressant use was higher before pregnancy than during or after pregnancy (*8,9*). A study of approximately 343,000 privately insured women with pregnancies during 2006–2011 using Truven Health MarketScan Commercial Claims and Encounters databases reported that 9.9% of pregnant women filled a prescription for an antidepressant in the 6 months before conception, and 6.5% filled a prescription for an antidepressant at any point during pregnancy (*8*). An analysis of antidepressant prescriptions filled by approximately 1.1 million pregnant women with Medicaid coverage during 2000–2007 determined that 6.5% of pregnant women filled a prescription for an antidepressant in the 90 days before their last menstrual period, and 8.1% filled a prescription during pregnancy (*9*). In these two reports, antidepressant claims typically decreased to slightly less than 4% during the second and third trimesters of pregnancy, possibly because the women stopped treatment after learning they were pregnant.

The findings in this report are subject to at least four limitations. First, although this analysis included approximately 5–7 million reproductive-aged women each year, these data are a convenience sample of privately insured women and might not be generalizable across other populations. Approximately 50% of births in the United States occur to women with Medicaid coverage (*10*), and previous studies have suggested that antidepressant use might be higher in this population (*9*). In addition, an average of 2.6 million women (range = 2.1–2.9 million) were excluded from each year of the analysis because they were enrolled for <11 months during the calendar year. Restricting the analysis to women who were enrolled for ≥11 months during a calendar year might have increased the likelihood that the sample would include

FIGURE 2. Age distribution of reproductive-aged women* who filled a prescription† for an antidepressant, by antidepressant type — Truven Health MarketScan Commercial Claims and Encounters data, 2008–2013



* Women aged 15–44 years who were enrolled in a private health plan that included prescription drug coverage for ≥11 months of the year and who filled a prescription for the most common antidepressant medications.
† Women could have filled prescriptions for more than one medication type.

women with a health condition requiring treatment (*11*). Second, the number and type of health plans included in the database have changed over time; therefore, caution must be exercised in analyzing time trends. Third, no information was available about women who paid for their prescriptions in cash or obtained free samples, or about whether women took the dispensed antidepressants. Finally, this analysis did not identify women who were pregnant or ascertain whether antidepressant prescription claims were limited to women who were infertile or using contraception; an estimated 62% of women of reproductive age use contraception.†

This analysis used a large, geographically diverse database to estimate the proportion of privately insured reproductive-aged women who filled a prescription for an antidepressant from an outpatient pharmacy. The high prevalence of antidepressant claims in this population highlights the need for more research to support development of evidence-based guidance for informed decision making by health care providers and reproductive-aged women. To help address this need, CDC's Treating for Two: Safer Medication Use in Pregnancy Initiative§ aims to accelerate research on antidepressant safety during pregnancy to provide evidence-based information for health care providers to effectively weigh the risks and benefits of treatment options for reproductive-aged women who could become pregnant.

† http://www.cdc.gov/nchs/data/nhsr/nhsr060.pdf.

§ http://www.cdc.gov/pregnancy/meds/treatingfortwo.

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Increases in Acute Hepatitis B Virus Infections — Kentucky, Tennessee, and West Virginia, 2006–2013

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As many as 2.2 million persons in the United States are chronically infected with hepatitis B virus (HBV) (*1*), and approximately 15%–25% of persons with chronic HBV infection will die prematurely from cirrhosis or liver cancer (*2*). Since 2006, the overall U.S. incidence of acute HBV infection has remained stable; the rate in 2013 was 1.0 case per 100,000 persons (*3*). Hepatitis B vaccination is highly effective in preventing HBV infection and is recommended for all infants (beginning at birth), all adolescents, and adults at risk for HBV infection (e.g., persons who inject drugs, men who have sexual contact with men, persons infected with human immunodeficiency virus [HIV], and others). Hepatitis B vaccination coverage is low among adults: 2013 National Health Interview Survey data indicated that coverage with ≥3 doses of hepatitis B vaccine was 32.6% for adults aged 19–49 years (*4*). Injection drug use is a risk factor for both hepatitis C virus (HCV) and HBV. Among young adults in some rural U.S. communities, an increased incidence of HCV infection has been associated with a concurrent increase of injection drug use (*5*); and recent data indicate an increase of acute HCV infection in the Appalachian region associated with injection drug use (*6*). Using data from the National Notifiable Diseases Surveillance System (NNDSS) during 2006–2013, CDC assessed the incidence of acute HBV infection in three of the four Appalachian states (Kentucky, Tennessee, and West Virginia) included in the HCV infection study (*6*). Similar to the increase of HCV infections recently reported, an increase in incident cases of acute HBV infection in these three states has occurred among non-Hispanic whites (whites) aged 30–39 years who reported injection drug use as a common risk factor. Since 2009, cases of acute HBV infection have been reported from more non-urban than urban regions. Evidence-based services to prevent HBV infection are needed.

Data from confirmed cases of acute HBV infection reported to CDC from Kentucky, Tennessee, and West Virginia during 2006–2013, including demographic and risk characteristics, were obtained from NNDSS. These states used the CDC/Council of State and Territorial Epidemiologists case definition to identify cases of acute HBV infection.[†] Cases of acute HBV infection were categorized as "urban" if the infected person lived in a metropolitan county with a population ≥50,000 and as "non-urban" if the infected person lived in a nonmetropolitan county with a population <50,000.[§] Data were analyzed by year of report and urban/non-urban county resident status to assess annual incidence (per 100,000 persons), demographic characteristics, and injection drug use in persons with reported acute HBV infections during 2006–2013. To calculate annual incidence, the number of cases reported through NNDSS was used as the numerator and midyear (July) population estimates from the U.S. Census Bureau were used as the denominator. Statistical significance of a monotonic trend in annual incidence of acute HBV infection by urban/non-urban status was tested with the Spearman rank correlation test. A 20% increase in incident HBV infections was observed from 2009 to 2010; therefore, the data are presented for two reporting time periods: 2006–2009 and 2010–2013. Chi-square tests were used to determine whether cases reported during the two time periods differed significantly by demographic characteristics and reported injection drug use. Statistical significance was defined as $p<0.05$.

During 2006–2013, a total of 3,305 cases of acute HBV infection were reported to CDC from Kentucky, Tennessee, and West Virginia. During 2009–2013, incidence of acute HBV infection increased 114% in these three states, but remained stable in the United States overall (Figure 1). Comparing the number of cases of acute HBV infection reported during 2006–2009 and 2010–2013, the proportion of cases among whites and persons aged 30–39 years increased during 2010–2013 (Table). Among cases in which at least one risk factor was reported, the proportion of persons reporting injection drug use as a risk factor was significantly greater in 2010–2013, compared with 2006–2009 (75% versus 53%; $p<0.001$).

Among 3,185 of 3,305 (96%) total cases where urban and non-urban classification for HBV-infected persons could be determined, 1,344 (42%) were classified as residing in non-urban counties. During 2006–2013, the incidence of acute HBV infections from both urban and non-urban counties increased, but the increase was statistically significant only among cases occurring in non-urban counties (Figure 2) (p-value for trend <0.001).

[†] A person with acute illness with a discrete onset of symptoms and either jaundice or elevated serum alanine aminotransaminase levels and a positive test result for immunoglobulin M antibody to hepatitis B core antigen and hepatitis B surface antigen (http://wwwn.cdc.gov/nndss/conditions/hepatitis-b-acute/).

[§] http://www.cdc.gov/nchs/data/series/sr_02/sr02_166.pdf.

Summary

What is already known on this topic?

The national incidence of hepatitis B virus (HBV) infection has remained stable during 2006–2013 at 1 case per 100,000 persons. Currently, as many as 2.2 million persons are chronically infected with HBV. Injection drug use is a risk factor for HBV transmission.

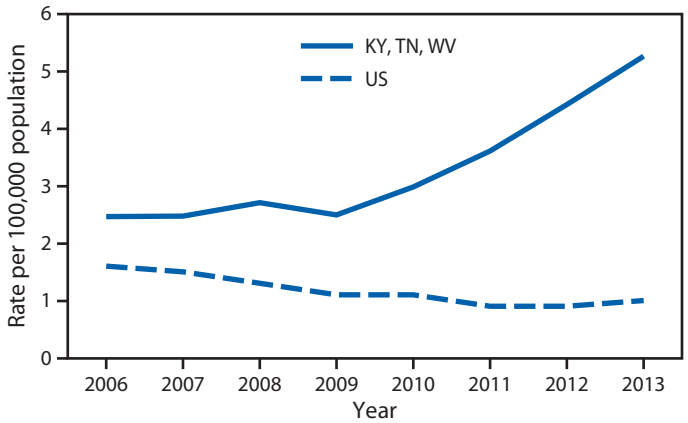
What is added by this report?

Since 2009, three states in the Appalachian region have reported an increase in cases of acute HBV infection, among non-Hispanic whites, persons aged 30–39 years, and injection drug users. Compared with cases that occurred during 2006–2009, a significant increase in the proportion of cases in which injection drug use was reported during 2010–2013.

What are the implications for public health practice?

The increase in incident HBV-infections has the potential to impede the nation's hepatitis B elimination strategy. Evidence-based prevention strategies, including increasing hepatitis B vaccination coverage, testing and linkage to care, and implementing education campaigns that target persons who inject drugs are urgently needed.

FIGURE 1. Incidence of acute hepatitis B virus infection, by year—United States and Kentucky, Tennessee, and West Virginia, 2006–2013



Abbreviations: KY = Kentucky; TN = Tennessee; US = United States; WV = West Virginia..

Discussion

Population-based surveillance data from Kentucky, Tennessee, and West Virginia indicate a 114% increase in acute HBV infection during 2006–2013; this increase occurred after 2009, among whites, aged 30–39 years who reported injection drug use. In an analysis of 6 years of enhanced surveillance data for hepatitis B, Tennessee reported similar findings, including a large increase among white adults, with both injection and noninjection drug use as a commonly reported risk factor during 2006–2011 (*7*).

TABLE. Demographic characteristics and injection drug use behavior for 3,305 reported cases of acute hepatitis B virus infection, by reporting period — Kentucky, Tennessee, and West Virginia, 2006–2013

	Reporting period		
Characteristic*	**2006–2009 (n = 1,243) No. (%)**	**2010–2013 (n = 2,062) No. (%)**	**p-value**
Age group (yrs)			<0.001
0–18	6 (0.5)	7 (0.3)	
19–29	290 (23.3)	371 (18.0)	
30–39	354 (28.5)	763 (37.0)	
40–49	356 (28.7)	537 (26.0)	
50–59	153 (12.3)	254 (12.3)	
≥60	83 (6.7)	128 (6.2)	
Sex			**0.582**
Male	736 (59.4)	1,196 (58.4)	
Female	503 (40.6)	851 (41.6)	
Race			**<0.001**
Non-Hispanic black	128 (12.5)	128 (7.6)	
Non-Hispanic white	869 (84.6)	1,503 (88.9)	
Hispanic	13 (1.3)	20 (1.2)	
Other	17 (1.7)	39 (2.3)	
Injection drug use†			**<0.001**
Yes	180 (52.9)	342 (75.2)	
No	160 (47.1)	113 (24.8)	

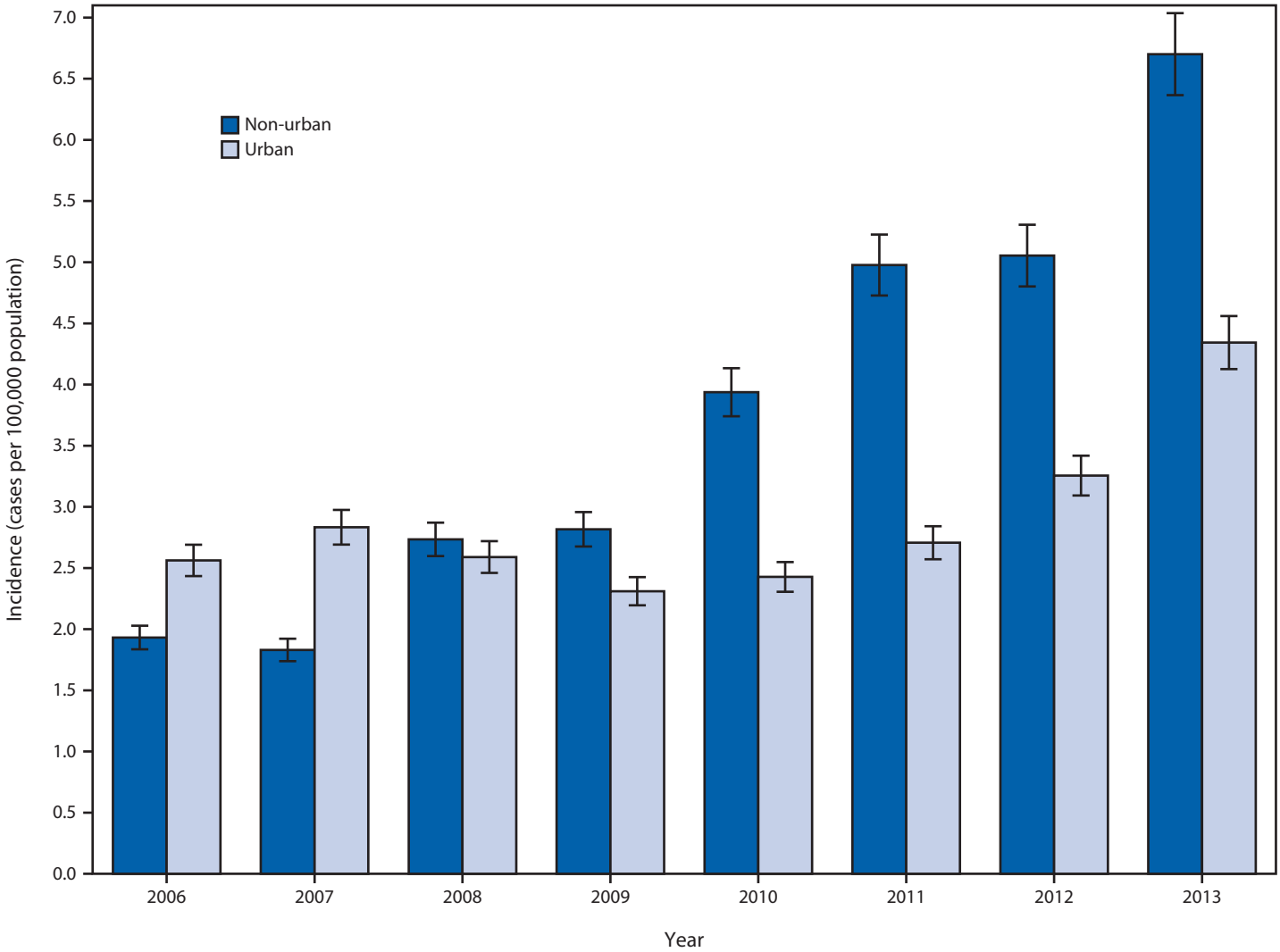
* Percentage among patients with a valid response; unknown and missing not included.

† Among patients with at least one reported risk factor on the data abstraction form; N=795 (2006–2009: n= 340; 2010–2013: n=455); unknown and missing not included.

Forty-two percent of cases of acute HBV infection in this report occurred among persons residing in non-urban counties, which is where the largest increases in incidence of acute HBV infection occurred. A similar increase of acute HCV infections occurred among young adults residing in non-urban areas in Kentucky, Tennessee, Virginia, and West Virginia (*6*). The concurrent increase in reports of acute HBV and HCV infections, as well as an increase in injection drug use reported among this population is concerning. Together, the increase in cases of acute HBV infection among persons who reported injection drug use and the typically low hepatitis B vaccination coverage among young adults are likely contributing to the increase in acute HBV infection incidence in Kentucky, Tennessee, and West Virginia. A concomitant increase in the number of substance abuse treatment admissions for opioid dependency in Appalachian states during 2006–2013 was also observed: admissions for prescription opioid and heroin abuse increased among young adults by 17.1% and 7.4%, respectively (*6*). In 2015, a rural county in Indiana was the site of a large outbreak of HIV infection and HCV infection among young (median age = 32 years) injection drug users (*8*).

Hepatitis B vaccination is recommended as primary prevention for adults who are at increased risk for HBV infection,

FIGURE 2. Incidence* of acute hepatitis B virus infection by urban/non-urban† county of residence — Kentucky, Tennessee, and West Virginia, 2006–2013



* With 95% confidence intervals as error bars.
† Trend significant among non-urban residence data at p<0.001.

including injection drug users who were not previously infected (*9*). Data from the National Health Interview Survey indicate that hepatitis B vaccination coverage is low among adults in the general population (*4*), and it is likely to be lower among injection drug users. Routine hepatitis B vaccination has been recommended for infants since 1991 and for children aged ≤18 years since 1999; thus, adults aged ≥33 years in 2013 would be too old to have benefited from routine hepatitis B vaccination recommendations, and would be susceptible to HBV infection.

In response to this increase in acute HBV infections, state health officials are employing various prevention strategies. Since 2012, Tennessee has partnered with county jails to increase hepatitis B vaccination coverage among incarcerated persons. West Virginia has collaborated with addiction centers and harm reduction services to provide viral hepatitis prevention trainings. West Virginia is establishing an adult hepatitis B vaccination pilot project in the 17 counties with the highest incidence of acute HBV infection. To enhance viral hepatitis surveillance in Kentucky, reporting of HBV infection among pregnant women and children aged <5 years, in addition to all acute HBV infection cases, is mandatory. Kentucky has also increased hepatitis B awareness campaigns through annual statewide hepatitis conferences, health care provider education, and legislative amendments allowing syringe exchange programs.

The National Viral Hepatitis Action Plan recommends full vaccination of adolescents, as well as ensuring that injection drug users have access to viral hepatitis prevention, care, and

treatment services (*10*). This can be accomplished by mobilizing community resources to identify persons at risk, increase hepatitis B vaccination coverage among all adolescents and adult injection drug users, screen and test for HBV, HCV, and HIV infections, and link persons with viral hepatitis to care. A goal for hepatitis B elimination is vaccination of all vulnerable youth and adults; thus, the delivery of hepatitis prevention and care should be expanded to include correctional facilities and abuse treatment centers.

The findings in this report are subject to at least five limitations. First, NNDSS is a passive surveillance system, and therefore, unreported cases might have been missed. Second, the current case definition for acute HBV infection captures only symptomatic persons and excludes persons with asymptomatic HBV infection, and therefore might result in underreporting of total acute HBV cases. Third, acute HBV infection case reports typically originate from past or present medical care; thus, certain populations at high risk (e.g., persons who are incarcerated, homeless, and uninsured) with limited access to care could potentially be underrepresented. Fourth, increased reporting and changes in testing practices might have contributed to the increase in HBV incidence observed in the three Appalachian states in this report. However, an upward trend in incidence was not seen in other areas of the country, and began before the release of the CDC HCV testing recommendations that might have affected HBV testing and reporting. Finally, risk factor data, including injection drug use, were not available for all reported cases.

A hepatitis B epidemic is emerging in Kentucky, Tennessee, and West Virginia. The increase in incident HBV-infections might contribute to future increases in liver-related morbidity and mortality. Evidence-based prevention strategies, including increasing hepatitis B vaccination coverage, testing and linkage to care activities, and education campaigns targeting persons who inject drugs are urgently needed.

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Active Monitoring of Travelers Arriving from Ebola-Affected Countries — New York City, October 2014–April 2015

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The Ebola virus disease (Ebola) outbreak in West Africa has claimed approximately 11,300 lives (*1*), and the magnitude and course of the epidemic prompted many nonaffected countries to prepare for Ebola cases imported from affected countries. In October 2014, CDC and the Department of Homeland Security (DHS) implemented enhanced entry risk assessment and management at five U.S. airports: John F. Kennedy (JFK) International Airport in New York City (NYC), O'Hare International Airport in Chicago, Newark Liberty International Airport in New Jersey, Hartsfield-Jackson International Airport in Atlanta, and Dulles International Airport in Virginia (*2*). Enhanced entry risk assessment began at JFK on October 11, 2014, and at the remaining airports on October 16 (*3*). On October 21, DHS exercised its authority to direct all travelers flying into the United States from an Ebola-affected country to arrive at one of the five participating airports. At the time, the Ebola-affected countries included Guinea, Liberia, Mali, and Sierra Leone. On October 27, CDC issued updated guidance for monitoring persons with potential Ebola virus exposure (*4*), including recommending daily monitoring of such persons to ascertain the presence of fever or symptoms for a period of 21 days (the maximum incubation period of Ebola virus) after the last potential exposure; this was termed "active monitoring." CDC also recommended "direct active monitoring" of persons with a higher risk for Ebola virus exposure, including health care workers who had provided direct patient care in Ebola-affected countries. Direct active monitoring required direct observation of the person being monitored by the local health authority at least once daily (*5*). This report describes the operational structure of the NYC Department of Health and Mental Hygiene's (DOHMH) active monitoring program during its first 6 months (October 2014–April 2015) of operation. Data collected on persons who required direct active monitoring are not included in this report.

DOHMH began planning for the possible importation of an Ebola case in August 2014 and activated its Incident Command System on October 3, 2014, after the first importation of Ebola into the United States occurred in Texas (*6*). On October 23, a humanitarian aid worker who had recently returned from Guinea was hospitalized in NYC and received a diagnosis of Ebola (*7*). On October 25, DOHMH, having been informed that CDC would be issuing guidance on monitoring travelers on October 27, opened the Active Monitoring Call Center (AMCC) to monitor personnel who had contact with the NYC patient or with laboratory specimens and medical waste originating from the patient. Active monitoring also was implemented for travelers who had been in an Ebola-affected country within the preceding 21 days. Almost all of these travelers were designated as at low (but not zero) risk for an Ebola virus exposure because they had been in countries with widespread Ebola virus transmission but had no known exposures (*8*).

DHS personnel at ports of entry collected information about travelers requiring active monitoring for Ebola, which was entered into a database and then transmitted to DOHMH through CDC's Epidemic Information Exchange (Epi-X),* a secure notification system (*3*). Additional information could also be collected through other domestic public health investigations. Risk classification of travelers (i.e., high risk, some risk, low [but not zero] risk, or no identifiable risk) (*4*) was generally performed by CDC staff members at ports of entry and was included in the Epi-X notification.

DOHMH assigned a unique identification number to each traveler and sent an e-mail to the traveler with instructions for contacting the AMCC. DOHMH then assigned travelers who required active monitoring to AMCC phone operators, who made at least two call attempts to all available telephone numbers, including to telephones issued to incoming travelers by CDC. Operators asked travelers to report two separate temperature recordings from the previous 24-hour period, any episodes of vomiting, diarrhea, or unexplained bleeding or bruising, and any plans for overnight travel outside of NYC. Any traveler who reported a temperature ≥100.0°F (37.8°C) or symptoms was referred to the DOHMH physician on call for Ebola monitoring for evaluation. Possible outcomes after referral included continuing to monitor the traveler per usual protocol, increasing the frequency of monitoring (with or without restriction of movement), or transporting the traveler to a health care facility for further evaluation.

AMCC operators documented all call attempts regardless of outcome. A daily report was generated for AMCC leadership review; the report indicated which travelers did not provide monitoring data for 2 calendar days, including monitoring data collected previously, if any, and which travelers had incorrect contact information. For those travelers who did not respond to multiple contact attempts over 2 days, AMCC leadership

* http://www.cdc.gov/24-7/savinglives/epi-x/index.html.

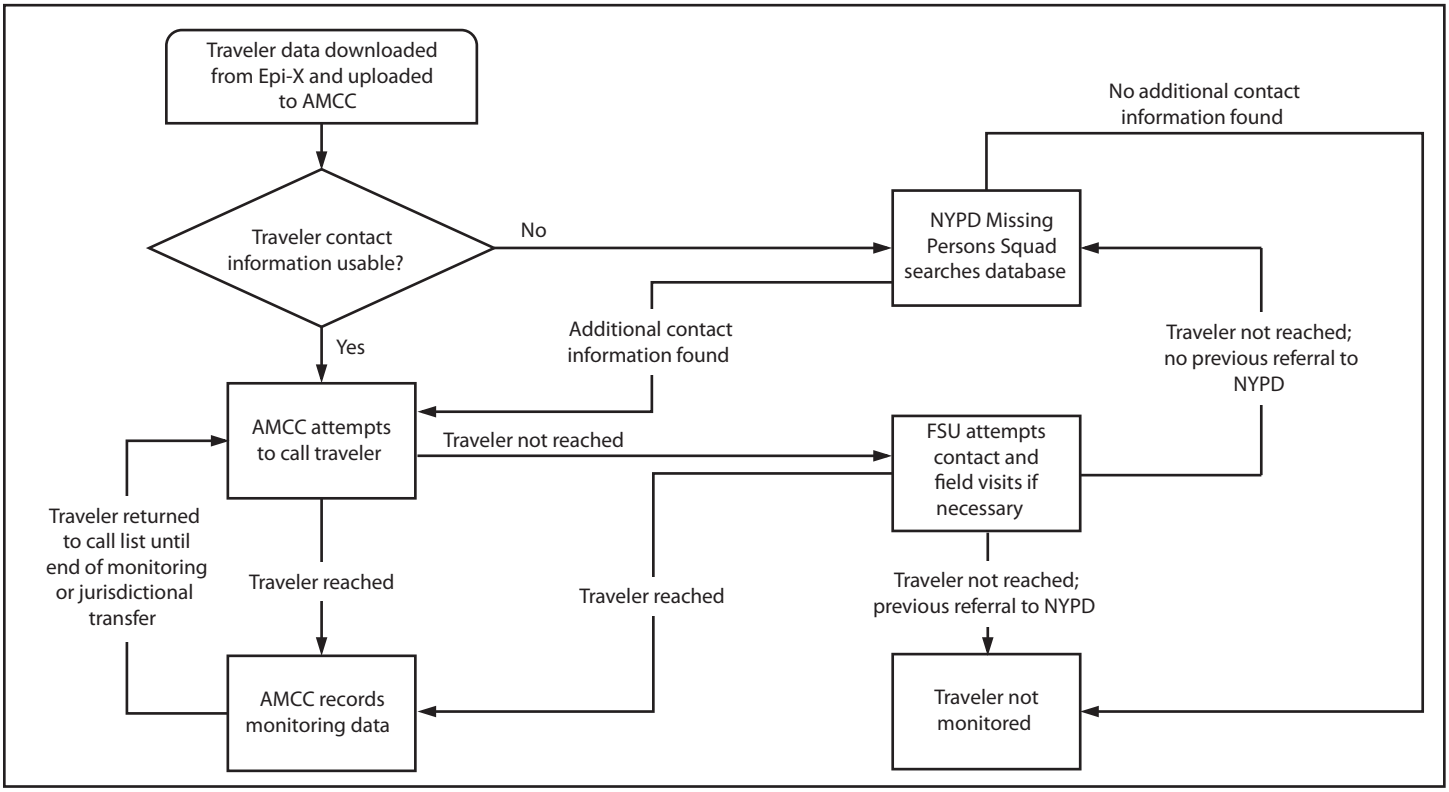
decided to either make additional call attempts that evening, or refer the travelers' records to the NYC Police Department Missing Persons Squad to conduct a database search for additional contact information or the DOHMH Field Surveillance Unit to visit any addresses listed, including those of emergency contacts. Daily monitoring reports for the NYC Office of the Mayor and weekly reports for CDC also were generated (Figure).

During October 25, 2014–April 30, 2015, CDC referred 2,452 travelers to DOHMH for active monitoring. The number of travelers referred each day ranged from 1–106 (mean = 13 travelers, standard deviation [SD] = 10). Travelers arrived from all the Ebola-affected countries, with 47.4% originating in Guinea. Among all travelers, 44.0% were female; the mean age was 39 years, and 28.3% were U.S. citizens. Only 57.7% reported feeling comfortable communicating in English for the purpose of active monitoring (Table 1). Overall, 2,407 (98.1%) referred travelers required active monitoring. The 45 (1.9%) travelers who did not require monitoring were either transiting to another jurisdiction or had errors in their itineraries. The number of travelers called by AMCC operators ranged from eight to 301 per day (mean = 192, SD = 53).

Whereas some travelers were monitored for the full 21-day period, a traveler's monitoring period could be <21 days if, for example, the traveler spent time in another jurisdiction between leaving an Ebola-affected country and arriving in NYC. During October 25, 2014–April 30, 2015, monitoring data were successfully collected for >75% of the traveler's monitoring period for 2,138 (88.8%) travelers, for 50%–75% of the monitoring period for 100 (4.2%) travelers, and for <50% of the monitoring period for 61 (2.5%) travelers. For 108 (4.5%) travelers, no monitoring data were collected (Table 2). Successful collection of monitoring data for travelers requiring active monitoring improved over time. For example, during October 25, 2014–December 31, 2014, data were successfully collected for >75% of the travelers' monitoring period for 556 of 796 (69.8%) travelers compared with 1,582 of 1,611 (98.2%) travelers during January 1, 2015–April 30, 2015 ($p<0.01$). Among the 2,299 (94%) travelers reached for monitoring, 785 (34.1%) left NYC during their monitoring period, including travelers who left the country or were transferred to another local health authority to continue active monitoring.

Approximately 98% of monitored travelers reported no fever or symptoms. Twenty-six (1.1%) reported fever only; 27 (1.2%) reported symptoms including diarrhea, vomiting or unexplained bleeding or bruising but no fever, and one (0.04%) reported fever and symptoms. All travelers reporting

FIGURE. Flowchart showing protocol for active monitoring of travelers arriving from Ebola-affected countries — New York City, October 2014–April 2015



Abbreviations: AMCC = Active Monitoring Call Center; Epi-X = CDC's Epidemic Information Exchange; FSU = Field Surveillance Unit; NYPD = New York City Police Department.

TABLE 1. Characteristics of travelers arriving from Ebola-affected countries who were referred to the Department of Health and Mental Hygiene for active monitoring — New York City, October 25, 2014–April 30, 2015

Characteristic	No. (%)
Travelers referred for active monitoring*	**2,452 (100.0)**
Ebola-affected country visited	
Guinea	1,162 (47.4)
Liberia	546 (22.3)
Sierra Leone	339 (13.8)
Mali†	264 (10.8)
More than one country	88 (3.6)
Unknown	53 (2.1)
Sex	
Male	1,371 (56.0)
Female	1,081 (44.0)
Citizenship	
Non-United States§	1,371 (56.0)
United States	695 (28.3)
Unknown	386 (15.7)
Comfortable being monitored in English¶	
Yes	1,414 (57.7)
No	643 (26.2)
Unknown	395 (16.1)

* A mean of 13 (range = 1–106) travelers were referred each day (standard deviation [SD] = 10). Mean age of travelers = 39 years (SD = 16 years); range = 3–86 years.
† Travelers from Mali were monitored from November 17, 2014 to January 6, 2015.
§ Travelers' passports were from 67 countries and the United Nations.
¶ Travelers who responded to an optional language preference question listed sign language and eight other languages (Bombara, Chinese, Creole, French, Fulani, Mandinga, and Pular). The Active Monitoring Call Center staff included bilingual personnel to facilitate communication with persons with non-English language preferences.

TABLE 2. Monitoring results for travelers arriving from Ebola-affected countries who were referred to the Department of Health and Mental Hygiene for active monitoring — New York City, October 25, 2014–April 30, 2015

Monitoring result	No. (%)
Travelers referred for active monitoring	**2,452 (100.0)**
Travelers requiring active monitoring	2,407 (98.1)
Active monitoring not required*	45 (1.9)
Completeness of monitoring data collected for travelers	
Monitoring data collected for >75% of monitoring period†	2,138 (88.8)
Monitoring data collected for 50%–75% of monitoring period	100 (4.2)
Monitoring data collected for <50% of monitoring period	61 (2.5)
No monitoring data collected§	108 (4.5)
Travelers' jurisdictional transfer and symptom data¶	
Transferred out of NYC at any point during monitoring period	785 (34.1)
Reported temperature ≥100.0°F	26 (1.1)
Reported symptom(s)**	27 (1.2)
Reported temperature ≥100.0°F and symptom(s)**	1 (0.04)

* Includes travelers transferred >21 days after departure date from an Ebola-affected country, travelers who did not travel to the Ebola-affected countries but had been referred because of an itinerary error, and travelers found to be in other jurisdictions.
† Travelers monitored >75% of the time increased from 556 of 796 (69.8%) travelers during October 25, 2014–December 31, 2014, to 1,582 of 1,611 (98.2%) travelers during January 1, 2015–April 30, 2015 (p<0.01).
§ Travelers not monitored decreased from 98 during October 25, 2014–December 31, 2014 to 10 during January 1, 2015–April 30, 2015.
¶ Percentages based on 2,299 travelers reached for monitoring.
** Includes diarrhea, vomiting, and unexplained bleeding or bruising.

fever or symptoms were evaluated by the DOHMH physician on-call for Ebola monitoring to assess the evolution of illness and provide recommendations for any additional steps to take while the traveler remained ill. No cases of Ebola were detected among travelers reporting fever or symptoms during their monitoring period.

Discussion

The design and implementation of the Ebola active monitoring program by DOHMH required substantial resources. Although preparation for an imported Ebola case was under way in NYC since August 2014, the recommendation to actively monitor all travelers from Ebola-affected countries was not anticipated, and the program was established with little advance planning. The active monitoring program relied largely on existing funding, personnel, and technology, much of which was immediately available only because of continuous federal investment toward strengthening local public health capacity and public health emergency preparedness. Enhanced entry risk assessment and active monitoring for Ebola were new processes for CDC and local health authorities, and in the early stages of the national rollout, challenges included poor data quality, lack of standard procedures for active monitoring of travelers as they moved between jurisdictions, and lack of standard methods of communication among local health authorities.

Despite the challenges, DOHMH created a robust system that benefited from continuous quality improvement as inefficiencies were assessed and addressed over time. Database software was updated to improve workflow operations, the flexibility of the information technology system, and report generation, which enhanced the coordination of monitoring activities. Epi-X data quality improved, especially with the accuracy of contact numbers following the provision of CDC-issued telephones to arriving travelers. As the program developed, staffing of the AMCC was able to transition to temporary workers, thus permitting DOHMH personnel to return to their regular duties. These improvements reduced reliance on DOHMH resources, and enabled the system to accommodate unexpected additions of up to 106 new travelers in a single day while continuing to conduct monitoring of an average of 192 travelers each day.

At present, CDC no longer recommends active monitoring of returning travelers returning from Mali, Liberia, Sierra Leone, or Guinea unless there is an identified potential Ebola virus exposure (*9*). DOHMH ended its active monitoring program on December 29, 2015. Maintaining the active monitoring program for the duration of the Ebola epidemic in West Africa required sustained effort and resources drawn

Summary

What is already known on this topic?

The Ebola virus disease (Ebola) outbreak in West Africa prompted many nonaffected countries to prepare for possible importation of Ebola cases. State and local health departments in the United States developed programs to implement active monitoring of returning travelers from Ebola-affected countries.

What is added by this report?

During October 25, 2014–April 30, 2015, CDC referred 2,452 travelers to the New York City Department of Health and Mental Hygiene's (DOHMH's) active monitoring program. A total of 2,407 (98.1%) of referred travelers required active monitoring; no cases of Ebola were detected.

What are the implications for public health practice?

The DOHMH's active monitoring program was successful in monitoring travelers returning from Ebola-affected countries; however, maintenance of the active monitoring program required sustained effort and resources drawn from core public health functions. Public health authorities should continue to work together and identify best practices to enhance information sharing and minimize duplication of efforts for future public health emergencies.

from core public health functions. Public health authorities should continue to work together and identify best practices to enhance information sharing and minimize unnecessary duplication of efforts for future public health emergencies.

Acknowledgments

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Zika Virus Spreads to New Areas — Region of the Americas, May 2015–January 2016

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Zika virus is a mosquito-borne flavivirus that was first identified in Uganda in 1947 (*1*). Before 2007, only sporadic human disease cases were reported from countries in Africa and Asia. In 2007, the first documented outbreak of Zika virus disease was reported in Yap State, Federated States of Micronesia; 73% of the population aged ≥3 years is estimated to have been infected (*2*). Subsequent outbreaks occurred in Southeast Asia and the Western Pacific (*3*). In May 2015, the World Health Organization reported the first local transmission of Zika virus in the Region of the Americas (Americas), with autochthonous cases identified in Brazil (*4*). In December, the Ministry of Health estimated that 440,000–1,300,000 suspected cases of Zika virus disease had occurred in Brazil in 2015 (*5*). By January 20, 2016, locally-transmitted cases had been reported to the Pan American Health Organization from Puerto Rico and 19 other countries or territories in the Americas* (Figure) (*6*). Further spread to other countries in the region is being monitored closely.

Although local transmission of Zika virus has not been documented in the continental United States, Zika virus infections have been reported in returning travelers (*7*). In light of the recent outbreaks in the Americas, the number of Zika virus disease cases among travelers visiting or returning to the United States is likely to increase. These imported cases might result in local human-to-mosquito-to-human spread of the virus in limited areas of the continental United States that have the appropriate mosquito vectors.

Zika virus is transmitted primarily by *Aedes aegypti* mosquitoes (*1*,*7*). *Aedes albopictus* mosquitoes also might transmit the virus. *Aedes aegypti* and *Ae. albopictus* mosquitoes are found throughout much of the Americas, including parts of the United States, and also transmit dengue and chikungunya viruses. In addition to mosquito-to-human transmission, Zika virus infections have been documented through intrauterine transmission resulting in congenital infection, intrapartum transmission from a viremic mother to her newborn, sexual transmission, blood transfusion, and laboratory exposure (*5*). There is a theoretical concern that transmission could occur through organ or tissue transplantation, and although Zika virus RNA has been detected in breast milk, transmission through breastfeeding has not been documented (*5*).

During outbreaks, humans are the primary amplifying host for Zika virus. An estimated 80% of persons who are infected with Zika virus are asymptomatic (*2*). Symptomatic disease generally is mild and characterized by acute onset of fever, maculopapular rash, arthralgia, or nonpurulent conjunctivitis. Symptoms usually last from several days to 1 week. Based on information from previous outbreaks, severe disease requiring hospitalization is uncommon, and fatalities are rare. During the current outbreak in Brazil, Zika virus RNA has been identified in tissues from several infants with microcephaly and from fetal losses in women who were infected during pregnancy (*5*,*7*,*8*). The Brazil Ministry of Health has reported a marked increase in the number of infants born with microcephaly in 2015, although it is not known how many of these cases are associated with Zika virus infection (*8*). Guillain-Barré syndrome also has been reported in patients following suspected Zika virus infection (*5*). Studies are under way to evaluate the risks for Zika virus transmission during pregnancy, the spectrum of outcomes associated with congenital infection, and the possible association between Zika virus infection and Guillain-Barré syndrome.

Zika virus infection should be considered in patients with acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis, who traveled to areas with ongoing transmission in the 2 weeks preceding illness onset. Because dengue and chikungunya virus infections share a similar geographic distribution with Zika virus and symptoms of infection are similar, patients with suspected Zika virus infections also should be evaluated and managed for possible dengue or chikungunya virus infection (*9*,*10*). Other considerations in the differential diagnosis include malaria, rubella, measles, parvovirus, adenovirus, enterovirus, leptospirosis, rickettsia, and group A streptococcal infections.

There is no commercially available test for Zika virus. Zika virus testing is performed in the United States at CDC and four state health department laboratories, and CDC is working to expand laboratory diagnostic testing to additional states. Health care providers should contact their state or local health department to facilitate testing. To evaluate for evidence of Zika virus infection, reverse transcription–polymerase chain reaction (RT-PCR) testing should be performed

* Barbados, Bolivia, Brazil, Colombia, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, and Venezuela.

FIGURE. Countries and territories with documented local transmission of Zika virus infection reported to the Pan American Health Organization — Region of the Americas, 2015–2016

on serum specimens collected within the first week of illness (*11*). Immunoglobulin M and neutralizing antibody testing should be performed on specimens collected ≥4 days after onset of illness; however, these serologic assays can be positive because of cross-reacting antibodies against related flaviviruses (e.g., dengue and yellow fever viruses). Virus-specific cross-neutralization testing can be used to discriminate between cross-reacting antibodies in primary flavivirus infections, although neutralizing antibodies might still yield cross-reactive results in persons who were previously infected or vaccinated against a related flavivirus (i.e., secondary flavivirus infection).

No specific antiviral treatment is available for Zika virus disease. Treatment is generally supportive and can include rest, fluids, and use of analgesics and antipyretics. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue can be ruled out to reduce the risk of hemorrhage. Febrile pregnant women should be treated with acetaminophen. Persons infected with Zika, dengue, or

chikungunya virus should be protected from further mosquito exposure during the first few days of illness to reduce the risk for local transmission.

No vaccine to prevent Zika virus infection is available. The best way to prevent Zika virus infection is to avoid mosquito bites by using air conditioning or window and door screens when indoors, wearing long sleeves and pants, using permethrin-treated clothing and gear, and using insect repellents when outdoors. Most Environmental Protection Agency (EPA)–registered repellents, including N,N-diethyl-m-toluamide (DEET), can be used on children aged >2 months (*12*). When used according to the product label, EPA-registered insect repellents also are safe for pregnant and lactating women. All travelers should take steps to avoid mosquito bites to prevent Zika virus infection and other mosquito-borne diseases.

Until more is known, and out of an abundance of caution, pregnant women should consider postponing travel to any area where Zika virus transmission is ongoing.[†] Pregnant women who do travel to one of these areas should talk to their health care provider before traveling and strictly follow steps to avoid mosquito bites during travel. Pregnant women who develop a clinically compatible illness during or within 2 weeks of returning from an area with Zika virus transmission should be tested for Zika virus infection (*13*). Fetuses and infants of women infected with Zika virus during pregnancy should be evaluated for possible congenital infection.

Health care providers are encouraged to report suspected Zika virus disease cases[§] to their state or local health departments to facilitate diagnosis and mitigate the risk for local transmission in areas where *Aedes* species mosquitoes are currently active. State health departments are requested to report laboratory-confirmed cases to CDC. CDC is working with the Council of State and Territorial Epidemiologists and other partners to develop a surveillance case definition, to provide further guidance and mechanisms for evaluating and reporting cases, and to track the outcomes of pregnant women infected with Zika virus and their babies.

[†] CDC. Traveler's health notices. http://wwwnc.cdc.gov/travel/notices/.

[§] The interim case definition for suspected Zika virus disease is an illness characterized by acute onset of two or more of the following: fever, maculopapular rash, arthralgia, or nonpurulent conjunctivitis not explained by other medical conditions, in a person who resides in or has visited an area with ongoing Zika virus transmission within 2 weeks before the onset of symptoms.

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Summary

What is already known on this topic?

Zika virus is a mosquito-borne flavivirus transmitted primarily by *Aedes aegypti* mosquitoes. Most infections are asymptomatic, and symptomatic disease generally is mild. In May 2015, the first local transmission of Zika virus in the Region of the Americas was reported in Brazil. Following the spread of Zika virus in Brazil, there has been a marked reported increase in the number of infants born with microcephaly; it is not known how many of these cases are associated with Zika virus infection.

What is added by this report?

By mid-January 2016, local Zika virus transmission had been reported to the Pan American Health Organization from 20 countries or territories in the Region of the Americas; spread to other countries in the region is likely. Although local transmission of Zika virus has not been documented in the continental United States, infections have been reported among travelers visiting or returning to the United States, and these likely will increase. Imported cases might result in local transmission in limited areas of the continental United States.

What are the implications for public health practice?

The best way to prevent Zika virus infection is to avoid mosquito bites by avoiding exposure and eliminating mosquito breeding areas. Until more is known, pregnant women should consider postponing travel to any area with ongoing Zika virus transmission. Health care providers should contact their state or local health department about testing patients with symptoms of Zika virus infection and a compatible travel history.

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Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015

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In early 2015, an outbreak of Zika virus, a flavivirus transmitted by *Aedes* mosquitoes, was identified in northeast Brazil, an area where dengue virus was also circulating. By September, reports of an increase in the number of infants born with microcephaly in Zika virus-affected areas began to emerge, and Zika virus RNA was identified in the amniotic fluid of two women whose fetuses had been found to have microcephaly by prenatal ultrasound. The Brazil Ministry of Health (MoH) established a task force to investigate the possible association of microcephaly with Zika virus infection during pregnancy and a registry for incident microcephaly cases (head circumference ≥2 standard deviations [SD] below the mean for sex and gestational age at birth) and pregnancy outcomes among women suspected to have had Zika virus infection during pregnancy. Among a cohort of 35 infants with microcephaly born during August–October 2015 in eight of Brazil's 26 states and reported to the registry, the mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy, 25 (71%) infants had severe microcephaly (head circumference >3 SD below the mean for sex and gestational age), 17 (49%) had at least one neurologic abnormality, and among 27 infants who had neuroimaging studies, all had abnormalities. Tests for other congenital infections were negative. All infants had a lumbar puncture as part of the evaluation and cerebrospinal fluid (CSF) samples were sent to a reference laboratory in Brazil for Zika virus testing; results are not yet available. Further studies are needed to confirm the association of microcephaly with Zika virus infection during pregnancy and to understand any other adverse pregnancy outcomes associated with Zika virus infection. Pregnant women in Zika virus-affected areas should protect themselves from mosquito bites by using air conditioning, screens, or nets when indoors, wearing long sleeves and pants, using permethrin-treated clothing and gear, and using insect repellents when outdoors. Pregnant and lactating women can use all U.S. Environmental Protection Agency (EPA)-registered insect repellents according to the product label.

An outbreak of Zika virus infection was recognized in northeast Brazil in early 2015 (*1*). In September 2015, health authorities began to receive reports from physicians in this region of an increase in the number of infants born with microcephaly. In October, the MoH confirmed an increase in birth prevalence of microcephaly in northeast Brazil, compared with previously reported estimates (approximately 0.5/10,000 live births), which are based on review of birth certificates and include descriptions of major congenital anomalies. The MoH rapidly established a microcephaly registry in Brazil. On November 17, 2015, the MoH reported the increase in microcephaly cases, and possible association of microcephaly with Zika virus infection during pregnancy on its website;* and the Pan American Health Organization (PAHO) published an alert regarding the increase in occurrence of microcephaly in Brazil (*2*). In December, PAHO reported the identification of Zika virus RNA by reverse transcription-polymerase chain reaction (RT-PCR) in amniotic fluid samples from two pregnant women whose fetuses were found to have microcephaly by prenatal ultrasound, and the identification of Zika virus RNA from multiple body tissues, including the brain, of an infant with microcephaly who died in the immediate neonatal period (*3*). These events prompted new alerts from the MoH, the European Centre for Disease Prevention and Control (*4*), and CDC (*5*) concerning the possible association of microcephaly with the recent outbreak of Zika virus infection.

A comprehensive protocol for notification and investigation of all infants with microcephaly and all women with suspected Zika virus infection during pregnancy was developed by the MoH and implemented nationwide. In addition, the Brazilian Society of Medical Genetics established the Zika Embryopathy Task Force (SBGM–ZETF), which includes clinical geneticists, obstetricians, pediatricians, neurologists, and radiologists, to review all incident cases of microcephaly as well as all infants born to mothers with suspected Zika virus infection during pregnancy. Task force members collect data concerning the pregnancy (including exposure history, symptoms, and laboratory testing), physical examination of the infant, and any additional studies using a standardized spreadsheet. Microcephaly was defined as neonatal head circumference ≥2 SD below the mean for gestational age and sex of the infant at birth. Infection with Zika virus is difficult to confirm retrospectively because

*http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saudedivulga-boletim-epidemiologico.

serological immunological tests might cross-react with other flaviviruses, especially dengue virus (*6*). Therefore a mother's report of a rash illness during pregnancy was used as a proxy indicator of potential Zika virus infection.

Although 37 infants with microcephaly were evaluated, only 35 cases are included in this report. Two infants with microcephaly were excluded from the original cohort of 37 babies: one had autosomal recessive microcephaly with sibship recurrence, and one had cytomegalovirus infection. Overall, 26 (74%) mothers of infants with microcephaly reported a rash during the first (n = 21) or second (5) trimester (Table). Residence in or travel during pregnancy to areas where Zika virus is circulating was confirmed for all mothers, including women without a history of rash. Twenty-five (74%) infants had severe microcephaly (head circumference >3 SD below the mean for gestational age). Computed tomography scans and transfontanellar cranial ultrasounds showed a consistent pattern of widespread brain calcifications, mainly in the periventricular, parenchymal, and thalamic areas, and in the basal ganglia, and was associated in approximately one third of cases with evidence of cell migration abnormalities (e.g., lissencephaly, pachygyria). Ventricular enlargement secondary to cortical/subcortical atrophy was also frequently reported. Excessive and redundant scalp skin, reported in 11 (31%) cases, also suggests acute intrauterine brain injury, indicating and arrest in cerebral growth, but not in growth of scalp skin. Four (11%) infants had arthrogryposis (congenital contractures), indicative of central or peripheral nervous system involvement (*7*). All 35 infants in the cohort tested negative for syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus infections. CSF samples from all infants enrolled in the cohort were sent to a reference laboratory in Brazil for Zika virus testing; the results are not yet available.

Discussion

Microcephaly usually results from abnormal brain development. The long-term consequences of microcephaly depend on underlying brain anomalies and can range from mild developmental delays to severe motor and intellectual deficits, like cerebral palsy. In addition to congenital infections, microcephaly can result from chromosomal abnormalities; exposure to drugs, alcohol, or other environmental toxins; premature fusion of the bones of the skull (craniosynostosis); and certain metabolic disorders. The sudden increase in the number of infants born with microcephaly associated with cerebral damage characteristically seen in congenital infections in a region where an outbreak of a newly circulating virus has recently occurred is suggestive of a possible relationship. The association between maternal infections and congenital anomalies has long been recognized, especially when infection occurs during the first 12 weeks of pregnancy (*8*). Brazil's vaccination program has eliminated some infections that result in congenital anomalies, such as rubella. Congenital infections can affect multiple organ systems, and many are associated with specific brain damage, including microcephaly, calcifications (predominantly periventricular, but also in the basal ganglia and in cerebral parenchyma), ventriculomegaly, neuronal migration disorders (pachygyria, polymicrogyria, lissencephaly, and schizenchephaly), cerebellar hypoplasia, and white matter anomalies (*8*). Ongoing surveillance and evaluation of new cases are important to describe the phenotypic spectrum of potential Zika virus-associated congenital infections. In addition, special studies, including case-control studies, are needed to confirm the association, determine the magnitude of the potential risk, and identify other possible risk factors.

CDC recently tested samples from two pregnancies that ended in miscarriage and from two infants with microcephaly who died shortly after birth. All four cases were from Brazil and were positive for Zika virus infection, indicating that the infants had become infected during pregnancy. Zika virus was present in the brain of the full term infants, and genetic sequence analyses show that the virus in all four cases was the same as the Zika virus strain currently circulating in Brazil. All four mothers reported having experienced a febrile rash illness during their pregnancies.[†]

Prevention strategies established by the MoH include aggressive efforts to eliminate mosquito breeding areas by removing standing water containers, as well as recommendations for personal protective measures, including preventing mosquito bites among pregnant women by applying insect repellents, wearing long-sleeved shirts and long pants, and using mosquito nets, as well as risk communication and community mobilization (*3*). Pregnant and lactating women can use all EPA-registered insect repellents according to the product label.

This findings in this report are subject to at least four limitations. First, historical birth prevalence of microcephaly in Brazil, approximately 0.5 cases per 10,000 live births, calculated from birth certificates, was lower than expected estimates of 1–2 cases per 10,000 live births (*9*), which might indicate general underascertainment of microcephaly in Brazil. However, during the second half of 2015 alone, >3,000 suspected cases of microcephaly (approximately 20 cases per 10,000 live births) were reported to the MoH through the special notification protocol, suggesting a sharp increase in birth prevalence, although the special notification protocol might have also increased case reporting. Second, before the November MoH alert, although descriptions of congenital anomalies were reported, infant head circumference was not routinely recorded. Hence, it is possible that mild cases of microcephaly might not have been reported. Since the MoH alert

[†] http://www.cdc.gov/media/releases/2016/t0116-zika-virus-travel.html.

Summary

What is already known about this topic?

An outbreak of Zika virus infection, a flavivirus transmitted by *Aedes* mosquitoes, was first recognized in northeastern Brazil in early 2015. In September, a sharp increase in the number of reported cases of microcephaly was reported in areas affected by the outbreak.

What is added by this report?

The Brazil Ministry of Health developed a case definition for Zika virus–related microcephaly (head circumference ≥2 standard deviations [SD] below the mean for sex and gestational age at birth). A task force and registry were established to investigate Zika virus–related cases of microcephaly and to describe the clinical characteristics of cases. Among the first 35 cases of microcephaly reported to the registry, 74% of mothers reported a rash illness during pregnancy, 71% of infants had severe microcephaly (>3 SD below the mean), approximately half had at least one neurologic abnormality, and among 27 who had neuroimaging studies, all were abnormal. Cerebrospinal fluid from all infants is being tested for Zika virus; results are not currently available.

What are the implications for public health practice?

The increased occurrence of microcephaly associated with cerebral damage characteristically seen in congenital infections in Zika virus-affected areas is suggestive of a possible relationship. Additional studies are warranted to confirm the association and to more fully characterize the phenotype. In addition to removing potential breeding areas for mosquitoes, pregnant women in Zika-affected areas should wear protective clothing, apply a U.S. Environmental Protection Agency (EPA)-approved insect repellent, and sleep in a screened room or under a mosquito net.

and the attendant media coverage of the outbreak, surveillance for microcephaly and physician reporting of suspected cases have increased. Third, because Zika virus infection was not laboratory-confirmed in infants or their mothers, the history of a nonspecific rash illness during pregnancy is subject to recall bias and might have resulted in misclassification of potential Zika virus exposure. Finally, this report does not comment on other features characteristic of intrauterine infections such as hepatosplenomegaly, rash, and chorioretinitis, or on some features that have been reported in cases with presumed Zika including hearing loss, pale maculas, and swallowing difficulties.

As of January 2016, there has been confirmed autochthonous transmission of Zika virus in 19 countries in the Americas outside Brazil (*10*). Although other countries in the Americas, including Uruguay and Argentina, have not reported autochthonous Zika virus, the presence of a competent vector, *Ae. aegypti*, in these countries poses a potential risk for further spread of the virus.

TABLE. Main phenotypical findings of the first 35 patients enrolled in the Brazilian Society of Medical Genetics–Zika Embryopathy Task Force Registry — Brazil, 2015

Characteristic	n (%)
Reported maternal rash during pregnancy	
First trimester	21 (57)
Second trimester	5 (14)
Not reported	9 (26)
Sex	
Female	21 (60)
Male	14 (40)
Gestational age at birth (34)*	
Term	31 (91)
Preterm	3 (9)
Weight	
≥2,500g	26 (74)
<2,500g	9 (26)
Defect	
Head circumference >3 SD	25 (71)
Head circumference >2 SD to 3 SD	10 (29)
Excessive and redundant scalp skin	11 (31)
Talipes (clubfoot)	5 (14)
Arthrogryposis (contractures)	4 (11)
Other defects (microphthalmia)	1 (3)
Abnormal funduscopic examination (11)	2 (18)
Neurologic examination	
Any abnormality	17 (49)
Hypertonia/Spasticity	13 (37)
Hyperreflexia	7 (20)
Irritability	7 (20)
Tremors	4 (11)
Seizures	3 (9)
Neuroimaging (27)	
Any abnormality	27 (100)
Calcifications	20 (74)
Ventricular enlargement	12 (44)
Neuronal migration disorders (lissencephaly, pachygyria)	9 (33)

Abbreviation: SD = standard deviations.
* Number of patients sampled was less than total (35).

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Interim Guidelines for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection — United States, 2016

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CDC has developed interim guidelines for health care providers in the United States who are caring for infants born to mothers who traveled to or resided in an area with Zika virus transmission during pregnancy. These guidelines include recommendations for the testing and management of these infants. Guidance is subject to change as more information becomes available; the latest information, including answers to commonly asked questions, can be found online (http://www.cdc.gov/zika). Pediatric health care providers should work closely with obstetric providers to identify infants whose mothers were potentially infected with Zika virus during pregnancy (based on travel to or residence in an area with Zika virus transmission [http://wwwnc.cdc.gov/travel/notices]), and review fetal ultrasounds and maternal testing for Zika virus infection (see Interim Guidelines for Pregnant Women During a Zika Virus Outbreak*) (*1*). Zika virus testing is recommended for 1) infants with microcephaly or intracranial calcifications born to women who traveled to or resided in an area with Zika virus transmission while pregnant; or 2) infants born to mothers with positive or inconclusive test results for Zika virus infection. For infants with laboratory evidence of a possible congenital Zika virus infection, additional clinical evaluation and follow-up is recommended. Health care providers should contact their state or territorial health department to facilitate testing. As an arboviral disease, Zika virus disease is a nationally notifiable condition.

Zika virus is a mosquito-borne flavivirus primarily transmitted by *Aedes aegypti* mosquitoes (*2*,*3*). *Aedes albopictus* mosquitoes also might transmit the virus. *Ae. aegypti* and *Ae. albopictus* mosquitoes are found throughout much of the Region of the Americas, including parts of the United States, and also transmit dengue and chikungunya viruses (*4*). Zika virus infections have also been documented through both intrauterine transmission resulting in congenital infection and intrapartum transmission from a viremic mother to her newborn (*5*,*6*). Zika virus RNA has been detected in breast milk, but Zika virus transmission through breastfeeding has not been documented (*5*).

* http://www.cdc.gov/mmwr/volumes/65/wr/mm6502e1.htm.

During outbreaks, humans are the primary host for Zika virus. An estimated 80% of persons infected with Zika virus are asymptomatic (*2*,*7*). Symptomatic disease generally is mild and characterized by acute onset of fever, maculopapular rash, arthralgia, or nonpurulent conjunctivitis. Symptoms typically last from several days to 1 week. Based on information from previous outbreaks, severe disease requiring hospitalization is uncommon and fatalities are rare (*6*,*7*). During the current outbreak in Brazil, Zika virus RNA has been identified in specimens (i.e., brain tissue, placenta, and amniotic fluid) from several infants with microcephaly and from fetal losses in women infected with Zika virus during pregnancy (*6*,*8*,*9*). The Brazil Ministry of Health has reported a marked increase from previous years in the number of infants born with microcephaly and intracranial calcifications in 2015, although it is not known how many of these cases are associated with Zika virus infection (*6*,*8*–*11*).

Zika Virus Testing Considerations and Classification

The diagnosis of Zika virus infection is made through molecular and serologic testing (*2*). This includes reverse transcription-polymerase chain reaction (RT-PCR) for viral RNA, and immunoglobulin (Ig) M ELISA and plaque reduction neutralization test (PRNT) for Zika virus antibodies. Because it is currently not known which type of testing most reliably establishes the diagnosis of congenital infection, CDC recommends both molecular and serologic testing of infants who are being evaluated for evidence of a congenital Zika virus infection (Box 1). No commercial tests for Zika virus are available; Zika virus testing is performed at CDC and some state and territorial health departments. Health care providers should contact their state or territorial health department to facilitate testing.

Zika virus RT-PCR testing should be performed on serum specimens collected from the umbilical cord or directly from the infant within 2 days of birth (*12*). In addition, cerebrospinal fluid (CSF) obtained for other studies, and frozen and fixed placenta obtained at delivery, should also be tested by RT-PCR. IgM ELISA for Zika virus and dengue virus should be performed on infant serum, infant CSF, and maternal serum; however, results of these assays can be falsely positive because of cross-reacting antibodies (*9*,*12*). PRNT can be

performed to measure virus-specific neutralizing antibodies and to discriminate between cross-reacting antibodies from closely related flaviviruses (e.g., dengue or yellow fever viruses). Finally, immunohistochemical staining to detect Zika virus antigen on fixed placenta and umbilical cord tissues can be considered.

An infant is considered congenitally infected if Zika virus RNA or viral antigen is identified in any of the samples submitted, including testing of amniotic fluid and testing of the placenta or umbilical cord. In addition, Zika virus IgM antibodies with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in the infant serum or CSF constitute evidence of a congenital Zika virus infection. If Zika virus neutralizing antibody titers are <4-fold higher than dengue, results are considered inconclusive.

Recommendations for Infants with Microcephaly or Intracranial Calcifications Detected Prenatally or at Birth Whose Mothers Were Potentially Infected with Zika Virus During Pregnancy

For the purpose of evaluating an infant for possible congenital Zika virus infection, microcephaly is defined as occipitofrontal circumference less than the third percentile, based on standard growth charts (e.g., Fenton, Olsen, CDC, or WHO growth curves) for sex, age, and gestational age at birth (*13*). For a diagnosis of microcephaly to be made, the occipitofrontal circumference should be disproportionately small in comparison with the length of the infant and not explained by other etiologies (e.g., other congenital disorders). If an infant's occipitofrontal circumference is equal to or greater than the third percentile but is notably disproportionate to the length of the infant, or if the infant has deficits that are related to the central nervous system, additional evaluation for Zika virus infection might be considered.

When an infant is born with microcephaly or intracranial calcifications to a mother who was potentially infected with Zika virus during pregnancy, the infant should be tested for Zika virus infection (Figure 1) (Box 1). In addition, further clinical evaluation and laboratory testing is recommended for the infant (Box 2). The mother should also be tested for a Zika virus infection, if this testing has not already been performed during pregnancy. An ophthalmologic evaluation, including retinal examination, should occur during the first month of life, given reports of abnormal eye findings in infants with possible congenital Zika virus infection (*11*).

For infants with any positive or inconclusive test findings for Zika virus infection, health care providers should report the case to the state, territorial, or local health department and assess the infant for possible long-term sequelae (Box 3). This includes a repeat hearing screen at age 6 months, even if the initial hearing screening test was normal, because of the potential for delayed hearing loss as has been described with other infections such as cytomegalovirus (*14*).

BOX 1. Recommended Zika virus laboratory testing for infants when indicated*

- Test infant serum for Zika virus RNA, Zika virus immunoglobulin (Ig) M and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies. The initial sample should be collected either from the umbilical cord or directly from the infant within 2 days of birth, if possible.
- If cerebrospinal fluid is obtained for other studies, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.
- Consider histopathologic evaluation of the placenta and umbilical cord with Zika virus immunohistochemical staining on fixed tissue and Zika virus RT-PCR on fixed and frozen tissue.
- If not already performed during pregnancy, test mother's serum for Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.

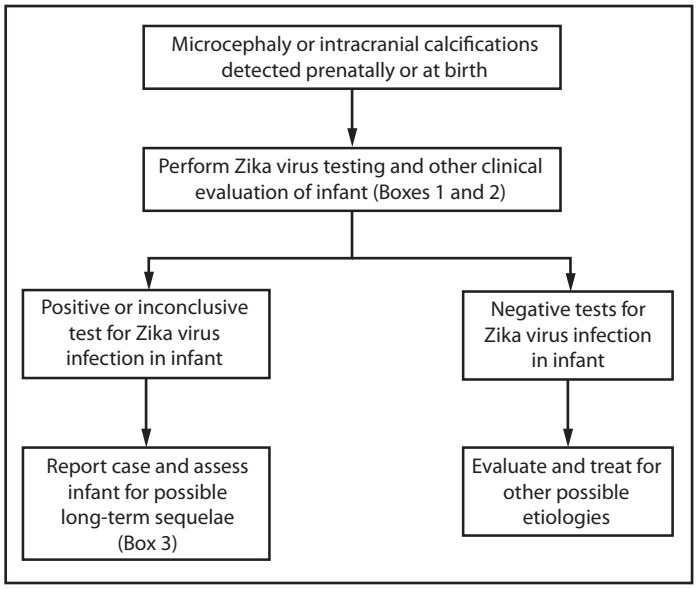
* Indications for testing include 1) infants with microcephaly or intracranial calcifications born to women who traveled to or resided in an area with Zika virus transmission while pregnant, or 2) infants born to mothers with positive or inconclusive test results for Zika virus infection.

For infants with microcephaly or intracranial calcifications who have negative results on all Zika virus tests performed, health care providers should evaluate for other possible etiologies and treat as indicated.

Recommendations for Infants without Microcephaly or Intracranial Calcifications Whose Mothers Were Potentially Infected with Zika Virus During Pregnancy

For an infant without microcephaly or intracranial calcifications born to a mother who was potentially infected with Zika virus during pregnancy, subsequent evaluation is dependent on results from maternal Zika virus testing (Figure 2). If the test results for the mother were negative for Zika virus infection, the infant should receive routine care (e.g., newborn metabolic and hearing screens). If the mother received positive or inconclusive results of tests for Zika virus infection, the infant should be tested for a possible congenital Zika virus infection (Box 1). If the results of all of the infant's tests are negative for evidence of Zika virus infection, then no further Zika virus testing and evaluation is recommended. If any of the infant's samples test positive or inconclusive, then the infant should undergo further clinical evaluation (Box 2). The infant should also be

FIGURE 1. Interim guidelines for the evaluation and testing of infants with microcephaly* or intracranial calcifications whose mothers traveled to or resided in an area with Zika virus transmission† during pregnancy§



* Microcephaly defined as occipitofrontal circumference less than the third percentile for gestational age and sex not explained by other etiologies.

† Areas with Zika virus transmission are listed on CDC's webpage. http://wwwnc.cdc.gov/travel/notices.

§ Laboratory evidence of Zika virus infection includes 1) detectable Zika virus, Zika virus RNA, or Zika virus antigen in any clinical sample, or 2) positive Zika virus immunoglobulin M with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum or cerebrospinal fluid. Testing would be considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

followed to assess for possible long-term sequelae (Box 3), and the infant's case should be reported to the state, territorial, or local health department. Infant follow-up should include a cranial ultrasound to assess for subclinical findings, unless prenatal ultrasound results from the third trimester demonstrated no abnormalities of the brain. Ophthalmologic examination and a repeat hearing screen are also recommended, as previously described for infants with microcephaly or intracranial calcifications. Developmental monitoring and screening during the first year of life is recommended for all children with congenital Zika virus infection.

If the mother has not undergone any previous testing for Zika virus infection during pregnancy, CDC recommends that she receive testing only if she reported symptoms consistent with Zika virus disease during or within 2 weeks of any time spent in an area with ongoing Zika virus transmission while she was pregnant (*1*,*15*). If the mother has any positive or inconclusive findings from tests for Zika virus infection, then the infant should undergo testing for evidence of a congenital Zika virus infection (Box 1). If the mother has not received any

BOX 2. Recommended clinical evaluation and laboratory testing for infants with possible congenital Zika virus infection

For all infants with possible congenital Zika virus infection, perform the following:

- Comprehensive physical examination, including careful measurement of the occipitofrontal circumference, length, weight, and assessment of gestational age.
- Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions. Full body photographs and any rash, skin lesions, or dysmorphic features should be documented. If an abnormality is noted, consultation with an appropriate specialist is recommended.
- Cranial ultrasound, unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain.
- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial hearing screens should be referred to an audiologist for further evaluation.
- Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial eye evaluation should be referred to a pediatric ophthalmologist for further evaluation.
- Other evaluations specific to the infant's clinical presentation.

For infants with microcephaly or intracranial calcifications, additional evaluation includes the following:

- Consultation with a clinical geneticist or dysmorphologist.
- Consultation with a pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging, and electroencephalogram).
- Testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections. Consider consulting a pediatric infectious disease specialist.
- Complete blood count, platelet count, and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase, and bilirubin.
- Consideration of genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies.

BOX 3. Recommended long-term follow-up for infants with possible congenital Zika virus infection

- Report case to state, territorial, or local health department and monitor for additional guidance as it is released.
- Conduct additional hearing screen at age 6 months, plus any appropriate follow-up of hearing abnormalities detected through newborn hearing screening.
- Carefully evaluate occipitofrontal circumference and developmental characteristics and milestones throughout the first year of life, with use of appropriate consultations with medical specialists (e.g., pediatric neurology, developmental and behavioral pediatrics, physical and speech therapy).

previous testing for Zika virus, and did not report clinical illness consistent with Zika virus disease during pregnancy, no further testing of the mother or infant is recommended (Figure 2).

Management and Prevention of Congenital Zika Virus Infections

No specific antiviral treatment is available for Zika virus infections and no vaccine against Zika virus is available (*2*). Treatment of congenital Zika virus infection is supportive and should address specific medical and neurodevelopmental issues for the infant's particular needs; investigations are ongoing to better understand what services will be most effective for these children as they grow (*16*). Mothers are encouraged to breastfeed infants even in areas where Zika virus is found, as available evidence indicates the benefits of breastfeeding outweigh any theoretical risks associated with Zika virus infection transmission through breast milk (*5*,*17*).

The only way to prevent congenital Zika virus infection is to prevent maternal infection, either by avoiding areas where Zika virus transmission is ongoing or strictly following steps to avoid mosquito bites (*15*,*18*). Mosquito-bite prevention includes using air conditioning or window and door screens when indoors, wearing long sleeves and pants, using permethrin-treated clothing and gear, and using insect repellents. When used according to the product label, U.S. Environmental Protection Agency-registered insect repellents are safe for pregnant women (*18*).

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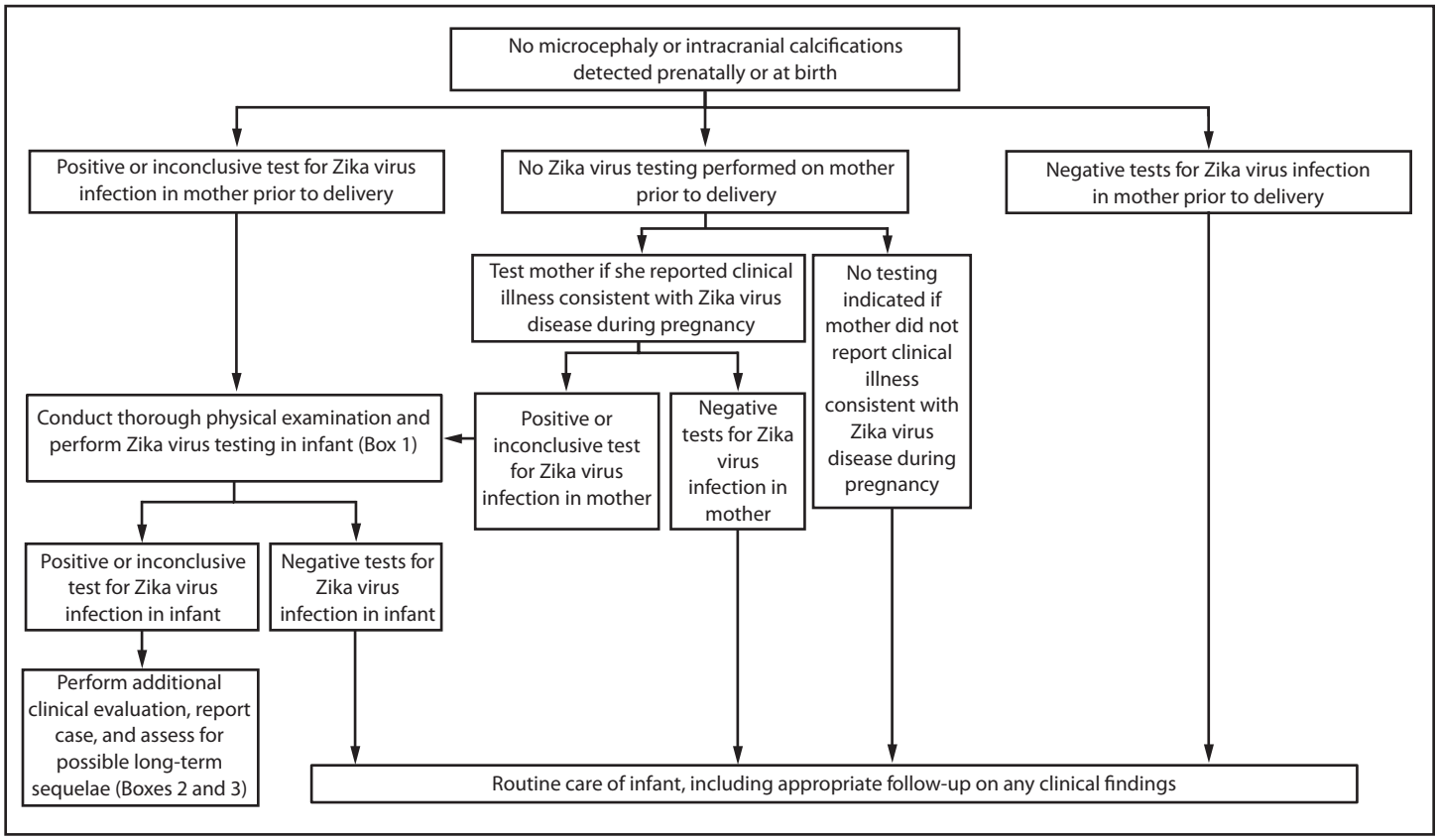
FIGURE 2. Interim guidelines for the evaluation and testing of infants without microcephaly* or intracranial calcifications whose mothers traveled to or resided in an area with Zika virus transmission† during pregnancy§,¶,**



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† Areas with Zika virus transmission are listed on CDC's webpage. http://wwwnc.cdc.gov/travel/notices.

§ Laboratory evidence of Zika virus infection includes 1) detectable Zika virus, Zika virus RNA, or Zika virus antigen in any clinical sample, or 2) positive Zika virus Immunoglobulin M (IgM) with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum or cerebrospinal fluid. Testing would be considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

¶ If mother reported clinical illness consistent with Zika virus disease during pregnancy and testing is indicated, perform Zika virus reverse transcription-polymerase chain reaction testing on serum specimen collected ≤7 days after illness onset when possible. Perform Zika and dengue virus IgM and neutralizing antibodies on serum specimens collected ≥4 days after illness onset.

** Clinical illness is consistent with Zika virus disease if two or more symptoms (including acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) are present during or within 2 weeks of any time spent in an area with ongoing Zika virus transmission.

Notes from the Field

Ongoing Cholera Outbreak — Kenya, 2014–2016

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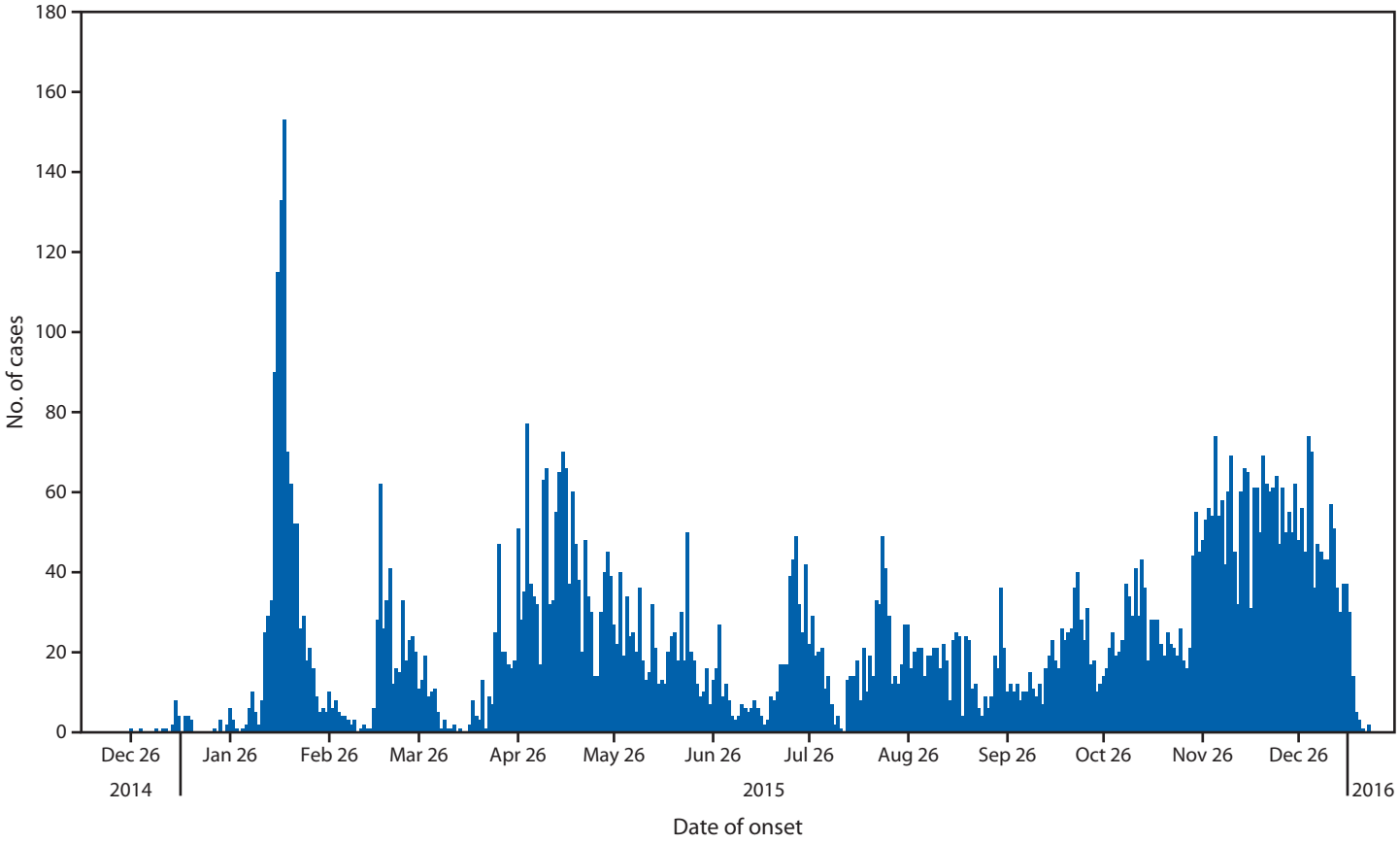
On January 6, 2015, a man aged 40 years was admitted to Kenyatta National Hospital in Nairobi, Kenya, with acute watery diarrhea. The patient was found to be infected with toxigenic *Vibrio cholerae* serogroup O1, serotype Inaba. A subsequent review of surveillance reports identified four patients in Nairobi County during the preceding month who met either of the Kenya Ministry of Health suspected cholera case definitions: 1) severe dehydration or death from acute watery diarrhea (more than four episodes in 12 hours) in a patient aged ≥5 years, or 2) acute watery diarrhea in a patient aged ≥2 years in an area where there was an outbreak of cholera. An outbreak investigation was immediately initiated. A confirmed cholera case was defined as isolation of *V. cholerae* O1 or O139 from the stool of a patient with suspected cholera or a suspected cholera case that was epidemiologically linked to a confirmed case. By January 15, 2016, a total of 11,033 suspected or confirmed cases had been reported from 22 of Kenya's 47 counties (Table). The outbreak is ongoing.

Reference laboratory confirmation of selected isolates from several counties indicated that the predominant outbreak strain was toxigenic *V. cholerae* serogroup O1, serotype Ogawa, biotype El Tor, susceptible to tetracycline, a proxy for doxycycline, which is used for treatment of severely ill cholera patients in conjunction with hydration. The majority of isolates subtyped shared an indistinguishable pulsed-field gel electrophoresis profile. Although the first identified case was documented as serotype Inaba, only a small number of the many isolates tested were subsequently confirmed as the Inaba strain.

The outbreak has been characterized by multiple peaks of varying size as cholera has spread from county to county, with the largest peak occurring in February 2015 (Figure). More than half of all cases have been reported from three

FIGURE. Number of reported cholera cases by date of onset — Kenya, December 26, 2014–January 15, 2016



counties: Wajir (2,426; 22.0%), Nairobi (1,824; 16.5%) and Migori (1,521 cases; 13.8%). Overall, 178 cholera-related deaths have been reported (case fatality rate = 1.6%) (Table). The national case fatality rate has consistently ranged between 1.6% and 2.0% throughout the outbreak. With appropriate case management (administration of oral rehydration salts in most cases), the case fatality rate from cholera should remain below 1%. By county, case fatality rates have ranged from zero (0 of 22 cases in Narok, 0 of 46 in Turkana, and 0 of 26 in Marsabit counties) to 13.0% (3 of 23) in Trans-Nzoia County. As of January 15, 2016, the Kenya Ministry of Health determined that 16 of 22 affected counties had controlled the outbreak, which was defined as reporting zero cases during the preceding 10 days.

To identify risk factors for acquiring cholera during the current outbreak, the Ministry of Health Field Epidemiology and Laboratory Training Program conducted case-control studies in four counties (Homa Bay, Migori, Nairobi, and Nakuru). In each county, 52 case-patients and 104 age- and residence-matched controls were enrolled. Compared with controls, cholera case-patients in all counties were more commonly found to have 1) lack of health education regarding cholera and diarrheal diseases, 2) lack of access to safe water and hygienic sanitation services, 3) inadequate hand washing practices, and 4) eaten food outside the home. The findings were disseminated to county leaders to aid in targeting cholera prevention measures, including public health education and water and sanitation interventions.

In three counties (Nairobi, Homa Bay, and Mombasa), knowledge, attitudes, and practices surveys were conducted to evaluate response efforts among 1,418 community members, 61 health care workers, 44 health facilities, and 51 community health extension workers. The survey results indicated that the communities had high cholera awareness, but cholera prevention knowledge was inadequate, as was access to safe water and appropriate sanitation facilities. In addition, health care workers had inadequate knowledge of critical signs of severe dehydration and appropriate use of antibiotics for cholera, and health facilities often lacked adequate lifesaving supplies, particularly intravenous fluids.

Community health extension workers were integral to the promotion of prevention messaging and distribution of supplies. In addition to scaling up preparedness, continued active surveillance, laboratory confirmation of cases, and implementation of recommended interventions continue to be critical (*1*). Such efforts are especially important given that heavy El Niño rains in Kenya continued into 2016 in some areas* and that cholera outbreaks are ongoing in neighboring and nearby countries including Tanzania, South Sudan, and the Democratic Republic of the Congo (*2*). This nationwide outbreak is one example of a public health emergency to which a proposed national public health institute could help respond (*3*).

TABLE. Number (N = 11,033) and percentage of reported cholera cases, number of deaths, and case fatality rate — 22 counties, Kenya, December 26, 2014–January 15, 2016

County	No. of cases (%)	No. of deaths	Case fatality rate
Wajir	2,426 (22.0)	35	1.4
Nairobi	1,824 (16.5)	32	1.8
Migori	1,521 (13.8)	25	1.6
Garissa	1,388 (12.6)	11	0.8
Muranga	745 (6.8)	5	0.7
Homabay	489 (4.4)	6	1.2
Kirinyaga	443 (4.0)	3	0.7
Nakuru	392 (3.6)	17	4.3
Mombasa	300 (2.7)	11	3.7
Bomet	272 (2.5)	2	0.7
Embu	234 (2.1)	3	1.3
Baringo	209 (1.9)	1	0.5
Kiambu	154 (1.4)	7	4.5
Siaya	146 (1.3)	8	5.5
Kisumu	125 (1.1)	2	1.6
Kilifi	100 (0.9)	1	1.0
Marsabit	86 (0.8)	0	0
Machakos	80 (0.7)	5	6.3
Turkana	46 (0.4)	0	0
Trans-Nzoia	23 (0.2)	3	13.0
Narok	22 (0.2)	0	0
Isiolo	8 (0.1)	1	12.5
Total	**11,033 (100.0)**	**178**	**1.6**

* http://www.meteo.go.ke/.

Acknowledgments

County health teams involved in cholera case reporting and outbreak response efforts; Kenya National Public Health Laboratories; CDC-Kenya enterics laboratories; Enteric Diseases Laboratory Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

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Announcement

Fifty Years of Global Immunization at CDC — 1966–2015

During the early 1960s, concern that smallpox could be imported into the United States, and a broader interest in solving health challenges facing humanity, catalyzed the U.S. government's commitment for global smallpox eradication, which culminated on November 23, 1965, with a White House press release announcing plans for smallpox and measles vaccination campaigns for West Africa. Shortly afterward, in January 1966, the CDC Smallpox Eradication Program was established in the Office of the CDC Director, demonstrating strong agency-wide commitment to smallpox eradication and enabling deployment of resources across the agency. Ultimately, approximately 300 CDC staff members participated in the eradication initiative, and smallpox was declared eradicated by the World Health Organization in 1980.

January 2016 marks the 50th anniversary of the establishment of CDC's Smallpox Eradication Program and the beginning of CDC's leadership in global immunization. This year CDC will begin implementing a new Strategic Framework for Global Immunization, 2016–2020, that articulates CDC's vision of a world with healthy persons protected from vaccine preventable disease (VPD), disability, and death.

A major focus during the next 5 years will be to provide scientific leadership and evidence-based guidance to achieve a world free of polio. CDC will also build on and leverage achievement of polio eradication to increase focus on preventing VPD importation into the United States; preventing, detecting, and responding to VPD outbreaks globally as part of the Global Health Security Agenda (https://ghsagenda.org); achieving a world free of measles and rubella; ending VPD deaths among children aged <5 years; and reducing chronic disease and cancer deaths from VPDs.

Notice to Readers

MMWR Series Now Available in Responsive Design and with Other Enhancements

With the launch of Volume 65 on January 15, 2016, the MMWR Series has modified its production processes to better accommodate the demands of digital publishing, including the conversion of its website into a responsive design, availability of individual reports in portable document format (PDF), conversion of content into extensible markup language (XML), and inclusion of digital object identifiers (DOIs). In addition, the MMWR Express app is now available for Android devices, and there is an update to the existing MMWR Express iOS version.

Responsive design. Responsive design improves webpage performance and allows content to automatically adapt to any mobile device a reader is using; viewing MMWR content on tablets and smartphones becomes easier.

Individual PDFs. This new feature allows readers to download a single report PDF instead of the entire issue by clicking on the format button at the right below the report title and selecting "PDF."

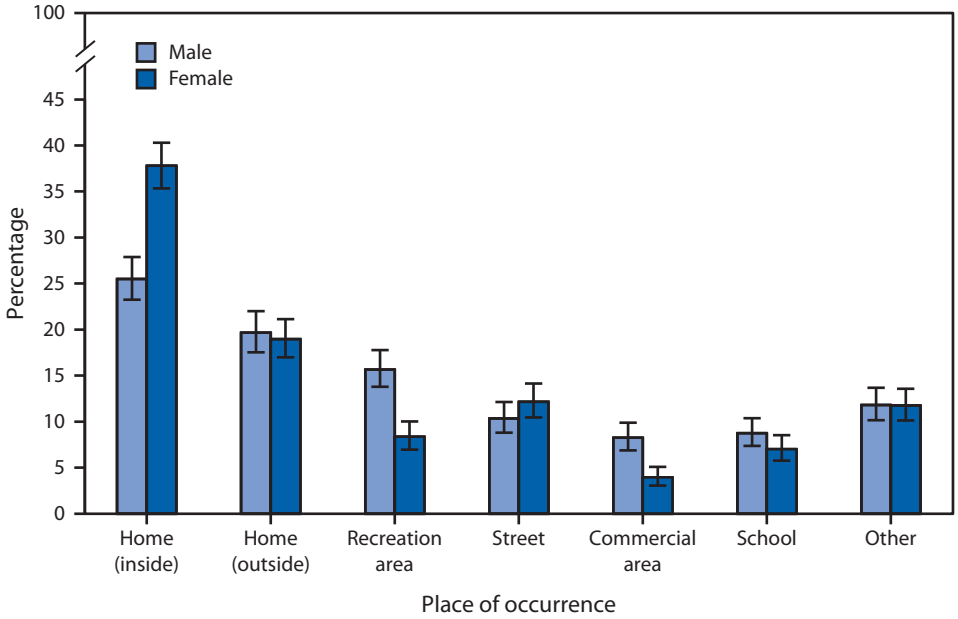
XML and DOIs. Using XML, a universal standard for data exchange, allows greater distribution of MMWR content through PubMed Central and Web of Science. DOIs are persistent identification numbers for digital content, enabling permanent archiving of digital reports.

MMWR Express app for iOS and Android. This mobile application provides immediate access to the summary information on the MMWR Weekly and links to full reports. Summaries can be viewed by publication date or by searching for a specific subject (e.g., Salmonella). When online, MMWR Express quickly checks for and then downloads new content, ensuring that users always have the most up-to-date information. Users also can choose to be notified when new content is available, and share content with others via e-mail, text message, Facebook, or Twitter. Both the Android version (https://play.google.com/store/apps/details?id=gov.cdc.mmwrexpress&hl=en) and the iOS version (https://itunes.apple.com/us/app/mmwr-express/id868245971?mt=8) are online.

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage of Nonfatal Injuries Among Males and Females,* by Place of Occurrence†,§ —National Health Interview Survey,¶ United States, 2012–2014



* With 95% confidence intervals as error bars.
† Respondents were asked, "Where were you when the injury/poisoning happened?"
§ Recreation area includes sport facilities, athletic fields, playgrounds, parks, rivers, lakes, streams, and oceans; Street includes public and nonpublic roadways, highways, sidewalks, and parking lots; Commercial area includes shopping centers, restaurants, places of business, farms, and industrial or construction areas; School includes nonresidential schools, preschools, and child care centers.
¶ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population and are for nonfatal, medically attended injuries that occurred in the place first mentioned by the respondents during the 5 weeks preceding the interview.

During 2012–2014, an average of 39 million injury episodes occurred each year. The home, whether inside or outside, was the most frequent place of injury occurrence for both sexes. The percentage of injuries occurring inside the home was greater among females (38%) than males (26%). In contrast, males were more likely than females to sustain injuries in recreational areas (16% versus 8%) and in commercial areas (8% versus 4%).

Source: CDC. National Health Interview Survey data, 2012–2014 (http://www.cdc.gov/nchs/nhis.htm).

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The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit *MMWR*'s free subscription page at *http://www.cdc.gov/mmwr/mmwrsubscribe.html*. Paper copy subscriptions are available through the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Readers who have difficulty accessing this PDF file may access the HTML file at *http://www.cdc.gov/mmwr/index2015.html*. Address all inquiries about the *MMWR* Series, including material to be considered for publication, to Executive Editor, *MMWR* Series, Mailstop E-90, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30329-4027 or to mmwrq@cdc.gov.

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