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Resurgence of Progressive Massive Fibrosis in Coal Miners — Eastern Kentucky, 2016

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Coal workers' pneumoconiosis, also known as "black lung disease," is an occupational lung disease caused by overexposure to respirable coal mine dust. Inhaled dust leads to inflammation and fibrosis in the lungs, and coal workers' pneumoconiosis can be a debilitating disease. The Federal Coal Mine Health and Safety Act of 1969 (Coal Act),* amended in 1977, established dust limits for U.S. coal mines and created the National Institute for Occupational Safety and Health (NIOSH)–administered Coal Workers' Health Surveillance Program with the goal of reducing the incidence of coal workers' pneumoconiosis and eliminating its most severe form, progressive massive fibrosis (PMF),† which can be lethal. The prevalence of PMF fell sharply after implementation of the Coal Act and reached historic lows in the 1990s, with 31 unique cases identified by the Coal Workers' Health Surveillance Program during 1990–1999. Since then, a resurgence of the disease has occurred, notably in central Appalachia (Figure 1) (*1*,*2*). This report describes a cluster of 60 cases of PMF identified in current and former coal miners at a single eastern Kentucky radiology practice during January 2015–August 2016. This cluster was not discovered through the national surveillance program. This ongoing outbreak highlights an urgent need for effective dust control in coal mines to prevent coal workers' pneumoconiosis, and for improved surveillance to promptly identify the early stages of the disease and stop its progression to PMF.

On June 9, 2016, a radiologist contacted NIOSH to report a sharp increase during the past 2 years in the number of PMF cases among patients who were coal miners seen at his practice serving the easternmost counties of Kentucky. The radiologist requested assistance in conducting an investigation and developing and implementing interventions to reduce the prevalence of disease in the community. NIOSH personnel traveled to Pike County, Kentucky, to assist with the investigation. A case of practice-identified PMF was defined as an International Labor Office classification of large opacity category A, B, or C pneumoconiosis (PMF) in a current or former coal miner receiving a chest radiograph from a single

* http://arlweb.msha.gov/solicitor/coalact/69act.htm.
† PMF is a fibrotic pneumoconiotic lesion at least 1 cm in diameter; both coal workers' pneumoconiosis and silicosis can progress to PMF.

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radiology practice in Pike County, Kentucky, during January 1, 2015–August 17, 2016, with completed radiograph classification and occupational history forms. All radiographic classifications were performed by the reporting radiologist, who is an experienced, board-certified radiologist and a NIOSH-certified B Reader (i.e., a physician certified by NIOSH as proficient in classifying radiographs of pneumoconioses) (*3*).

Sixty male patients who were active or former coal miners had radiographic findings consistent with PMF, including 49 (82%) whose radiographs were taken during 2016. Fifty-six (93%) patients were residents of Kentucky; 48 (86%) of the 56 resided in four contiguous counties (Floyd, Knott, Letcher, and Pike) in the southeastern part of the state that are part of the central Appalachian coalfield. The mean age of patients was 60.3 years (range = 44.9–77.4 years; median = 59.4 years). The mean coal mining tenure was 29.2 years (range = 15–47 years; median = 30.0 years). Thirty-one patients (52%) were determined to have category A PMF (one or more large opacities each >10 mm in diameter with combined dimension ≤50 mm); 23 (38%) had category B (combined dimension >50 mm but not exceeding equivalent area of right upper lung zone); and six (10%) had category C (size larger than category B).[§] All 60 patients had radiographic evidence of pneumoconiosis, including 12 (20%) with a small opacity profusion classified as major category 1, 30 (50%) classified as major category 2, and 18 (30%) classified as major category 3. Seven patients had large, rounded opacities, a finding associated with silicosis lung pathology (*4*). Twenty-six patients reported being roof bolters (persons who install the bolts that support the roof of an underground coal mine) for most of their careers, and 20 reported being operators of continuous miners, a type of mining machine that produces a constant flow of coal or other solid material from the working face of the mine (Figure 2).

[§] Radiographs for the pneumoconioses are classified by small opacity profusion and large opacity size, compared with standard radiograph images from the International Labour Office. Large opacities are classified as category A, B, or C. Small opacity profusion is classified into four major categories (0, 1, 2, 3), with category 1 or higher considered to be radiographic evidence of pneumoconiosis (http://www.cdc.gov/niosh/topics/chestradiography/breader.html).

Discussion

The voluntary Coal Workers' Health Surveillance Program stipulates that active coal miners be offered no-cost medical monitoring that includes a chest radiograph at entry into coal mining and then at approximately 5-year intervals. During August 2011–July 2016, a total of 99 unique cases of PMF were detected nationwide by the Coal Workers' Health Surveillance Program, including 19 in Kentucky residents. Although surveillance data have indicated a resurgence of PMF in recent years (Figure 1), this large cluster of cases brought to the attention of NIOSH by a single local radiologist was not discovered through the national surveillance program offered to active miners. The finding in the current report of 56 cases among Kentucky residents indicates that many cases were not identified through routine national surveillance; however, this finding is consistent with historically low Coal Workers' Health

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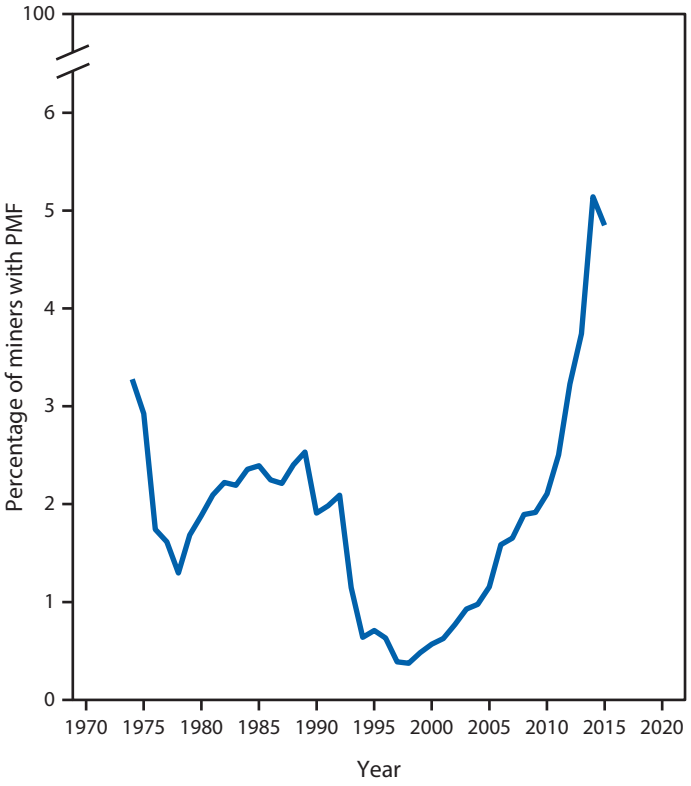
FIGURE 1. Prevalence of progressive massive fibrosis (PMF)* among underground-working coal miners with ≥25 years of underground mining tenure — Coal Workers' Health Surveillance Program, Kentucky, Virginia, and West Virginia, 1974–2015



Source: Blackley DJ, Halldin CN, Laney AS. Resurgence of a debilitating and entirely preventable respiratory disease among working coal miners. Am J Respir Crit Care Med 2014;190:708–9. Adapted with permission.

* Data are 5-year moving average (e.g., data plotted for 1974 = [PMF_{1970} + PMF_{1971} + PMF_{1972} + PMF_{1973} + PMF_{1974}] / [Total participants$_{1970–1974}$]); surveillance is conducted on a 5-year national cycle.

FIGURE 2. Photographs of workers and equipment under typical conditions in an underground coal mine*

A.

B.

* A. Two miners use a roof-bolting machine to install the bolts that support the roof of an underground coal mine. B. A continuous miner machine extracts coal from the mine face with a rotating drum.

Surveillance Program participation rates among Kentucky coal miners: during 2011–16 only 17% of Kentucky coal miners participated (personal communication, Coal Workers' Health Surveillance Program data, October 5, 2016).

The factor or combination of factors that led to this increase in cases of PMF in eastern Kentucky and whether there are more unrecognized cases in neighboring coal mining regions are unknown. Because PMF takes years to become manifest, the specific exposures or mining practices that led to these cases are also unknown. New or modified mining practices in the region might be causing hazardous dust exposures. While obtaining detailed occupational histories, the reporting physician identified the practice of "slope mining" (*5*) as a potential exposure in eastern Kentucky (slope mining involves teams of miners operating continuous miner machines, designed to cut coal and other soft rock, to cut shafts through hundreds of feet of sandstone to reach underground coal seams) (Figure 2). The sandstone formation underlying eastern Kentucky is >90% quartz (*6*), and dust generated during the slope cutting could expose miners to hazardous dust containing high concentrations of respirable crystalline silica. Previous research found that 25 of 37 (68%) Kentucky and Virginia coal miners with "advanced pneumoconiosis" (defined as PMF or simple coal workers' pneumoconiosis with high small opacity profusion) reported working as roof bolters, a mining job associated with high silica dust exposure (*7*). The current investigation was limited to miners with PMF and found that 26 (43%) reported working as roof bolters, and 20 (33%) reported working as continuous miner operators. Operating a continuous miner machine has typically been considered a "coal-face position" (i.e., a work position located at the face, or seam, of coal), and therefore not a position usually associated with higher silica dust exposures.

However, the use of a continuous miner machine during shaft cutting or thin seam coal mining (i.e., occurring when the height of the coal seam requires that rock above and below the coal seam is cut along with the coal) requires cutting through rock and creates the potential for respirable silica exposures, which might explain why working as a continuous miner operator could pose an increased risk for PMF.

In addition, recent industry trends might have led to a higher number of miners seeking radiographs, either to gather information about their health status or to seek benefits through state workers' compensation or federal black lung programs. A steep decline in coal miner employment and coal production during recent years has occurred (*8*), with 1,501 jobs lost in Kentucky (17.9% of state coal workforce) during the first quarter of 2016. Miners might feel that future coal-related employment is unlikely and that previous barriers to health-seeking behaviors have been removed. For example, in Kentucky a miner has 3 years to file a state compensation claim "after the last injurious exposure to the occupational hazard or after the employee first experiences a distinct manifestation of an occupational disease in the form of symptoms reasonably sufficient to apprise the employee that he or she has contracted the disease, whichever shall last occur."[¶] Because the earlier stages of coal workers' pneumoconiosis can be associated with few or no overt symptoms, and because coal mining jobs have historically been among the best-paying in the region, some miners might have chosen to not seek radiographs or other health-related information during the earlier stages of their career to avoid threatening their ability to continue working in the industry.

The findings in this report are subject to at least three limitations. First, the cases highlighted in this report represent the recent experience of one single-radiologist practice in eastern Kentucky and might underestimate the actual extent of PMF in coal miners in the broader region. Second, classifications of chest radiographs were performed by a single B Reader, who was aware of miners' occupational histories and other clinical data, such as results of chest computed tomography scans. For classifications performed for worker monitoring and surveillance, NIOSH recommends that a single reader is generally sufficient, particularly for radiographs that are clearly normal or abnormal. However, for radiographs with findings at the boundary between normal and abnormal, or for settings such as epidemiologic research or contested proceedings where it is important to ensure a high degree of accuracy, NIOSH recommends summary classifications derived from multiple independent readers (*3*) and is taking measures to obtain independent confirmation of the classifications by sending them to additional B-readers. Finally, cases in this report were not identified through standard coal workers' pneumoconiosis surveillance, and whether similar clusters of cases exist in other communities is not known. Thus, the actual extent of PMF in U.S. coal miners remains unclear. Because the cases described in this report were identified during a span of fewer than 2 years and previous radiographs were not available, it was not possible to ascertain the time of PMF onset for these patients.

Although PMF is preventable through well-established dust control practices, each of the 60 patients in this report was exposed to coal mine dust over a period of years in an amount sufficient to cause this severe disease. Finding these cases in such a small geographic area is a strong signal that action is needed in the area to identify existing cases at an earlier stage and prevent future cases. A new federal rule has been implemented to protect all U.S. coal miners through expansion of medical surveillance, including respiratory symptom assessment and spirometry testing (*9*). The rule also mandates lowering the amount of respirable dust allowed in U.S. coal mines and the use of a continuous personal dust monitor, a device that can measure respirable coal mine dust in real time. Availability of real-time respirable dust measurements, lower exposure limits, and expanded medical surveillance are intended to prevent future cases and identify early signs of respiratory impairment in coal miners before a disabling condition has developed.

The findings in this report serve as a reminder that more than 45 years after the Coal Act's passage, one of its core objectives has not been achieved. In the coming years, NIOSH will focus active surveillance measures on miners in central Appalachia and will continue to work with miners, mine

Summary

What is already known about this topic?

The prevalence of coal workers' pneumoconiosis fell precipitously after implementation of the Coal Mine Health and Safety Act and reached historic lows in the 1990s, with the most severe form, progressive massive fibrosis (PMF), nearly eradicated. Since that time, increases in the prevalence and severity of coal workers' pneumoconiosis have occurred, especially in central Appalachia.

What is added by this report?

During January 1, 2015–August 17, 2016, a total of 60 patients identified through a single radiologist's practice had radiographic findings consistent with PMF; 49 had their radiograph taken during 2016. Surveillance data have indicated a resurgence of PMF in recent years, but the cases described in this report represent a large cluster not discovered through routine surveillance.

What are the implications for public health practice?

Effective dust control, enhanced educational outreach, and improved surveillance are needed to protect the respiratory health of U.S. coal miners.

[¶] http://www.lrc.ky.gov/statutes/statute.aspx?id=32472.

operators, regulatory and disability compensation agencies, and others to better characterize the scope of the problem, expand educational outreach to miners to increase their awareness of the right to confidential medical screening, and prevent overexposures to coal mine dust.

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Assessing Change in Avian Influenza A(H7N9) Virus Infections During the Fourth Epidemic — China, September 2015–August 2016

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Since human infections with avian influenza A(H7N9) virus were first reported by the Chinese Center for Disease Control and Prevention (China CDC) in March 2013 (*1*), mainland China has experienced four influenza A(H7N9) virus epidemics. Prior investigations demonstrated that age and sex distribution, clinical features, and exposure history of A(H7N9) virus human infections reported during the first three epidemics were similar (*2*). In this report, epidemiology and virology data from the most recent, fourth epidemic (September 2015–August 2016) were compared with those from the three earlier epidemics. Whereas age and sex distribution and exposure history in the fourth epidemic were similar to those in the first three epidemics, the fourth epidemic demonstrated a greater proportion of infected persons living in rural areas, a continued spread of the virus to new areas, and a longer epidemic period. The genetic markers of mammalian adaptation and antiviral resistance remained similar across each epidemic, and viruses from the fourth epidemic remained antigenically well matched to current candidate vaccine viruses. Although there is no evidence of increased human-to-human transmissibility of A(H7N9) viruses, the continued geographic spread, identification of novel reassortant viruses, and pandemic potential of the virus underscore the importance of rigorous A(H7N9) virus surveillance and continued risk assessment in China and neighboring countries.

Epidemiology

As of August 31, 2016, mainland China had reported a total of 775 laboratory-confirmed human infections with A(H7N9) virus from 16 provinces and three municipalities during the four epidemics. In addition, travelers to mainland China accounted for 23 human cases of A(H7N9) virus infection, including four deaths; these infections were detected in Hong Kong (16 cases), Taiwan (four), Canada (two), and Malaysia (one).

Among 314 counties in China that reported at least one human A(H7N9) virus infection, 224 (71%) reported ≤2 infections. Most (83%) infections were reported in five eastern or southeastern coastal provinces. Whereas most infections in the first epidemic were identified during March–April 2013, the majority of infections identified in the subsequent three epidemics occurred during November–April of 2013–2014, 2014–2015, and 2015–2016 (Figure).

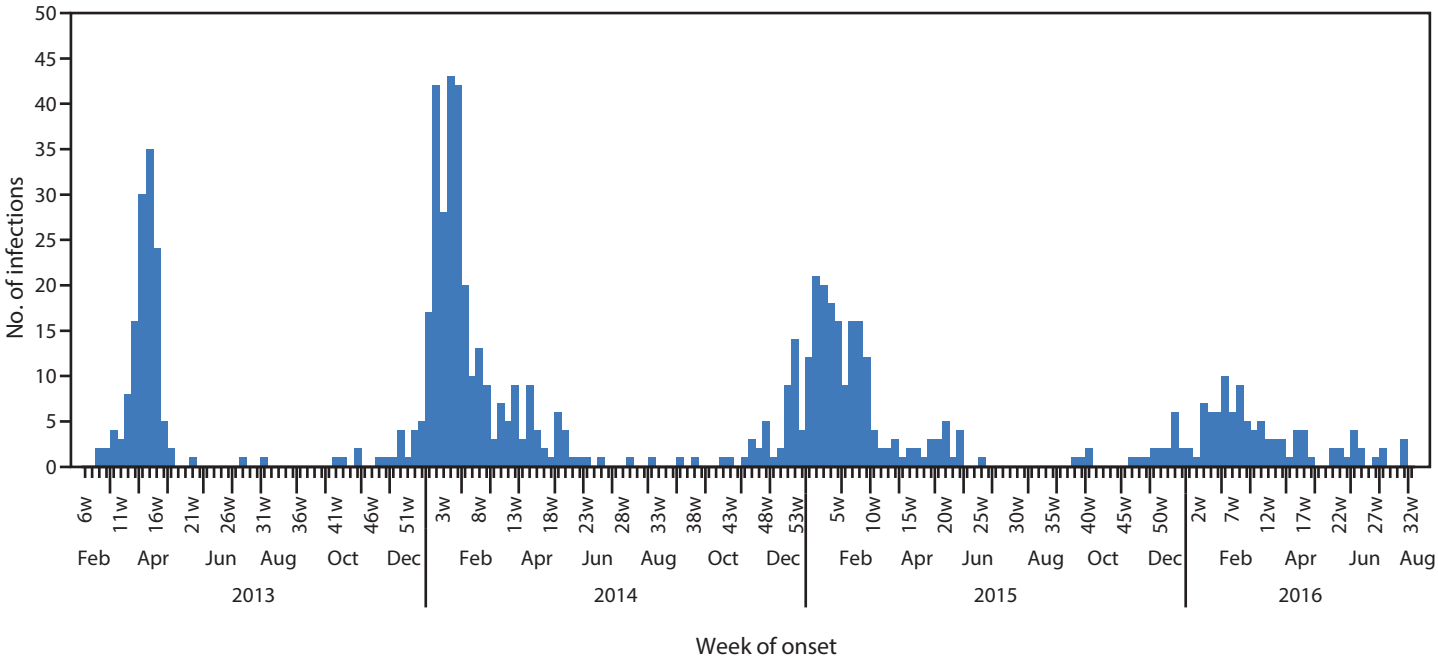
Among the 775 total reported infections, 659 (85%) patients reported exposure to live poultry in the 2 weeks preceding illness onset, including live-poultry markets (376 patients, 57%), backyard poultry (115, 17%), or both (120, 18%); and in other settings (48, 7%) (Table). Median age did not significantly differ between persons infected in the fourth epidemic (58 years) compared with the previous three epidemics (57 years). Twenty-five (3%) persons reported living with, working with, or having another epidemiologic link to a person infected with influenza A(H7N9) virus.

Among all 775 infections in the four epidemics, 55 (7%) were associated with 26 clusters (i.e., at least two epidemiologically linked infections), including 23 clusters of two infections each, and three clusters of three infections each. Most (23, 88%) clusters included family members only, and three involved nosocomial transmission (*3*,*4*). Among the index patients in the 26 clusters, 25 (96%) had a history of live poultry exposure in the 2 weeks before illness onset; secondary infections (29) in clusters resulted from possible human-to-human transmission (18), exposure to a common infectious source (three), or undetermined exposures (eight). The proportion of persons identified within clusters in the fourth epidemic was similar to the proportion in the three previous epidemics combined (10% compared with 7%, p = 0.16). There was no evidence of tertiary transmission in any cluster.

Fewer A(H7N9) infections were reported during the fourth epidemic (n = 118) than in the first (134), second (304), or third (219) epidemics. The epidemic period during which persons developed illness in the fourth epidemic (interquartile range = 73 days) was more than four times as long as that noted during the first epidemic (15 days), twice as long as the second (35 days), and more than one and a half times as long as the third epidemic (43 days). More than half of infections in the fourth epidemic were reported from two adjacent provinces located on the southeast coast of China; however, one province (Liaoning) and one municipality (Tianjin City) each reported their first A(H7N9) virus infection in the fourth epidemic, indicating spread of the virus to new areas. The percentage of A(H7N9) virus–infected persons living in rural areas in the fourth epidemic was higher than in the three previous epidemics combined (54% compared with 42%; p = 0.01).

*These authors contributed equally to this report.

FIGURE. Week of illness onset among persons infected with avian influenza A(H7N9) virus (N = 775) — mainland China, February 2013–August 2016



Since April 2013, the Ministry of Agriculture in China has published surveillance data on poultry samples tested for the presence of A(H7N9) virus. As of September 1, 2016, a total of 233 positive samples in 16 provinces were detected. All samples were from live-poultry markets, except one from a farmer's free-range backyard flock.

Clinical Features

Among the 775 persons with A(H7N9) infections during the four epidemics, 316 (41%) died. Among 547 (71%) patients with data on symptoms available, 95% (517 of 547) reported fever and 81% (445 of 547) cough. Fifty-three percent (289 of 545) of patients with medical history data had at least one underlying medical condition (Table). Ninety-one percent (480 of 526) of patients experienced at least one medical complication, including pneumonia, respiratory failure, or acute respiratory distress syndrome (Table); 68% (358 of 529) were admitted to an intensive care unit (ICU) and 85% (506 of 592) had severe illness[†] (Table). The median intervals (interquartile ranges) from illness onset to various medical outcomes ranged from 1 day (onset to first medical encounter) to 17 days (onset to death) (Table).

Although the proportion of patients with severe illness (91%) in the fourth epidemic was not statistically different from that in the three previous epidemics combined, persons infected in the fourth epidemic were more likely to develop pneumonia (99% compared with 87%, p = 0.003) and be admitted to the ICU (78% compared with 66%, p = 0.04) than were patients in the three previous epidemics (Table). The median interval between illness onset and initial medical consultation, hospitalization, diagnosis, time to antiviral treatment initiation, and death were similar between the fourth and the first three epidemics.

Laboratory Findings

Since the emergence of A(H7N9) virus, the majority of viruses from both humans and poultry have contained two hemagglutinin (HA) amino acid residues, 186V and 226L/I in H3 numbering (177 and 217 in H7 numbering), which are likely to increase human receptor binding (*5*). During the first three epidemics, the number of A(H7N9) viruses identified in humans retaining the avian receptor binding residues decreased (*5*). In the fourth epidemic, all 41 A(H7N9) viruses from humans and 10 from environmental samples contained these two mutations associated with increased human receptor binding (supplemental figure https://stacks.cdc.gov/view/cdc/42868). The majority of A(H7N9) viruses isolated from

[†] Based on the National Health and Family Planning Commission. Diagnosis and Treatment Protocol of Human Infection with A(H7N9) Avian Influenza Virus (2014 version), 2014.01.26, (http://www.moh.gov.cn/yzygj/s3593g/201401/3f69fe196ecb4cfc8a2d6d96182f8b22.shtml), severe illness was defined as an illness with any one of the following: chest radiograph indicative of multilobar lesions or >50% increase in size of lesions within a 48-hour period; dyspnea or respiratory rate >24 times per minute for adults; severe hypoxia, defined as ≤92% oxygen saturation while receiving 3–5 liters of supplemental oxygen per minute; or shock, acute respiratory distress syndrome, or multiple organ dysfunction syndrome.

TABLE. Number and percentage of patients with reported avian influenza A(H7N9) virus infection (N = 775), by demographic and clinical characteristics and period of illness — mainland China, February 19, 2013–August 31, 2016

Characteristic	Feb 2013–Aug 2016 Epidemics 1–4 (N = 775) (%)	Feb 2013–Aug 2015 Epidemics 1–3 (n = 657) (%)	Sep 2015–Aug 2016 Epidemic 4 (n = 118) (%)
Age group (yrs)			
0–19	49 (6)	47 (7)	2 (2)
20–39	122 (16)	105 (16)	17 (14)
40–59	269 (35)	222 (34)	47 (40)
60–79	291 (38)	245 (37)	46 (39)
≥80	44 (6)	38 (6)	6 (5)
Male	533 (69)	456 (69)	77 (65)
Area of residence			
City, town, suburb	438 (57)	384 (58)	54 (46)*
Countryside, village	337 (43)	273 (42)	64 (54)
Occupation			
Farmer	210 (27)	170 (26)	40 (34)
Retiree	184 (24)	162 (25)	22 (19)
Homemaker or unemployed	91 (12)	72 (11)	19 (16)
Other occupations†	290 (37)	253 (39)	37 (31)
Live poultry exposure, N, n/N	659 (85)	558 (85)	101 (86)
LPM or poultry from LPM	376/659 (57)	321/558 (58)	55/101 (54)
Household poultry	115/659 (17)	97/558 (17)	18/101 (18)
LPMs and household poultry	120/659 (18)	98/558 (18)	22/101 (22)
Other settings (e.g., neighboring backyard poultry farms)	48/659 (7)	42/558 (8)	6/101 (6)
Severe illness,§ n/N	506/592 (85)	431/510 (85)	75/82 (91)
Deaths, N	316 (41)	271 (41)	45 (38)
Main early symptoms, n/N			
Fever	517/547 (95)	444/471 (94)	73/76 (96)
Cough	445/547 (81)	385/471 (82)	60/76 (79)
Sore throat	107/547 (20)	94/471 (20)	13/76 (17)
Weakness	218/547 (40)	185/471 (39)	33/76 (43)
Sore muscles	124/547 (23)	107/471 (23)	17/76 (22)
Underlying medical conditions, n/N	289/545 (53)	241/469 (51)	48/76 (63)
Cardiovascular/cerebrovascular disease (including isolated hypertension)	187/545 (34)	159/469 (34)	28/76 (37)
Metabolic diseases	84/545 (15)	68/469 (14)	16/76 (21)
Chronic lung disease	63/545 (12)	50/469 (11)	13/76 (17)
Chronic liver diseases	37/545 (7)	32/469 (7)	5/76 (7)
Hematological diseases	16/545 (3)	14/469 (3)	2/76 (3)
Cancer	14/545 (3)	9/469 (2)	5/76 (7)*
Rheumatic autoimmune disease	12/545 (2)	11/469 (2)	1/76 (1)
Chronic kidney diseases	18/545 (3)	16/469 (3)	2/76 (3)
Antiviral treatment	481/529 (91)	412/453 (91)	69/76 (91)
Received antivirals ≤48 hours after symptom onset	54/476 (11)	49/412 (12)	5/64 (8)
Admitted to intensive care unit, n/N	358/529 (68)	299/453 (66)	59/76 (78)*
Complications, n/N	480/526 (91)	405/451 (90)	75/75 (100)*
Pneumonia	465/526 (88)	391/451 (87)	74/75 (99)*
Respiratory failure	369/526 (70)	310/451 (69)	59/75 (79)
Acute respiratory distress syndrome	352/526 (67)	297/451 (66)	55/75 (73)
Hepatic insufficiency	223/526 (42)	192/451 (43)	31/75 (41)
Renal insufficiency	180/526 (34)	151/451 (33)	29/75 (39)
Septic shock	167/526 (32)	140/451 (31)	27/75 (36)
Cardiac failure	146/526 (28)	124/451 (27)	22/75 (29)
Disseminated intravascular coagulation	29/526 (6)	25/451 (6)	4/75 (5)

See table footnotes on next page.

patients in each epidemic carried the PB2-627K mutation, which has been associated with mammalian adaptation. This mutation was found in 68% (62 of 91) of viruses in the first epidemic, 79% (122 of 154) in the second, 62% (52 of 84) in the third, and 71% (29 of 41) in the fourth epidemic. Almost all A(H7N9) viruses isolated from birds and humans had PB1-368V, which might also enhance A(H7N9) virus transmission to humans (*5*).

Among the 391 A(H7N9) viruses isolated from humans that were tested for the presence of substitutions associated with reduced sensitivity to neuraminidase (NA) inhibitors, only 16 (4%) possessed these substitutions in the NA protein: E119V (four), A246T (one), or R292K (11). These mutations were not identified in 498 A(H7N9) viruses sampled from birds or the environment, suggesting the mutations occurred during

TABLE. (*Continued*) Number and percentage of patients with reported avian influenza A(H7N9) virus infection (N = 775), by demographic and clinical characteristics and period of illness — mainland China, February 19, 2013–August 31, 2016

Characteristic	Feb 2013–Aug 2016 Epidemics 1–4 (N = 775) (%)	Feb 2013–Aug 2015 Epidemics 1–3 (n = 657) (%)	Sep 2015–Aug 2016 Epidemic 4 (n = 118) (%)
Interval, median days (IQR)			
Onset to first clinic visit	1 (0–4)	1 (0–4)	2 (0–5)
Onset to first hospitalization	4 (3–7)	4 (3–7)	4 (3–6)
Onset to diagnosis	8 (6–11)	9 (6–11)	8 (6–11)
Onset to starting anti-viral treatment	6 (4–8)	6 (4–8)	6 (5–7)
Onset to death	17 (10–28)	17 (10–30)	15 (8–24)

Abbreviations: IQR = interquartile range; LPM = live-poultry market.
* Significant difference between Epidemic 4 and Epidemics 1–3 (p<0.05).
† Other occupations include laborers, persons working in government or government-affiliated institutions, business service providers, children, and students.
§ Illness with any one of following: chest radiograph indicative of multilobar lesions or >50% increase in size of lesions within a 48-hour period; dyspnea or respiratory rate >24 times per minute for adults; severe hypoxia defined as <92% oxygen saturation while receiving 3–5 liters of supplemental oxygen per minute; or shock, acute respiratory distress syndrome, or multiple organ dysfunction syndrome.

human infection or as a result of antiviral drug treatment. Antigenic analysis of viruses from all four epidemics showed that viruses were well inhibited by postinfection ferret antisera raised against the candidate vaccine virus, A/Anhui/1/2013, indicating that recent A(H7N9) viruses remain antigenically well matched to current candidate vaccine viruses (*5*). Reassortment with A(H9N2) virus internal genes continues to be detected, which might mediate future host adaptation and interspecies transmission of A(H7N9) virus (*6*).

Discussion

Many characteristics and clinical features of human infections with influenza A(H7N9) virus in China reported during the fourth epidemic (September 2015–August 2016) were similar to those in the previous three epidemics since 2013, including age and sex distribution, and exposure history. However, during the fourth epidemic, infections continued to be reported from areas that had not reported infections in the past, a higher proportion of infected persons lived in rural areas, and a higher percentage of patients required ICU admission. In addition, the duration of the epidemic has been increasing each year.

Viruses collected from both humans and environmental samples from the fourth epidemic showed few genetic changes in the HA and NA genes compared with viruses from earlier epidemics. Although genetic markers of mammalian adaptation continue to be identified in viral polymerase genes, their frequency remains consistent across each epidemic. Few antigenic differences were identified between the viruses from the fourth epidemic and vaccine strains available for manufacturing, suggesting that recently circulating viruses remain antigenically well matched to currently developed candidate vaccine viruses. As the A(H7N9) epidemic season occurs during China's winter seasonal influenza peak, ongoing viral genome risk assessment is needed to monitor mutations and reassortment.

Since 2013, local governments have implemented numerous prevention and control measures, including temporary closure of live-poultry markets and disinfection protocols, which have decreased the prevalence of A(H7N9) virus in live-poultry market environments (*7*,*8*). However, because the A(H7N9) virus is a low pathogenic avian influenza virus and infections in poultry are subclinical, identifying when the virus is spreading among poultry or when humans might be at risk for infection is challenging. The continued identification of the virus in new areas highlights the need for a national containment-control-eradication program in poultry.

The findings in this report are subject to at least three limitations. First, although fewer infections were reported during the fourth epidemic than the first three, the percentages of patients who developed pneumonia and were admitted to the ICU were higher. It is possible that this observed increase in clinical severity in the fourth epidemic represents a surveillance artifact. Several provinces with the highest prevalence of human A(H7N9) virus infections recently established provincial pneumonia surveillance systems, which might have increased identification and reporting of pneumonia in persons with A(H7N9) virus infection. In addition, mild illnesses might be less likely to be detected (*9*) as concern about A(H7N9) virus as a public health threat declined over time, possibly leading to a decrease in identification and reporting of less severe infections. Further, as more infections occur in rural areas with fewer health care resources, there might be less ability to both identify and promptly treat persons before they develop severe illness. Second, data on medical history, illness presentation, and clinical course were missing for nearly one third of all persons with infections. Finally, for all four epidemics, self-reported exposure history was subject to recall bias.

There is no evidence of increased transmissibility of A(H7N9) virus from poultry or environmental exposures to humans in China or sustained human-to-human transmission; however, using the Influenza Risk Assessment Tool (*10*), CDC

Summary

What is already known about this topic?

Influenza A(H7N9) virus is a low pathogenic avian influenza virus that can cause severe illness in humans, with a case-fatality rate of 40%. Since March 2013, China has experienced four annual avian influenza A(H7N9) virus epidemics with human infections. Most human infections have been associated with exposure to live poultry, particularly in live-poultry markets. In the first three annual epidemics, there was no evidence of sustained human-to-human transmission.

What is added by this report?

Epidemiology and virology data from the most recent (fourth) epidemic, September 2015–August 2016, suggest no evidence of increased transmissibility of A(H7N9) virus from poultry or environmental exposures to humans or of sustained human-to-human transmission. Characteristics of the fourth epidemic included greater percentages of patients admitted to intensive care units and with diagnoses of pneumonia, identification of the virus in new areas, a greater percentage of infected persons living in rural areas, and a longer epidemic period. Genetic changes in the virus have not been sufficient to alter antigenic properties or cause mismatch with candidate vaccines.

What are the implications for public health practice?

There is a need for a national containment-control-eradication program in poultry, in addition to effective A(H7N9) virus surveillance and continued risk assessment among humans and poultry in China and neighboring countries.

found that A(H7N9) virus has the highest potential pandemic risk of any novel influenza A viruses that have been assessed. The recent geographic spread, the identification of divergent virus lineages, and the pandemic potential of the virus underscore the importance of effective A(H7N9) virus surveillance and continued risk assessment among humans and poultry in China and neighboring countries.

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Leading Causes of Cancer Mortality — Caribbean Region, 2003–2013

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Cancer is one of the leading causes of deaths worldwide (*1*); in 2012, an estimated 65% of all cancer deaths occurred in the less developed regions of the world (*2*). In the Caribbean region, cancer is the second leading cause of mortality, with an estimated 87,430 cancer-related deaths reported in 2012 (*3*). The Pan American Health Organization defines the Caribbean region as a group of 27 countries that vary in size, geography, resources, and surveillance systems.* CDC calculated site- and sex-specific proportions of cancer deaths and age-standardized mortality rates (ASMR) for 21 English- and Dutch-speaking Caribbean countries, the United States, and two U.S. territories (Puerto Rico and the U.S. Virgin Islands [USVI]), using the most recent 5 years of mortality data available from each jurisdiction during 2003–2013. The selection of years varied by availability of the data from the countries and territories in 2015. ASMR for all cancers combined ranged from 46.1 to 139.3 per 100,000. Among males, prostate cancers were the leading cause of cancer deaths, followed by lung cancers; the percentage of cancer deaths attributable to prostate cancer ranged from 18.4% in Suriname to 47.4% in Dominica, and the percentage of cancer deaths attributable to lung cancer ranged from 5.6% in Barbados to 24.4% in Bermuda. Among females, breast cancer was the most common cause of cancer deaths, ranging from 14.0% of cancer deaths in Belize to 29.7% in the Cayman Islands, followed by cervical cancer. Several of the leading causes of cancer deaths in the Caribbean can be reduced through primary and secondary preventions, including prevention of exposure to risk factors, screening, early detection, and timely and effective treatment.

Among the 21 countries† that submitted mortality data to the Caribbean Public Health Agency during 2003–2013, the proportions of all cancer deaths and ASMR by cancer site and sex were calculated for the most recent 5 years of available data for 21 English- and Dutch-speaking Caribbean countries. ASMRs are reported for the leading 10 causes of cancer deaths determined by the proportions of all cancer deaths. Calculations were completed using SEER*Stat software (*4*) and age-standardized to the Segi World Standard population (in millions) (*5*,*6*). Population data from the 21 Caribbean Public Health Agency countries, based on census data, were not available from any country for all 5 years; in these cases, the most recent year of available data (i.e., census or estimates) was used to populate subsequent years with missing population data. Proportions and ASMRs are not presented where there were fewer than six cases and were not included when determining ASMR ranges. Because data were not available from all contributing countries for any single year during the study period, regional cancer-specific mortality rates could not be calculated. Using the same criteria, ASMR for USVI, Puerto Rico, and the United States were calculated to provide a more comprehensive picture of the region, using mortality data from CDC's National Center for Health Statistics.

The total number of cancer deaths among males and females (*International Classification of Diseases, 10th revision* [ICD-10]: C00–C97) reported by countries and territories ranged from 32 in Turks and Caicos to 26,135 in Puerto Rico (Table 1). ASMR for all sites (all cancer-related deaths combined) ranged from 46.1 per 100,000 in Turks and Caicos to 139.3 per 100,000 in St. Kitts and Nevis. Among the 21 English- and Dutch-speaking Caribbean countries, prostate cancer was the most common cause of cancer-related deaths among males in 20 of the countries, accounting for 18.4%–47.4% of cancer deaths, followed by cancer of the lung and bronchus (lung), which accounted for 5.6%–24.4% of cancer deaths (Table 1) (supplemental figures https://stacks.cdc.gov/view/cdc/42948; https://stacks.cdc.gov/view/cdc/42949). Among females, breast cancer was the most common cause of cancer deaths in 16 of the 18 countries for which data were reported, accounting for 14.0%–29.7% of cancer deaths, followed by cervical cancer, which accounted for 4.5%–18.2% of cancer deaths (Table 1) (supplemental figures https://stacks.cdc.gov/view/cdc/42950; https://stacks.cdc.gov/view/cdc/42951). For both sexes, cancer of the colon and rectum (colorectal) was the third most common cause of cancer death (Table 1).

Among males, ASMR for prostate cancer ranged from 15.1 to 74.1 per 100,000 standard population, for lung cancer, from 4.6 to 34.0 per 100,000, and for colorectal cancer, from 4.9 to 18.1 per 100,000 (Table 2). Among females, ASMR for breast cancer ranged from 10.0 to 27.3 per 100,000, for cervical cancer, from 4.1 to 15.5 per 100,000, and for colorectal cancer, from 3.7 to 13.9 per 100,000 (Table 2).

*Pan American Health Organization countries and centers. http://www.paho.org/hq/index.php?option=com_wrapper&Itemid=2005.

†Anguilla, Antigua and Barbuda, Aruba, The Bahamas, Barbados, Belize, Bermuda, Bonaire, St Eustatius and Saba (BES), British Virgin Islands, Cayman Islands, Curacao, Dominica, Grenada, Guyana, Haiti, Jamaica, Montserrat, St. Lucia, St. Kitts and Nevis, St. Maarten, St. Vincent and the Grenadines, Suriname, Trinidad and Tobago, and Turks and Caicos Islands

TABLE 1. Top 10 causes of cancer deaths, by sex, based on 5-year cumulative proportion — 21 countries in the Caribbean region, United States, U.S. Virgin Islands, and Puerto Rico, 2003–2013*

Males	Colon/ Rectum No. (%)	Esophagus No. (%)	Leukemia No. (%)	Liver/ Intra-hepatic bile duct No. (%)	Lung/ Bronchus No. (%)	Non-Hodgkin lymphoma No. (%)	Oral cavity/ Pharynx No. (%)	Pancreas No. (%)	Prostate No. (%)	Stomach No. (%)	All sites† No. (%)
Caribbean countries											
Anguilla§	NR	NR	NR	NR	NR	NR	NR	NR	25 (44.6)	NR	56 (100)
Antigua and Barbuda§	20 (8.1)	6 (2.4)	NR	12 (4.9)	23 (9.3)	6 (2.4)	9 (3.7)	NR	110 (44.7)	9 (3.7)	246 (100)
Aruba§	34 (9.9)	12 (3.5)	9 (2.6)	19 (5.5)	72 (20.9)	13 (3.8)	12 (3.5)	12 (3.5)	74 (21.5)	30 (5.8)	344 (100)
Bahamas¶	96 (10.5)	35 (3.8)	30 (3.3)	26 (2.8)	114 (12.5)	21 (2.3)	26 (2.8)	31 (3.4)	247 (27.1)	53 (5.8)	912 (100)
Barbados¶	151 (11.6)	28 (2.1)	31 (2.4)	17 (1.3)	73 (5.6)	22 (1.7)	48 (3.7)	51 (3.9)	507 (38.9)	60 (4.6)	1,302 (100)
Belize§	26 (6.2)	9 (2.1)	21 (4.9)	38 (8.9)	62 (14.6)	12 (2.8)	6 (1.4)	13 (3.1)	106 (24.9)	37 (8.7)	425 (100)
Bermuda**	29 (9.4)	9 (2.9)	11 (3.6)	9 (2.9)	75 (24.4)	10 (3.3)	10 (3.3)	18 (5.9)	62 (20.2)	11 (3.6)	307 (100)
British Virgin Islands††	8 (13.1)	NR	NR	NR	6 (9.8)	NR	NR	NR	13 (21.3)	NR	61 (100)
Cayman Islands§	8 (7.5)	NR	NR	NR	23 (21.7)	NR	NR	NR	28 (26.4)	NR	106 (100)
Curacao§§	81 (11.0)	37 (5.0)	11 (1.5)	18 (2.4)	142 (19.3)	14 (1.9)	21 (2.8)	34 (4.6)	191 (25.9)	38 (5.2)	737 (100)
Dominica¶¶	18 (5.0)	6 (1.7)	NR	10 (2.9)	26 (7.2)	9 (2.5)	9 (2.5)	20 (5.6)	170 (47.4)	32 (8.9)	359 (100)
Grenada§	30 (6.5)	20 (4.3)	NR	10 (2.1)	36 (7.7)	27 (5.8)	18 (3.9)	17 (3.7)	193 (41.5)	22 (4.7)	465 (100)
Guyana¶	77 (7.7)	19 (1.9)	43 (4.3)	71 (7.1)	65 (6.5)	23 (2.3)	32 (3.2)	42 (4.2)	342 (34.0)	52 (5.2)	1,005 (100)
Jamaica¶	624 (7.3)	179 (2.1)	247 (2.9)	228 (2.7)	1,466 (17.1)	252 (2.9)	171 (2.0)	204 (2.4)	2,919 (34.0)	587 (6.8)	8,576 (100)
Montserrat¶¶	NR	NR	NR	NR	NR	NR	NR	NR	8 (33.3)	NR	24 (100)
St. Kitts and Nevis§	10 (6.7)	NR	NR	15 (10.1)	10 (6.7)	4 (2.7)	NR	NR	69 (46.3)	NR	149 (100)
St. Lucia§	25 (5.2)	17 (3.6)	17 (3.6)	11 (2.3)	55 (11.5)	14 (2.9)	16 (3.3)	19 (4.0)	152 (31.8)	47 (9.8)	478 (100)
St. Vincent and the Grenadines§	27 (7.4)	6 (1.6)	12 (3.3)	16 (4.4)	21 (5.8)	13 (3.6)	12 (3.3)	17 (4.7)	162 (44.5)	20 (5.5)	364 (100)
Suriname§	124 (12.9)	NR	30 (3.1)	75 (7.8)	151 (15.7)	32 (3.3)	33 (3.4)	45 (4.7)	177 (18.4)	51 (5.3)	963 (100)
Trinidad and Tobago***	389 (10.5)	58 (1.6)	122 (3.3)	84 (2.3)	470 (12.7)	115 (3.1)	98 (2.6)	190 (5.1)	1,302 (35.1)	157 (4.2)	3,706 (100)
Turks and Caicos Islands***	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	15 (100)
Total for the Caribbean countries	**1,785 (8.7)**	**455 (2.2)**	**604 (2.9)**	**668 (3.2)**	**2,897 (14.1)**	**591 (2.9)**	**533 (2.6)**	**726 (3.5)**	**6,861 (33.3)**	**1,209 (5.9)**	**20,600 (100)**
United States and U.S Caribbean territories											
United States§	134,482 (9.0)	56,503 (3.8)	65,373 (4.4)	69,183 (4.6)	437,358 (29.1)	55,783 (3.7)	29,161 (1.9)	92,683 (6.2)	140,333 (9.3)	33,258 (2.2)	1,500,932 (100)
USVI§	54 (14.1)	13 (3.4)	9 (2.3)	7 (1.8)	54 (14.1)	12 (3.1)	11 (2.9)	13 (3.4)	100 (26.1)	22 (5.7)	383 (100)
Puerto Rico¶¶	1,912 (13.1)	462 (3.2)	480 (3.3)	1,017 (6.9)	1,988 (13.6)	429 (2.9)	485 (3.3)	704 (4.8)	2,522 (17.2)	628 (4.3)	14,641 (100)

See table footnotes on next page.

The proportion of unknown/missing/invalid cause of death codes reported by the 21 English- and Dutch-speaking Caribbean countries ranged from 2.3% to 12.9%, with three (14%) countries reporting >10% unknown/missing/invalid cause of death codes, compared with USVI and Puerto Rico, where these percentages were <1%. In addition, 5.3%–15.6% of cancers were coded as "miscellaneous malignant cancer" in the Caribbean countries.

Although data on pediatric cancers (cancers in persons aged <20 years) are not presented, 16 (76%) of the 21 countries and Puerto Rico reported pediatric cancers and ASMR in countries with ≥6 reported cases (11 of 16 countries) ranged from 2.9 per 100,000 in Curacao to 8.8 per 100,000 in Grenada, and 4.2 per 100,000 in Puerto Rico. The majority of pediatric cancer deaths were attributable to leukemia, brain and other nervous system cancers, and cancers of the bones and joints.

Cancer was the leading cause of death in approximately half of the countries when compared with heart disease alone; when compared with all cardiovascular disease (ICD-10: I00–I99), including heart disease, hypertension without heart disease, cerebrovascular diseases, atherosclerosis, aortic aneurysm and dissection, and other diseases of arteries combined, cancer was the second leading cause of death in all countries. There is wide variation in cancer-specific mortality rates within the English- and Dutch-speaking Caribbean region, USVI, and Puerto Rico; however, prostate and breast cancers were consistently the leading causes of cancer-related deaths among males and females, respectively. When compared with the United States,

TABLE 1. (*Continued*) Top 10 causes of cancer deaths, by sex, based on 5-year cumulative proportion — 21 countries in the Caribbean region, United States, U.S. Virgin Islands, and Puerto Rico, 2003–2013*

Females	Breast No. (%)	Cervix No. (%)	Colon/ Rectum No. (%)	Liver/ Intra-hepatic bile duct No. (%)	Lung/ Bronchus No. (%)	Non-Hodgkin lymphoma No. (%)	Ovary No. (%)	Pancreas No. (%)	Stomach No. (%)	Uterine corpus No. (%)	All sites† No. (%)
Caribbean countries											
Anguilla§	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	20 (100)
Antigua and Barbuda§	51 (26.1)	15 (7.7)	27 (13.8)	NR	11 (5.6)	NR	16 (8.2)	NR	10 (5.1)	11 (5.6)	195 (100)
Aruba§	88 (24.9)	16 (4.5)	28 (7.9)	14 (4.0)	33 (9.3)	12 (3.4)	23 (6.5)	20 (5.6)	16 (4.5)	14 (3.9)	354 (100)
Bahamas¶	255 (28.8)	68 (7.7)	79 (8.9)	23 (2.6)	45 (5.1)	28 (3.2)	52 (5.9)	25 (2.8)	31 (3.5)	44 (5.0)	885 (100)
Barbados¶	280 (23.2)	64 (5.3)	166 (13.7)	21 (1.7)	52 (4.3)	46 (3.8)	46 (3.8)	52 (4.3)	34 (2.8)	77 (6.4)	1,207 (100)
Belize§	57 (14.0)	74 (18.2)	28 (6.9)	30 (7.4)	27 (6.6)	NR	8 (2.0)	17 (4.2)	21 (5.2)	33 (8.1)	406 (100)
Bermuda**	53 (19.6)	NR	45 (16.7)	NR	38 (14.1)	6 (2.2)	13 (4.8)	15 (5.6)	9 (3.3)	11 (4.1)	270 (100)
British Virgin Islands††	8 (19.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	42 (100)
Cayman Islands§	27 (29.7)	NR	9 (9.9)	NR	9 (9.9)	NR	NR	NR	NR	NR	91 (100)
Curacao§§	153 (25.7)	27 (4.5)	86 (14.5)	14 (2.4)	37 (6.2)	11 (1.8)	39 (6.6)	24 (4.0)	29 (4.9)	34 (5.7)	595 (100)
Dominica¶¶	52 (22.5)	17 (7.4)	23 (10.0)	10 (4.3)	18 (7.8)	7 (3.0)	8 (3.5)	8 (3.5)	23 (10.0)	9 (3.9)	231 (100)
Grenada§	71 (19.8)	37 (10.3)	31 (8.7)	14 (3.9)	17 (4.7)	19 (5.3)	18 (5.0)	18 (5.0)	16 (4.5)	32 (8.9)	358 (100)
Guyana¶	221 (18.7)	183 (15.5)	69 (5.8)	43 (3.6)	39 (3.3)	20 (1.7)	74 (6.3)	35 (3.0)	29 (2.5)	101 (8.6)	1,181 (100)
Jamaica¶	1,395 (21.1)	813 (12.3)	653 (9.9)	188 (2.8)	404 (6.1)	201 (3.0)	267 (4.0)	219 (3.3)	330 (5.0)	414 (6.3)	6,618 (100)
Montserrat¶¶	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	8 (100)
St. Kitts and Nevis§	29 (20.6)	12 (8.5)	9 (6.4)	10 (7.1)	NR	NR	10 (7.1)	6 (4.3)	NR	7 (5.0)	141 (100)
St. Lucia§	89 (21.2)	40 (9.5)	35 (8.3)	12 (2.9)	20 (4.8)	15 (3.6)	21 (5.0)	24 (5.7)	25 (5.9)	16 (3.8)	420 (100)
St. Vincent and the Grenadines§	60 (23.4)	36 (14.1)	14 (5.5)	NR	9 (3.5)	NR	10 (3.9)	7 (2.7)	11 (4.3)	23 (9.0)	256 (100)
Suriname§	136 (16.1)	146 (17.2)	76 (9.0)	43 (5.1)	66 (7.8)	21 (2.5)	55 (6.5)	38 (4.5)	27 (3.2)	22 (2.6)	847 (100)
Trinidad and Tobago***	743 (23.2)	346 (10.8)	300 (9.4)	83 (2.6)	138 (4.3)	98 (3.1)	239 (7.5)	174 (5.4)	94 (2.9)	242 (7.6)	3,200 (100)
Turks and Caicos Islands***	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	17 (100)
Total for the Caribbean countries	**3,773 (21.8)**	**1,907 (11.0)**	**1,688 (9.7)**	**526 (3.0)**	**970 (5.6)**	**506 (2.9)**	**906 (5.2)**	**693 (4.0)**	**714 (4.1)**	**1,102 (6.4)**	**17,342 (100)**
United States and U.S. Caribbean territories											
United States§	204,342 (15.0)	20,022 (1.5)	125,567 (9.2)	33,266 (2.4)	351,939 (25.8)	45,973 (3.4)	72,120 (5.3)	91,208 (6.7)	22,894 (1.7)	41,342 (3.0)	1,366,172 (100)
USVI§	69 (24.8)	8 (2.9)	36 (12.9)	11 (4.0)	31 (11.2)	7 (2.5)	17 (6.1)	9 (3.2)	12 (4.3)	13 (4.7)	278 (100)
Puerto Rico¶¶	2,129 (18.5)	280 (2.4)	1,564 (13.6)	508 (4.4)	1,083 (9.4)	341 (3.0)	484 (4.2)	691 (6.0)	437 (3.8)	483 (4.2)	11,494 (100)

Abbreviations: NR = data not reported for countries with fewer than six cases; USVI = U.S. Virgin Islands.

* Individual countries contributed different 5-year data.

† All sites include top 10 leading cancers as well as other cancers reported by the countries.

§ Data available from 2008 to 2012.

¶ Data available from 2007 to 2011.

** Data available from 2006 to 2010.

†† Data available from 2004, 2006, and 2008 to 2010.

§§ Data available from 2003 to 2007.

¶¶ Data available from 2009 to 2013.

*** Data available from 2005 to 2009.

ASMRs associated with cervical cancers were 2–9 times higher in the Caribbean region, and ASMR for breast cancer was up to two times higher than that in the United States for all but four of the countries. Compared with the United States, prostate cancer ASMR was 2–8 times higher in the Caribbean region. Lung cancer-associated ASMRs were lower for males and females in all of the English- and Dutch-speaking Caribbean compared with those in the United States.

Discussion

Lung and cervical cancers are important preventable causes of morbidity and mortality in most of the Caribbean countries. Lung cancers can be prevented through primary prevention of exposure to risk factors such as smoking, and cervical cancers can be prevented through human papillomavirus vaccination. The leading causes of cancer deaths in the Caribbean region for both males and females also can be reduced through screening,

TABLE 2. Age-standardized 5-year mortality rates for the top 10 leading causes of cancer deaths, by sex — 21 countries in the Caribbean region, United States, U.S. Virgin Islands, and Puerto Rico, 2003–2013*

Males	Colon/ Rectum	Esophagus	Leukemia	Liver/ Intra-hepatic bile duct	Lung/ Bronchus	Non-Hodgkin lymphoma	Oral cavity/ Pharynx	Pancreas	Prostate	Stomach	All sites†
Caribbean countries											
Anguilla§	NR	NR	NR	NR	NR	NR	NR	NR	64.6	NR	148.1
Antigua and Barbuda§	9.5	3.4	NR	5.6	11.8	3.4	4.3	NR	46.8	4.1	113.7
Aruba§	10.1	3.4	2.6	5.5	20.6	3.7	3.3	3.2	21.6	5.7	99.3
Bahamas¶	14.3	5.2	4.0	4.1	16.3	2.7	3.6	5.0	44.8	8.3	142.5
Barbados¶	15.3	2.7	3.6	1.8	7.4	2.3	5.1	5.1	41.3	5.4	120.9
Belize§	4.9	1.6	3.0	6.8	11.8	1.9	1.3	2.1	17.7	6.0	73.3
Bermuda**	12.6	4.1	4.3	3.8	31.9	4.1	4.3	7.7	23.3	4.7	126.4
British Virgin Islands††	15.7	NR	NR	NR	12.3	NR	NR	NR	25.7	NR	113.3
Cayman Islands§	8.0	NR	NR	NR	22.7	NR	NR	NR	27.0	NR	101.1
Curacao§§	18.1	8.5	3.2	4.2	34.0	3.6	5.1	7.9	40.6	8.4	167.6
Dominica¶¶	8.5	3.4	2.0	5.8	14.1	4.8	4.2	10.6	62.9	13.6	157.8
Grenada§	11.3	8.5	2.4	3.7	14.9	11.2	6.6	6.0	60.5	8.4	167.5
Guyana¶	5.1	1.4	2.5	4.6	4.6	1.4	2.1	2.7	25.4	3.6	69.0
Jamaica¶	9.2	2.7	3.7	3.4	23.2	3.9	2.8	2.9	36.7	8.8	122.9
Montserrat¶¶	NR	NR	NR	NR	NR	NR	NR	NR	31.7	NR	97.6
St. Kitts and Nevis§	13.6	NR	NR	14.4	12.1	4.5	NR	NR	74.1	NR	166.3
St. Lucia§	5.5	3.8	3.8	2.1	11.3	3.4	3.7	4.5	28.1	10.2	98.8
St. Vincent and the Grenadines§	11.2	2.5	4.8	6.9	9.7	6.2	5.9	7.9	58.9	8.3	145.5
Suriname§	10.5	0.4	2.4	6.4	12.7	2.6	2.7	3.8	15.1	4.2	80.6
Trinidad and Tobago***	13.0	2.0	3.9	2.8	16.0	3.8	3.3	6.3	39.4	5.2	119.3
Turks and Caicos Islands***	NR	NR	NR	NR	5.7	NR	NR	NR	NR	NR	50.8
United States and U.S. Caribbean territories											
United States§	10.6	4.7	5.2	5.8	34.8	4.3	2.5	7.4	9.3	2.7	118.4
USVI§	12.3	2.5	1.8	1.6	11.9	2.5	2.3	2.8	20.1	5.5	81.4
Puerto Rico¶¶	11.8	3.0	3.1	6.6	11.9	2.8	3.3	4.3	12.3	3.7	88.1

See table footnotes on next page.

Summary

What is already known about this topic?

Cancer is one of the leading causes of deaths in countries in the Caribbean region; many of the leading causes of cancer deaths in these countries, including breast and cervical cancers, are preventable.

What is added by this report?

The most common causes of cancer deaths among Caribbean males were prostate (18.4% to 47.4%) and lung (5.6% to 24.4%) cancers. The most common causes of cancer deaths among Caribbean females for the majority of the countries were breast (14.0% to 29.7%) and cervical (4.5% to 18.2%) cancers.

What are the implications for public health practice?

The leading causes of cancer deaths in the Caribbean region for both males and females can largely be reduced and prevented through many strategies, including primary prevention, early detection, management, and treatment of patients with cancer. Prevention strategies include human papillomavirus vaccination and screening for cervical cancer, screening for breast cancer, and avoiding smoking for lung cancer.

early detection, and effective treatment for cervical, breast, and colorectal cancers (*7*). Although prostate cancer is the leading cause of cancer mortality among men in the Caribbean, effective screening strategies that result in reduced mortality have not yet emerged globally, highlighting the need for strengthening referral and treatment strategies (*8*).

The findings in this report are subject to at least five limitations that could result in either under- or overestimation of the presented mortality rates. First, denominator data were not available for the entire study period from any of the countries. Second, cancer-specific mortality rates for the region could not be calculated because there was no single year when all contributing countries submitted data to the Caribbean Public Health Agency. Third, some countries reported approximately 10% "unknown/missing/invalid" cause of death codes or "non-specific/miscellaneous malignant cancers" as the underlying cause of death, which can compromise the ability to rank the cancer sites accurately. Fourth, results should be interpreted with caution given that age-standardized mortality rates might be unreliable in some countries because of small numbers. Finally, it was not

TABLE 2 (*Continued*). Age-standardized 5-year mortality rates for the top 10 leading causes of cancer deaths, by sex — 21 countries in the Caribbean region, United States, U.S. Virgin Islands, and Puerto Rico, 2003–2013*

Females	Breast	Cervix	Colon/ Rectum	Liver/ Intra-hepatic bile duct	Lung/ Bronchus	Non-Hodgkin lymphoma	Ovary	Pancreas	Stomach	Uterine corpus	All sites†
Caribbean countries											
Anguilla§	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	50.5
Antigua and Barbuda§	20.4	6.2	10.4	NR	4.2	NR	6.5	NR	3.4	4.0	75.8
Aruba§	19.6	4.1	6.2	3.2	7.6	2.7	5.1	4.7	3.6	2.8	79.6
Bahamas¶	26.5	7.3	8.6	2.5	5.3	3.0	5.6	2.8	3.5	5.2	96.2
Barbados¶	23.5	5.4	12.0	1.6	3.8	3.6	4.1	4.0	1.9	6.1	94.7
Belize§	10.0	12.5	4.5	5.3	5.1	NR	1.3	3.4	3.8	6.1	71.0
Bermuda**	17.7	NR	12.6	NR	12.1	2.6	3.4	4.9	3.1	3.1	82.1
British Virgin Islands††	12.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	83.0
Cayman Islands§	21.7	NR	6.4	NR	7.2	NR	NR	NR	NR	NR	70.6
Curacao§§	27.3	5.0	13.9	2.2	5.9	1.9	6.4	4.0	4.3	5.6	100.7
Dominica¶¶	25.0	9.8	9.1	4.5	6.5	3.1	4.0	2.7	8.0	4.5	101.0
Grenada§	25.5	12.0	7.5	4.1	5.1	8.8	6.2	5.1	4.4	9.5	114.2
Guyana¶	11.6	9.7	3.7	2.4	2.0	1.0	4.0	2.1	1.6	5.6	63.1
Jamaica¶	19.5	12.1	8.1	2.7	5.5	2.9	3.8	2.8	4.1	5.7	90.5
Montserrat¶¶	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	32.1
St. Kitts and Nevis§	24.7	12.3	8.3	10.7	NR	NR	10.6	4.4	NR	6.1	123.3
St. Lucia§	17.8	7.7	7.1	2.1	3.9	3.0	4.3	4.2	4.1	2.8	79.6
St. Vincent and the Grenadines§	22.9	15.5	5.5	NR	2.8	NR	3.8	2.3	3.6	8.0	96.6
Suriname§	10.6	11.0	5.9	3.3	5.1	1.6	4.1	3.0	2.0	1.7	64.1
Trinidad and Tobago***	23.4	10.8	8.9	2.5	4.1	3.1	7.4	5.0	2.6	7.6	97.8
Turks and Caicos Islands***	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	41.7
United States and U.S. Caribbean territories											
United States§	14.1	1.7	7.3	2.1	22.6	2.5	4.8	5.4	1.4	2.8	87.2
USVI§	13.3	1.7	6.3	1.7	5.3	1.2	3.2	1.5	2.0	2.4	49.5
Puerto Rico¶¶	12.2	1.9	7.2	2.3	5.0	1.7	2.6	3.1	2.0	2.7	58.1

Abbreviations: NR = data not reported for countries with fewer than six cases; USVI = U.S. Virgin Islands.

* Individual countries contributed different 5-years of data. Rates are per 100,000 and age-standardized to the Segi World Standard population (million; 18 age groups); age-standardized mortality rates for countries with small number of deaths may be unreliable and should be interpreted with caution.

† All sites include top 10 leading cancers as well as other cancers reported by the countries.

§ Data available from 2008 to 2012.

¶ Data available from 2007 to 2011.

** Data available from 2006 to 2010.

†† Data available from 2004, 2006, and 2008 to 2010.

§§ Data available from 2003 to 2007.

¶¶ Data available from 2009 to 2013.

*** Data available from 2005 to 2009.

possible to account for the variability regarding the inclusion and exclusion of nonresident deaths in mortality statistics or of deaths of residents that occurred abroad.

Despite the limitations, these findings identify cancers that are leading causes of death among men and women in the Caribbean region; underscore the importance of establishing reliable cancer surveillance systems in the region to understand and assess the prevalence of cancer, and provide a foundation for cancer control plans and effective public health interventions; and might inform the strengthening of cancer prevention priorities and programs in the Caribbean including US territories such as USVI and Puerto Rico.

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Monitoring of Persons with Risk for Exposure to Ebola Virus — United States, November 3, 2014–December 27, 2015

Hyacinte Julien Kabore, DDS[1]; Rodel Desamu-Thorpe, MD[1]; Lisa Jean-Charles, MPH[1]; Karrie-Ann Toews, MPH[1]; Rachel Nonkin Avchen, PhD[1]

During November 3, 2014–December 27, 2015, CDC implemented guidance on movement and monitoring of persons in the United States with potential exposure to Ebola virus (Ebola) (*1*). Monitoring was concluded in December 2015. After CDC modified the guidance for monitoring travelers from Guinea (the last country for which monitoring of travelers was recommended) in late December 2015, jurisdictional reports were no longer collected by CDC. This report documents the number of persons monitored as part of the effort to isolate, test, and, if necessary, treat symptomatic travelers and other persons in the United States who had risk for exposure to Ebola during the period the guidance was in effect. Sixty jurisdictions, including all 50 states, two local jurisdictions, and eight territories and freely associated states, reported a total of 29,789 persons monitored, with >99% completing 21-day monitoring with no loss to follow-up exceeding 48 hours. No confirmed cases of imported Ebola were reported once monitoring was initiated. This landmark public health response demonstrates the robust infrastructure and sustained monitoring capacity of local, state, and territorial health authorities in the United States as a part of a response to an international public health emergency.

Monitoring of persons with risk for exposure to Ebola included active monitoring (daily reporting of temperature and other symptoms to public health officials) and direct active monitoring (daily reporting of temperature and other symptoms and daily direct observation by public health officials) (*2*). CDC defined three risk levels for the purpose of guiding monitoring and movement restrictions: "low but not zero risk" (low risk); "some risk," and "high risk." During November 3, 2014–March 9, 2015, reports to CDC consisted of individual-level daily submissions for all persons under monitoring from the included jurisdictions (*2*). After March 9, 2015, individual-level daily reporting was only submitted for symptomatic persons and persons with gaps in reporting exceeding 48 hours. Weekly aggregate monitoring data were collected from each jurisdiction for all persons under monitoring by epidemiologic risk category.

Complete monitoring (active monitoring or direct active monitoring) was defined as making contact with the monitored person, with no gaps of >48 hours in reporting of persons being actively monitored or in contact with persons receiving direct active monitoring (i.e., no loss to follow-up) during the 21-day monitoring period. The overall number of persons monitored included all persons who completed monitoring during the period of guidance implementation, in addition to any persons who left the United States before completing the full 21-day monitoring period and any persons under monitoring on December 27, 2015.

During November 3, 2014–December 27, 2015, in the 60 U.S. jurisdictions reporting,* 29,789 persons were monitored (Table). Overall, 97.0% of persons monitored were travelers at low risk, 1.5% were health care workers at low risk who provided patient care in the United States, and 1.6% were travelers at high or some risk (Figure 1). A median of 1,680 persons (range = 551–2,719) were monitored in a given reporting week. Among health care workers at low risk, 61% were monitored during November–December 2014, and 36% were monitored during March–April 2015, after caring for patients treated for Ebola in the United States. Among 442 persons at high or some risk (mostly health care workers who cared for patients in Ebola-affected countries), 90% were monitored during November 2014–May 2015. The number of persons monitored weekly decreased 46% from a peak in mid-May 2015 to mid-June 2015. This decrease corresponded to the first declaration by the World Health Organization that Liberia was free of Ebola and CDC's subsequent modification of the monitoring recommendation to self-observation for travelers from Liberia. The number of persons monitored decreased a further 63% during October–December 2015, after the United States stopped enhanced entry risk assessment and management for Liberia travelers and CDC's modification of monitoring guidance for Sierra Leone (Figure 1).

During a given week, a median of three persons for whom monitoring was indicated could not be contacted upon arriving in the jurisdiction responsible for their monitoring (0.3%; range = 0–48 persons per week). Among all persons ever contacted for monitoring, a median of five persons had gaps in monitoring >48 hours in a given week (0.3%; range = 0–26 persons per week). The median number of persons with >48-hour gaps in monitoring declined over time and decreased from three persons per week (0.2%) in February 2015 to two persons per week (0.1%) in December 2015.

During a given week, a median of 11 persons who developed symptoms while under monitoring (0.7%,

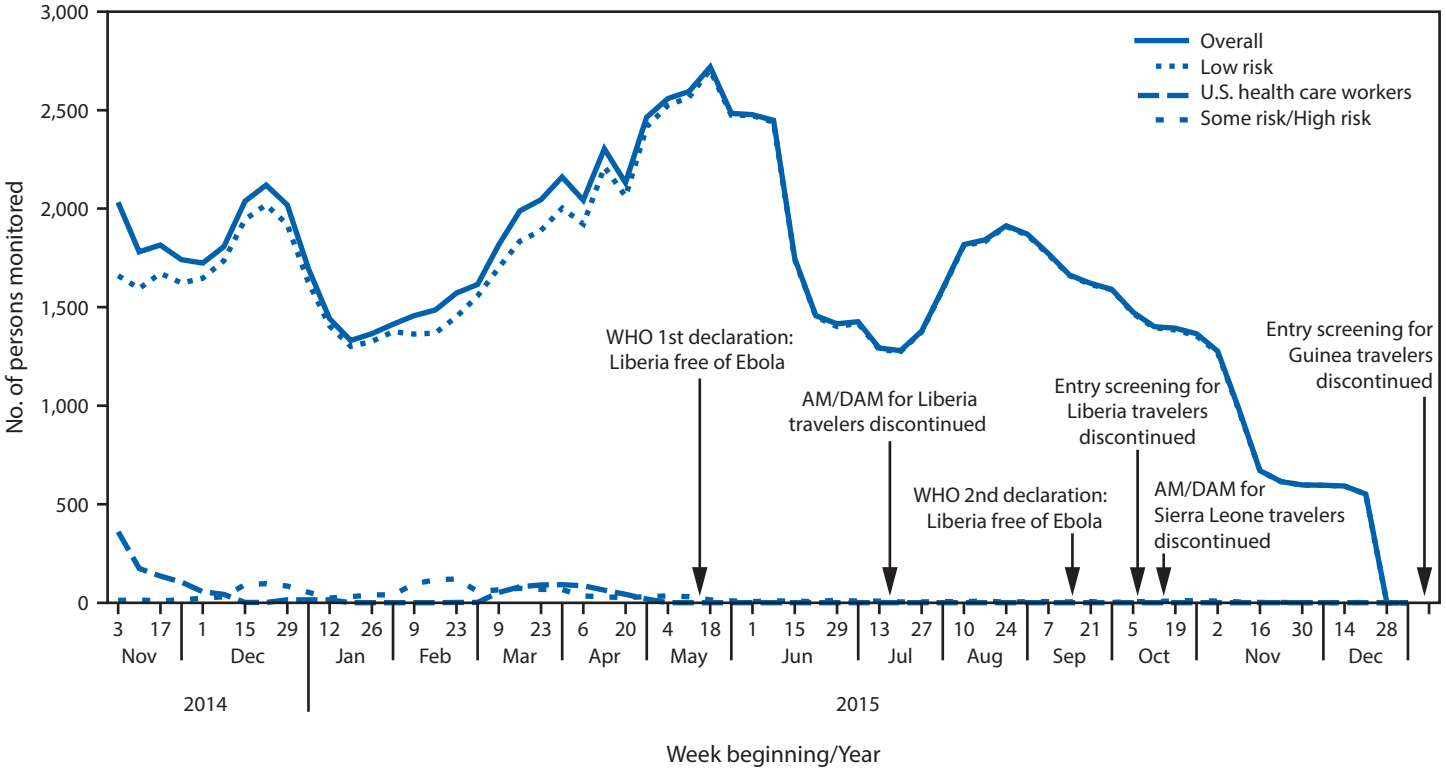
* 50 U.S. states, District of Columbia, New York City, Puerto Rico, U.S. Virgin Islands, American Samoa, Guam, Federated States of Micronesia, Northern Mariana Islands, Palau, and Marshall Islands.

TABLE. Ebola virus monitoring of persons with potential exposure, by epidemiologic risk category — 60 U.S. jurisdictions,* November 3, 2014–December 27, 2015

Monitoring element	High risk/Some risk	Low (but not zero) risk		Total
		Travelers	U.S. HCWs	
Type of daily monitoring	DAM	AM	DAM	—
Reporting frequency to CDC	Daily/Weekly	Weekly	Weekly	—
No. of persons monitored	442	28,759	598	**29,789**†
No. of jurisdictions conducting monitoring	47	54	12	**54**§

Abbreviations: AM = active monitoring; DAM = direct active monitoring; HCWs = health care workers, including laboratory personnel.
* 50 U.S. states, District of Columbia, New York City, Puerto Rico, U.S. Virgin Islands, American Samoa, Guam, Federated States of Micronesia, Northern Mariana Islands, Palau, and Marshall Islands.
† Adjusted for 10 persons whose risk category changed from some risk to low risk.
§ A jurisdiction could conduct monitoring of travelers in more than one risk category.

FIGURE 1. Number of persons (N = 29,789) with potential exposure who were monitored for Ebola virus, by epidemiologic risk category and week — United States, November 3, 2014–December 27, 2015



Abbreviations: AM/DAM = active monitoring/direct active monitoring; WHO = World Health Organization.

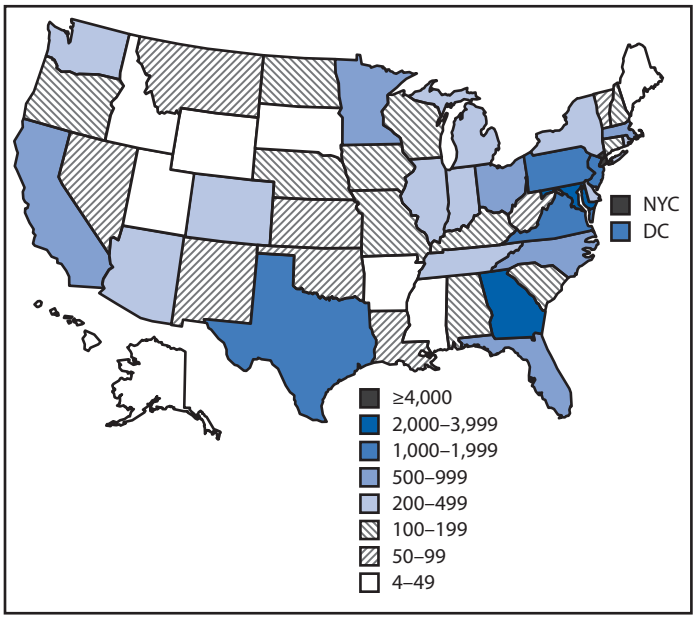
range = 1–43 persons) were reported to CDC. Among 796 symptomatic persons in the low-risk and some-risk categories, 104 (13%) were tested for Ebola during their monitoring period; none tested positive for Ebola. No persons at high risk reported Ebola-compatible symptoms.

All 50 states, plus the District of Columbia, New York City, Puerto Rico, and the U.S. Virgin Islands monitored persons at low risk. Forty-four states, the District of Columbia, New York City, and Puerto Rico monitored one or more persons at some or high risk. Three territories and three freely associated states had no persons under monitoring. Approximately half (53%) of all persons were monitored in five jurisdictions (New York City, Maryland, Georgia, Pennsylvania, and Virginia). New York City monitored the largest number of persons, followed by Maryland and Georgia (Figure 2).

Discussion

Fifty states and two local jurisdictions effectively monitored travelers arriving in the United States from Ebola-affected West African countries within 7 days of the release of updated CDC guidance on movement and monitoring on October 27, 2014; by the end of December 2014, all U.S. territories also

FIGURE 2. Number of persons (N = 29,789) with potential exposure who were monitored for Ebola virus, by jurisdiction — United States, November 3, 2014–December 28, 2015



Abbreviations: DC = District of Columbia; NYC = New York City.

Summary

What is already known about this topic?

Beginning in March 2014, West Africa (primarily the countries of Guinea, Liberia, and Sierra Leone) has experienced the largest outbreak of Ebola virus disease (Ebola) in history. During March 25, 2014–April 13, 2016, a total of 28,616 cases of Ebola were reported in West Africa, and 11,310 persons died. In October 2014, after the first case of imported Ebola in the United States, CDC issued monitoring and movement guidance. This guidance provided recommendations for U.S. monitoring of persons potentially exposed to Ebola.

What is added by this report?

Overall, 29,789 persons were monitored, with >99% completing 21-day monitoring with no loss to follow-up exceeding 48 hours. In a given reporting week, a median of 1,680 persons were monitored and approximately half (53%) of all persons were monitored in five jurisdictions. Among 796 symptomatic persons in the low-risk and some-risk categories, 104 (13%) were tested for Ebola during their monitoring period; none tested positive for Ebola.

What are the implications for public health practice?

The overall success in monitoring >99% of incoming travelers resulted, in part, because of the vigilance of state, local, and territorial health departments and the preparedness infrastructure that enabled jurisdictions to fully implement CDC guidance for monitoring of persons with potential Ebola exposure.

were reporting to CDC (*2*). The Movement and Monitoring Unit under the leadership of CDC's State Coordination Task Force assumed responsibility for coordinating the national response to monitor persons with potential exposure to Ebola. The Movement and Monitoring Unit 1) communicated CDC's movement and monitoring guidance to all partners, 2) activated monitoring, 3) collected and compiled reports from states and local health departments, and 4) provided information on the monitoring status of persons with risk for Ebola exposure to CDC, the U.S. Department of Health and Human Services, and the White House. As a result of this sustained effort, almost 30,000 travelers from Ebola-affected countries were monitored in the United States.

The findings in this report are subject to at least two limitations. First, weekly aggregate numbers masked precision and could be inexact. This might have occurred when a person's risk was reclassified or when individual-level daily reporting shifted to weekly reporting. Second, accounting for duplicate reporting of monitoring status was challenging. For example, aggregate weekly reporting could underestimate or overestimate monitoring numbers if a person transferred jurisdictions and was reported by both jurisdictions or by neither jurisdiction. However, efforts were made to remove duplicates from the analysis.

The overall success in monitoring >99% of incoming travelers resulted, in part, because of the vigilance of state, local, and territorial health departments and the preparedness infrastructure that enabled jurisdictions to fully implement and follow CDC guidance on monitoring of persons with potential Ebola exposure. This monitoring success also can be attributed to a range of methodologies and resources used throughout the implementation period, including an enhanced entry risk-assessment process that provided Check and Report Ebola kits and mobile telephones to all incoming travelers requiring monitoring, and collected personal locating information including telephone numbers, e-mail and physical addresses, and emergency contact information. Loss to follow-up was minimized by state and local health department partnerships with local police departments and Homeland Security's state fusion centers. Novel methods to contact persons via social media further facilitated communication and monitoring efforts. In most cases, initial failures in contact or loss to follow-up were attributed to missing or erroneous contact information, which can occur even with robust protocols. The monitoring of travelers from Ebola-affected countries exemplified a complex coordination of multiple agencies at multiple levels to successfully eliminate further cases of imported Ebola virus disease in the United States.

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Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices

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Introduction

Vaccination against human papillomavirus (HPV) is recommended to prevent HPV infections and HPV-associated diseases, including cancers. Routine vaccination at age 11 or 12 years has been recommended by the Advisory Committee on Immunization Practices (ACIP) since 2006 for females and since 2011 for males (*1*,*2*). This report provides recommendations and guidance regarding use of HPV vaccines and updates ACIP HPV vaccination recommendations previously published in 2014 and 2015 (*1*,*2*). This report includes new recommendations for use of a 2-dose schedule for girls and boys who initiate the vaccination series at ages 9 through 14 years. Three doses remain recommended for persons who initiate the vaccination series at ages 15 through 26 years and for immunocompromised persons.

Background

HPV infection causes cervical, vaginal, and vulvar cancers in women; penile cancers in men; and oropharyngeal and anal cancers as well as genital warts in both men and women (*3*).

Recommendations for use of vaccines in children, adolescents and adults are developed by the Advisory Committee on Immunization Practices (ACIP). ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of the Centers for Disease Control and Prevention (CDC) on use of vaccines and related agents for the control of vaccine-preventable diseases in the civilian population of the United States. Recommendations for use of vaccines in children and adolescents are harmonized to the greatest extent possible with recommendations made by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists (ACOG). Recommendations for routine use of vaccines in adults are harmonized with recommendations of AAFP, ACOG, and the American College of Physicians (ACP). ACIP recommendations approved by the CDC Director become agency guidelines on the date published in the Morbidity and Mortality Weekly Report (MMWR). *Additional information about ACIP is available at https://www.cdc.gov/vaccines/acip.*

Three HPV vaccines are licensed for use in the United States. All are noninfectious. Quadrivalent and 9-valent HPV vaccines (4vHPV and 9vHPV, Gardasil and Gardasil 9, Merck and Co, Inc., Whitehouse Station, New Jersey) are licensed for use in females and males aged 9 through 26 years (*1*). Bivalent HPV vaccine (2vHPV, Cervarix, GlaxoSmithKline, Rixensart, Belgium) is licensed for use in females aged 9 through 25 years (*1*). As of late 2016, only 9vHPV is being distributed in the United States. The majority of all HPV-associated cancers are caused by HPV 16 or 18, types targeted by all three vaccines. In addition, 4vHPV targets HPV 6 and 11, types that cause genital warts. 9vHPV protects against these and five additional types: HPV 31, 33, 45, 52, and 58. All three vaccines have been approved for administration in a 3-dose series at intervals of 0, 1 or 2, and 6 months. In October 2016, after considering new clinical trial results (*4*), the Food and Drug Administration (FDA) also approved 9vHPV for use in a 2-dose series for girls and boys aged 9 through 14 years (*5*). In October 2016, ACIP recommended a 2-dose schedule for adolescents initiating HPV vaccination in this age range. This report provides recommendations for use of 2-dose and 3-dose schedules for HPV vaccination.

Methods

During November 2015–October 2016, the ACIP HPV Vaccines Work Group held monthly telephone conferences to 1) review and evaluate the quality of the evidence assessing immunogenicity, efficacy, and postlicensure effectiveness of a 2-dose schedule; 2) consider benefits and harms of a 2-dose schedule; 3) weigh the variability in the values and preferences of patients and providers for a 2-dose schedule; and 4) examine health economic analyses. During teleconferences, summaries of findings were presented for Work Group discussion.

A systematic review was conducted to identify studies involving human subjects* that reported primary data on any important or critical health outcomes related to HPV vaccination† after 2 doses of 9vHPV, 4vHPV, or 2vHPV, administered at an interval of 0 and ≥6 months (±4 weeks) to

* No primary data on special populations or medical conditions, including immunocompromising conditions, were available for 2-dose intervals and age ranges specified.

† No primary data on other important and critical outcomes, including genital warts, precancers, oropharyngeal cancer, anal cancer, cervical cancer, vaginal/vulvar cancer, and penile cancer, were available for 2-dose intervals and age ranges specified.

persons aged 9 through 14 years. The review focused on this age group given available 2-dose trial data for 9vHPV (*4*). Immunogenicity outcomes of interest were seroconversion, geometric mean titers (GMTs), or antibody avidity. Studies were excluded if they lacked a comparison group in which efficacy of 3 doses of HPV vaccine against clinical endpoints was demonstrated in clinical trials (e.g., females aged 15 through 26 years).[§] Evidence regarding a 3-dose schedule for HPV vaccine was reviewed previously (*1*,*2*).

Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Detailed methods and GRADE tables can be found online (*6*). Other studies from the search and from the broader literature informed additional expert guidance that extended beyond the research question addressed formally via GRADE analysis (*7*). Evidence was reviewed by the Work Group, summarized, and publicly presented at the February and June 2016 ACIP meetings. CDC vaccine recommendations are developed using the GRADE framework (*8*). Proposed recommendations were presented, and after a public comment period, were approved unanimously[¶] by the voting ACIP members at the October 2016 ACIP meeting.

Summary of Key Findings

Immunogenicity. In the 9vHPV clinical trial that was the basis for FDA approval of a 2-dose series, participants were girls and boys aged 9 through 14 years, compared with young females aged 16 through 26 years (*4*). Among 1,377 participants, ≥97.9% seroconverted to all nine vaccine-preventable HPV types by 4 weeks after the last dose. For girls and boys who received 2 doses of 9vHPV 6 months apart (0, 6 month schedule) or 12 months apart (0, 12 month schedule), noninferiority criteria were met for seroconversion and GMTs. Furthermore, GMTs were significantly higher for all 9vHPV types among persons aged 9 through 14 years who received 2 doses compared with females aged 16–26 years who received 3 doses (0, 2, 6 month schedule). Six additional studies found similar results for 4vHPV and 2vHPV (*6*). Immunogenicity was found to be noninferior with 2 doses in persons aged 9 through 14 years compared with 3 doses in a group in which clinical efficacy was demonstrated (GRADE evidence type 3).

Efficacy and effectiveness. Although efficacy and postlicensure effectiveness studies were reviewed, none met the inclusion criteria detailed above. The prelicensure HPV vaccine efficacy trials were conducted with 3-dose series; post hoc analyses conducted with data from some of these trials found high efficacy against infection among vaccinees who received 2 doses and those who received 3 doses (*9*,*10*). A large study comparing 2 doses with 3 doses also suggested similar efficacy against infection (*11*). Postlicensure effectiveness studies have found lower effectiveness against various HPV-associated outcomes among vaccinees who received 2 doses compared with those who received 3 doses, but methodologic challenges with these studies limit interpretation of the findings.[**]

Duration of protection. Through 10 years of follow-up from clinical trials, no evidence of waning protection after a 3-dose series of HPV vaccine has been found (*1*). Because antibody kinetics are similar with 2-dose and 3-dose series, duration of protection is also expected to be long-lasting after a 2-dose series (*12*,*13*).

Health impact and cost-effectiveness modeling. Population-level effectiveness and cost-effectiveness of 2-dose and 3-dose schedules of 9vHPV in the United States have been modeled (*14*). Assuming both efficacy and duration of protection are similar with either schedule, a 2-dose series would be cost-saving and have similar population impact to a 3-dose series. Even if duration of protection is 20 years for a 2-dose series and lifelong for a 3-dose series, additional benefits of a 3-dose series would be relatively small, and a 2-dose series would be more cost-effective (*14*).

Rationale

HPV vaccines are highly effective and safe, and a powerful prevention tool for reducing HPV infections and HPV-associated cancers (*1*,*2*). Based on the available immunogenicity evidence, a 2-dose schedule (0, 6–12 months) will have efficacy equivalent to a 3-dose schedule (0, 1–2, 6 months) if the HPV vaccination series is initiated before the 15th birthday (GRADE evidence type 3) (*6*). ACIP recommends a 2-dose schedule for HPV vaccination of girls and boys who initiate the vaccination series at ages 9 through 14 years (Category A recommendation).

Recommendations

Routine and catch-up age groups. ACIP recommends routine HPV vaccination at age 11 or 12 years. Vaccination can be given starting at age 9 years. ACIP also recommends vaccination for females through age 26 years and for males through age 21 years who were not adequately vaccinated previously. Males aged 22 through 26 years may be vaccinated. (See also: Special populations, Medical conditions)

Dosing schedules. For persons initiating vaccination before their 15th birthday, the recommended immunization schedule is 2 doses of HPV vaccine. The second dose should be

[§] Studies were excluded when 2-dose interval was not ≥5 months.

[¶] Twelve votes to none, with one recusal.

[**] In studies conducted in the setting of a 3-dose HPV vaccine recommendation or policy, many 2-dose recipients received HPV vaccine doses at a 1–2 month interval; in addition, 2-dose recipients differed from 3-dose recipients in ways that suggested differences in HPV exposure.

TABLE. Recommended number of doses and intervals for human papillomavirus (HPV) vaccine, by age at series initiation and medical conditions — United States, 2016

Population	Recommended number of HPV vaccine doses	Recommended interval between doses
Persons initiating HPV vaccination at ages 9 through 14 years,* except immunocompromised persons†	2	0, 6–12 months§
Persons initiating HPV vaccination at ages 15 through 26 years¶ and immunocompromised persons† initiating HPV vaccination at ages 9 through 26 years	3	0, 1–2, 6 months**

* ACIP recommends routine HPV vaccination for adolescents at age 11 or 12 years; vaccination may be given starting at age 9 years.
† Persons with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity (see also: Medical conditions)
§ In a 2-dose schedule of HPV vaccine, the minimum interval between the first and second doses is 5 months.
¶ For persons who were not adequately vaccinated previously, ACIP recommends vaccination for females through age 26 years and for males through age 21 years; males ages 22 through 26 years may be vaccinated. Vaccination is recommended for some persons aged 22 through 26 years; see Medical conditions and Special populations.
** In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 5 months between the first and third doses.

administered 6–12 months after the first dose (0, 6–12 month schedule)†† (Table).

For persons initiating vaccination on or after their 15th birthday, the recommended immunization schedule is 3 doses of HPV vaccine. The second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule)§§ (Table).

Persons vaccinated previously. Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV before their 15th birthday, and received 2 doses of any HPV vaccine at the recommended dosing schedule (0, 6–12 months), or 3 doses of any HPV vaccine at the recommended dosing schedule (0, 1–2, 6 months), are considered adequately vaccinated.

Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV on or after their 15th birthday, and received 3 doses of any HPV vaccine at the recommended dosing schedule, are considered adequately vaccinated.

9vHPV may be used to continue or complete a vaccination series started with 4vHPV or 2vHPV.

For persons who have been adequately vaccinated with 2vHPV or 4vHPV, there is no ACIP recommendation regarding additional vaccination with 9vHPV.

Interrupted schedules. If the vaccination schedule is interrupted, the series does not need to be restarted. The number of recommended doses is based on age at administration of the first dose.

Special populations. For children with a history of sexual abuse or assault, ACIP recommends routine HPV vaccination beginning at age 9 years.

For men who have sex with men,¶¶ ACIP recommends routine HPV vaccination as for all males, and vaccination through age 26 years for those who were not adequately vaccinated previously.

For transgender persons, ACIP recommends routine HPV vaccination as for all adolescents, and vaccination through age 26 years for those who were not adequately vaccinated previously.

Medical conditions. ACIP recommends vaccination with 3 doses of HPV vaccine (0, 1–2, 6 months) for females and males aged 9 through 26 years with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity,*** such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasms, transplantation, autoimmune disease, or immunosuppressive therapy, because immune response to vaccination might be attenuated (Table) (*7*).

Contraindications and precautions. Contraindications and precautions, including those related to pregnancy, are unchanged from previous recommendations (*1*,*2*). Adverse events occurring after administration of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax, or by mail. Additional information about VAERS is available by telephone (1-800-822-7967) or online (https://vaers.hhs.gov).

†† In a 2-dose schedule of HPV vaccine, the minimum interval between the first and second doses is 5 months. If the second dose is administered after a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose.
§§ In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 5 months between the first and third doses. If a vaccine dose is administered after a shorter interval, it should be readministered after another minimum interval has elapsed since the most recent dose.

¶¶ Including men who identify as gay or bisexual, or who intend to have sex with men.
*** The recommendation for a 3-dose schedule of HPV vaccine does not apply to children aged <15 years with asplenia, asthma, chronic granulomatous disease, chronic liver disease, chronic lung disease, chronic renal disease, central nervous system anatomic barrier defects (e.g., cochlear implant), complement deficiency, diabetes, heart disease, or sickle cell disease.

Acknowledgments

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Preliminary Report of Microcephaly Potentially Associated with Zika Virus Infection During Pregnancy — Colombia, January–November 2016

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In Colombia, approximately 105,000 suspected cases of Zika virus disease (diagnosed based on clinical symptoms, regardless of laboratory confirmation) were reported during August 9, 2015–November 12, 2016, including nearly 20,000 in pregnant women (*1*,*2*). Zika virus infection during pregnancy is a known cause of microcephaly and serious congenital brain abnormalities and has been associated with other birth defects related to central nervous system damage (*3*). Colombia's *Instituto Nacional de Salud* (INS) maintains national surveillance for birth defects, including microcephaly and other central nervous system defects. This report provides preliminary information on cases of congenital microcephaly identified in Colombia during epidemiologic weeks 5–45 (January 31–November 12) in 2016. During this period, 476 cases of microcephaly were reported, compared with 110 cases reported during the same period in 2015. The temporal association between reported Zika virus infections and the occurrence of microcephaly, with the peak number of reported microcephaly cases occurring approximately 24 weeks after the peak of the Zika virus disease outbreak, provides evidence suggesting that the period of highest risk is during the first trimester of pregnancy and early in the second trimester of pregnancy. Microcephaly prevalence increased more than fourfold overall during the study period, from 2.1 per 10,000 live births in 2015 to 9.6 in 2016. Ongoing population-based birth defects surveillance is essential for monitoring the impact of Zika virus infection during pregnancy on birth defects prevalence and measuring the success in preventing Zika virus infection and its consequences, including microcephaly.

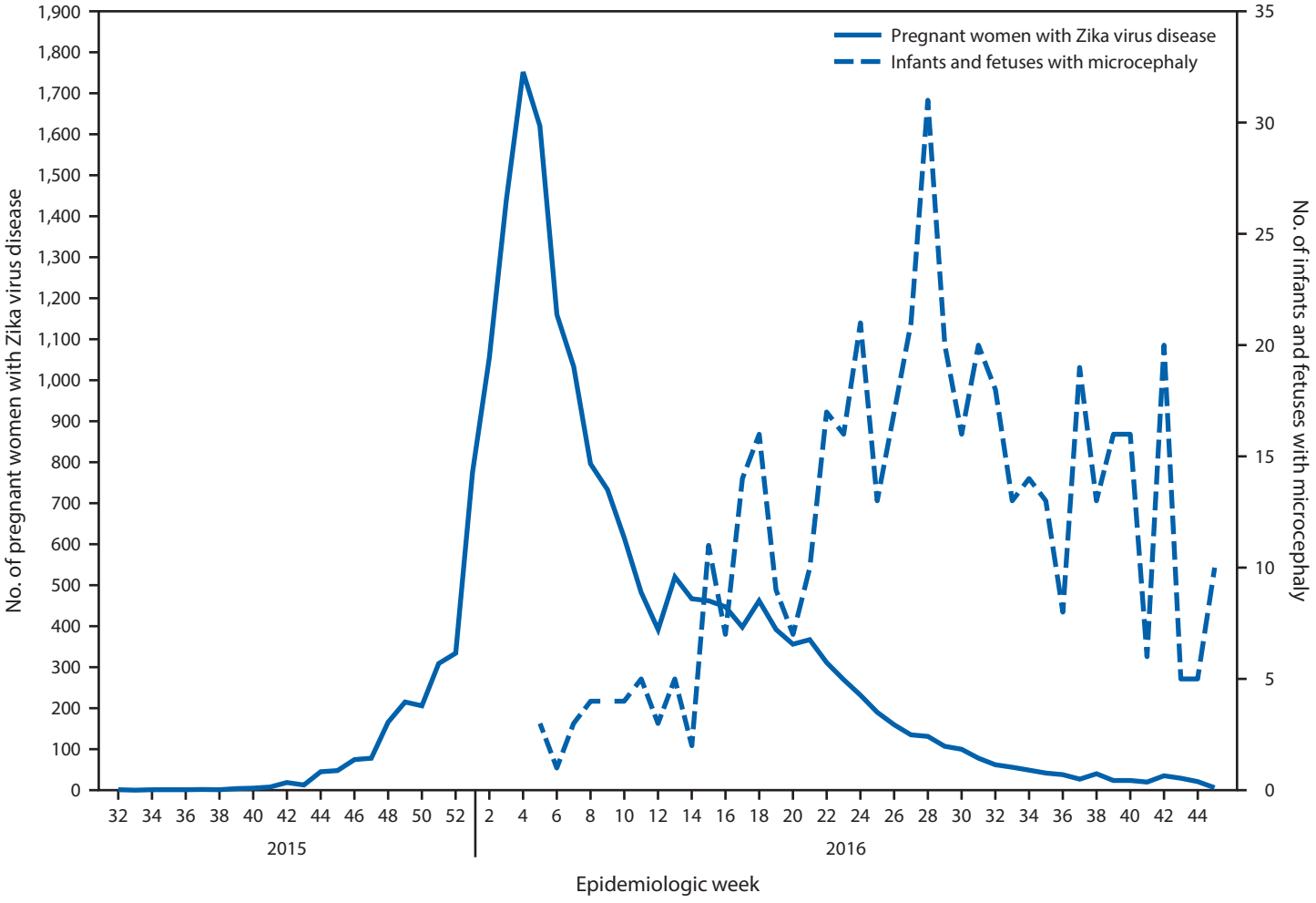
INS maintains ongoing passive, national surveillance in Colombia for both symptomatic Zika virus disease and major birth defects. Surveillance for Zika virus disease based on clinical symptoms and laboratory testing started in August 2015 in Colombia, and following a cluster of laboratory-confirmed cases of Zika virus disease, immediate mandatory reporting began in October 2015. At the time, symptomatic Zika virus disease was defined as illness with fever and at least one additional symptom (rash, nonpurulent conjunctivitis, headache, pruritus, arthralgia, myalgia, or malaise) of unknown etiology. Beginning December 24, 2015, the case definition has included both fever and rash, and at least one of the other symptoms. Colombia's birth defects surveillance system includes reporting of microcephaly (*International Classification of Disease, 10th Revision* code Q02) among live births and pregnancy losses (including spontaneous abortions, pregnancy terminations, and stillbirths) from all reporting areas.* Congenital microcephaly in a newborn is defined as having a head circumference below the third percentile for gestational age and sex. The following clinical specimens are requested for all infants and fetuses with microcephaly to ascertain whether the mother was infected with Zika virus during pregnancy: maternal serum, infant serum from cord and peripheral blood specimens, cerebrospinal fluid (if obtained from infant for clinical reasons), and tissues from fetal losses. Specimens are tested for Zika virus RNA by real-time reverse transcription–polymerase chain reaction (rRT-PCR), for serologic evidence of infection by Zika immunoglobulin M (IgM) antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), or for Zika viral antigens by immunohistochemistry, as well as for the presence of other infections (syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and other agents); high resolution karyotyping is also performed. The Colombian Ministry of Health recommends a diagnostic algorithm for testing of specimens from all products of conception and infants whose mothers had Zika virus infection during pregnancy; however, these specimens are not always collected soon after birth or submitted for Zika virus testing. Recommended neuroimaging includes cranial ultrasound for all infants, and if abnormalities are observed on cranial ultrasound then computed tomography scan or magnetic resonance imaging might be necessary. Microcephaly prevalence per 10,000 live births was calculated overall, by reporting area, and by month of pregnancy completion for epidemiologic weeks 5–45 in 2016. A prevalence ratio (PR) was calculated by dividing the prevalence in 2016 by the prevalence in 2015, and 95% confidence intervals (CIs) for the PR were calculated using Poisson regression.

* http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Protocolos%20SIVIGILA/PRO%20Microcefalia.pdf.

The outbreak of Zika virus disease among pregnant women in Colombia peaked during epidemiologic week 4 in 2016. Reported cases of microcephaly peaked during epidemiologic week 28 in 2016 (24 weeks after the peak of reported cases of Zika virus disease) (Figure 1). During epidemiologic weeks 5–45 in 2016, a total of 476 infants with microcephaly were reported in Colombia; 28 (85%) of the 33 reporting areas in Colombia reported at least one case of microcephaly (supplemental table https://stacks.cdc.gov/view/cdc/42918). Overall, the prevalence of reported microcephaly was approximately 9.6 per 10,000 live births. Among areas reporting at least one case of microcephaly, the prevalence ranged from two per 10,000 live births (Nariño and Quindío) to 29 (Amazonas) (Figure 2). Microcephaly cases were reported in areas that include locations >2000 meters (6,562 feet) above sea level (e.g., Bogotá) without active Zika virus transmission; these cases, if Zika-related, likely resulted from travel-associated or sexually transmitted Zika virus infections.

The prevalence of microcephaly increased more than fourfold during epidemiologic weeks 5–45 in 2016 compared with the same period in 2015 (PR = 4.5) (Table). Peak prevalence of microcephaly was registered in July 2016, when the prevalence was ninefold higher than in July 2015 (PR = 9.0). In 2016, among all microcephaly cases, 432 (91%) occurred in live born infants, and 44 (9%) occurred among pregnancy losses; in 2015, among 110 reported cases of microcephaly, 90 (82%) occurred in live born infants, and 20 (18%) occurred among pregnancy losses.

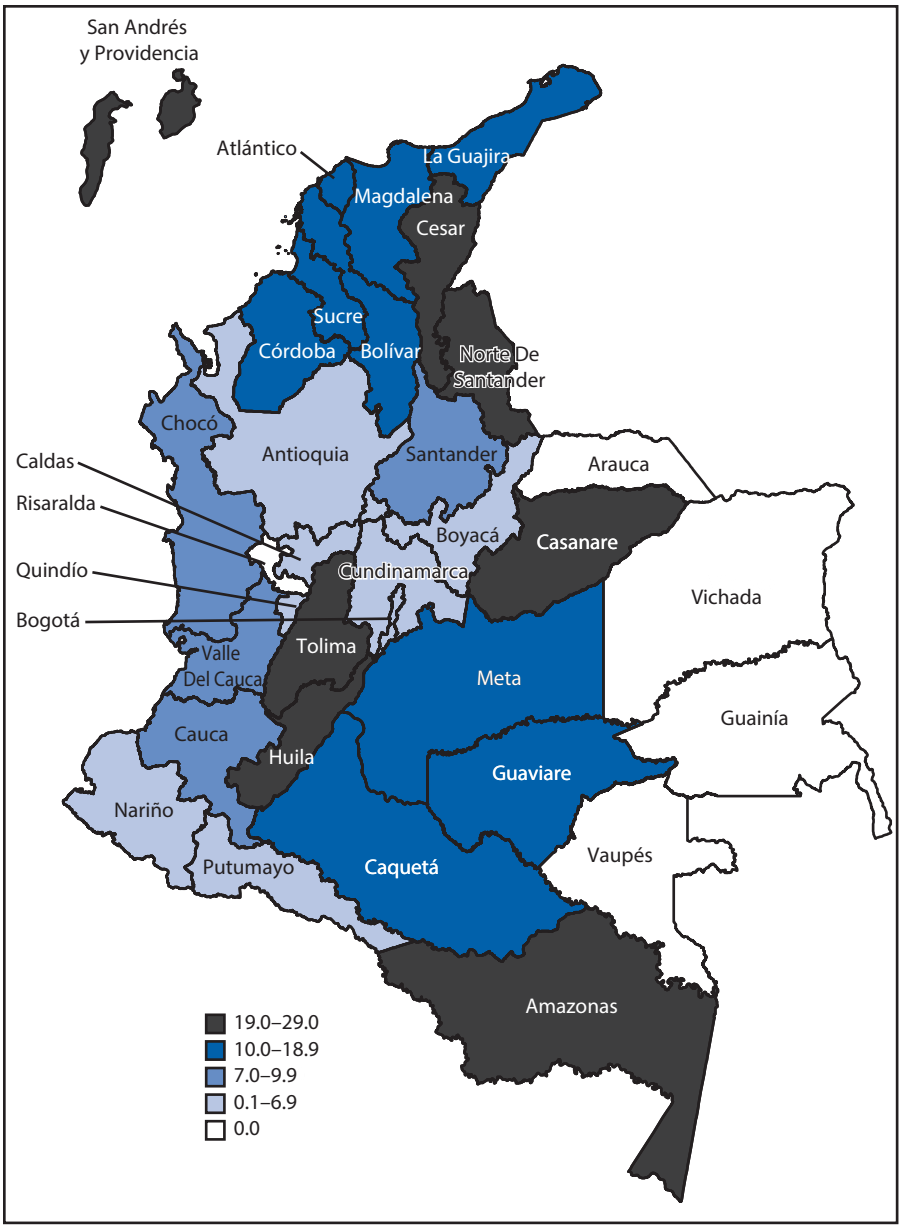
FIGURE 1. Date of symptom onset of reported cases of Zika virus disease among pregnant women* and date of birth of infants or of pregnancy loss for fetuses with reported microcephaly† — Colombia, August 9, 2015 (epidemiologic week 32)–November 12, 2016 (week 45)



* Pregnant women with Zika virus disease include women with symptoms of Zika virus disease, regardless of laboratory confirmation; epidemiologic week was based on date of symptom onset. Immediate mandatory reporting of clinical symptoms of Zika virus disease with laboratory testing began in Colombia in October 2015. During October–December 23, 2015, symptomatic Zika virus disease was defined as fever and at least one additional symptom (rash, nonpurulent conjunctivitis, headache, pruritus, arthralgia, myalgia, or malaise). Beginning December 24, 2015, it was defined as fever and rash with at least one of the other symptoms.

† Congenital microcephaly in a newborn is defined as head circumference less than the third percentile, compared with the normal standard adjusted for gestational age and sex; epidemiologic week was based on the date of birth or pregnancy loss.

FIGURE 2. Prevalence of congenital microcephaly per 10,000 live births during epidemiologic weeks 5–45 (January 31–November 12), by reporting area — Colombia, 2016



Among the 476 infants and fetuses with microcephaly reported during epidemiologic weeks 5–45 in 2016, a total of 306 (64%) were tested for Zika virus infection; 147 (48%) had laboratory evidence of Zika virus infection by RT-PCR or immunohistochemistry on any placental, fetal, or infant specimen, and five of six tested had serologic evidence of infection by MAC-ELISA. Among 121 infants tested for other pathogens, 26 (21%) had evidence of infection with other pathogens, including toxoplasmosis (15 infants), herpes simplex (six), cytomegalovirus (four) and syphilis (one); among these 26 infants, 17 (65%) had evidence of coinfection with Zika virus (14 of 15 with toxoplasmosis, two of six with herpes, and one of four with cytomegalovirus). Neuroimaging results were available for 32% of all microcephaly cases. Among 476 infants or fetuses with microcephaly, mothers of 164 (34%) reported having symptoms compatible with Zika virus infection during pregnancy.

Discussion

Based on an average full term gestation, the 24-week period from the peak of the Zika virus outbreak to the peak in reported microcephaly occurrence suggests that the greatest risk for microcephaly is associated with Zika virus infection during the first trimester and early in the second trimester of pregnancy. During epidemiologic weeks 5–45, there was more than a fourfold increase in reported microcephaly cases in Colombia in 2016, compared with the previous year. Although the microcephaly prevalence in 2016 among infants likely exposed to Zika virus in utero (9.6 per 10,000 live births) in Colombia was not much higher than the median of microcephaly prevalence (6.6 per 10,000 live births) reported by passive surveillance in 17 U.S. states during 2009–2013 (*4*), the comparison with 2015 Colombia data indicates the magnitude of the increase.

The Zika virus disease outbreak in the World Health Organization's Region of the Americas began in Brazil, which first reported a laboratory-confirmed Zika virus outbreak in May 2015; Colombia confirmed local transmission of Zika virus about 5 months later, in October 2015.[†] In 2015, microcephaly prevalence in Brazil was 5.5 per 10,000 live births, representing an approximate ninefold increase over the average prevalence during the previous 14 years (*5*,*6*). In Colombia, the relative increase has been smaller (fourfold); however, the baseline microcephaly prevalence was 2.1 per 10,000 live births in 2015, at least three times higher than Brazil's reported baseline. There are several possible reasons for differences between the reported baseline microcephaly prevalences in Brazil and Colombia, as well as the differences in increases of microcephaly in the context of the Zika virus outbreaks in the two countries. First, 50%–75% of the population of Colombia reside at altitudes above 2,000

[†] http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=36428&lang=en.

TABLE. Reported cases of congenital microcephaly* during epidemiologic weeks 5–45 (January 31–November 12) — Colombia, 2015 and 2016

Month pregnancy ended	No. of microcephaly cases reported		No. of live births		Prevalence of microcephaly per 10,000 live births		Prevalence ratio, comparing 2016 to 2015, (95% CI)
	2015	2016	2015	2016	2015	2016	
February	4	12	48,384	50,367	0.8	2.4	2.9 (0.9–8.9)
March	16	18	55,102	54,348	2.9	3.3	1.1 (0.6–2.2)
April	16	36	52,535	52,612	3.0	6.8	2.2 (1.2–4.0)
May	12	47	54,642	53,464	2.2	8.8	4.0 (2.1–7.5)
June	11	75	53,929	51,748	2.0	14.5	7.1 (3.8–13.4)
July	11	94	56,160	53,046	2.0	17.7	9.0 (4.8–16.9)
August	15	71	55,290	55,709	2.7	12.7	4.7 (2.7–8.2)
September	10	60	58,835	56,539	1.7	10.6	6.2 (3.2–12.2)
October†	11	49	56,870	49,262	1.9	9.9	5.1 (2.7–9.9)
November§	4	14	24,317	21,193	1.6	6.6	4.0 (1.3–12.2)
Total	**110**	**476**	**516,064**	**498,288**	**2.1**	**9.6**	**4.5 (3.6–5.5)**

Abbreviation: CI = confidence interval.

* Congenital microcephaly in a newborn is defined as head circumference less than the third percentile, compared with the normal standard adjusted for gestational age and sex. Table includes pregnancies ending during this period, regardless of Zika virus testing or pregnancy outcome (i.e., live births and pregnancy losses [spontaneous abortions, pregnancy terminations, and stillbirths combined]).

† October 2016 birth data are preliminary.

§ Number of cases of microcephaly and number of live births are for the period November 1–12 in both 2015 and 2016. November 1–12, 2016, birth data are preliminary.

meters, in areas without active, vectorborne Zika virus transmission (*7*). Second, microcephaly is a difficult birth defect to monitor because there are inconsistent definitions, obtaining accurate measurements is challenging, and terminology is inconsistent. Because of these challenges, prevalence estimates vary widely among countries and among surveillance systems within the United States (*4*). Third, the reports of microcephaly from Brazil might have served as an early warning. As evidence was emerging about the link between Zika virus infection and microcephaly, the Colombian Ministry of Health issued a recommendation in February 2016 advising women to consider delaying pregnancy for 6 months, which might have affected subsequent birth rates.§ The number of live births in Colombia during epidemiologic weeks 5–45 decreased by approximately 18,000 from 2015 to 2016.

The findings in this report are subject to at least four limitations. First, the report includes all cases of microcephaly and not just those linked to Zika virus. The majority of cases of microcephaly lacked laboratory confirmation of Zika virus infection. Possible explanations are that specimens were not submitted for all cases, specimens that were submitted were not collected within the recommended time frames (maternal serum specimens within 5 days of date of symptom onset for rRT-PCR testing and infant serum or fetal tissue specimens within 2 days of delivery), and neuroimaging studies were not available for the majority of patients (68%). Second, ascertainment of birth defects, including microcephaly, tends to be more complete among live born infants than among pregnancy losses, because of the condition of the fetus at the time of the loss as well as the relatively infrequent use of fetal autopsy to determine the cause of fetal death, leading to underestimation of the number of cases of microcephaly, especially among pregnancy losses (*8*). In addition, because microcephaly is a rare outcome, prevalence ratios comparing 2016 and 2015 might be unstable and should be interpreted with caution. Third, passive reporting systems tend to have less complete ascertainment of all birth defects compared with active surveillance systems (*9*). Finally, the ascertainment of birth defects generally does not capture infants or fetuses whose birth defects are not apparent prenatally or at delivery, but rather are identified several months after birth. Certain critical outcomes, such as deceleration of brain growth among infants who are born with normal head circumferences, are not captured by this surveillance (*10*).

Colombia's national population-based surveillance system for birth defects is based on passive reporting, which provides critical data for monitoring the impact of teratogens and describing trends but likely underestimates the actual prevalence of birth defects, including those defects associated with Zika virus infection during pregnancy. Also, Colombia's Zika virus surveillance is based on clinical symptoms, and asymptomatic Zika virus infections are not monitored by surveillance. Therefore, the overall percentage of women who are infected with Zika virus, or infected in early pregnancy or during the periconceptional period is unknown. To better understand the effects of Zika virus, INS and CDC are collaborating on "*Proyecto Vigilancia de Embarazadas con Zika*" (Enhanced Surveillance Project of Pregnant Women with Zika) to conduct intensified active monitoring in three cities in Colombia with high incidence of Zika virus disease in pregnant women. This project, which includes systematic collection of laboratory specimens for Zika virus testing, will provide more accurate estimates of the risk for microcephaly

§ https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/circular-0013-2016.pdf.

Summary

What is already known about this topic?

Zika virus infection during pregnancy can cause microcephaly and serious brain abnormalities in fetuses and infants exposed in utero. The Zika virus disease outbreak in the World Health Organization's Region of the Americas began in Brazil, which first reported a laboratory-confirmed Zika virus outbreak in May 2015; Colombia confirmed local transmission of Zika virus about 5 months later, in October 2015. Colombia's *Instituto Nacional de Salud* maintains national surveillance for birth defects, including microcephaly.

What is added by this report?

This report provides preliminary national birth defects surveillance data on congenital microcephaly following a large outbreak of Zika virus infection in Colombia. Microcephaly prevalence increased more than fourfold overall in 2016 compared with 2015, with a ninefold increase in July 2016 (the peak month) compared with July 2015. The temporal association between Zika virus infections and microcephaly, with the peak of reported microcephaly occurring approximately 24 weeks after the peak of the Zika outbreak, provides evidence that the greatest risk period is likely the first trimester of pregnancy and early in the second trimester of pregnancy.

What are the implications for public health practice?

Colombia has experienced a significant increase in congenital microcephaly in 2016 following the peak of the Zika virus disease outbreak. Ongoing population-based birth defects surveillance is essential for monitoring the impact of Zika virus infection during pregnancy on birth defects prevalence and measuring the success in preventing Zika virus infection and its consequences, including microcephaly.

and other adverse birth outcomes among fetuses and infants of mothers with Zika virus disease during pregnancy.

In the absence of a vaccine to prevent Zika virus infection or a specific medication for treatment, prevention strategies include avoiding travel to areas with active Zika virus transmission, preventing mosquito bites through personal protection and vector control, and avoiding sexual transmission. Ongoing population-based birth defects surveillance provides critical data for monitoring the impact of teratogens, including Zika virus infection, and will be an essential tool to evaluate success in preventing microcephaly and congenital Zika syndrome.

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Notes from the Field

New Delhi Metallo-ß-Lactamase–Producing Carbapenem-Resistant Enterobacteriaceae Identified in Patients Without Known Health Care Risk Factors — Colorado, 2014–2016

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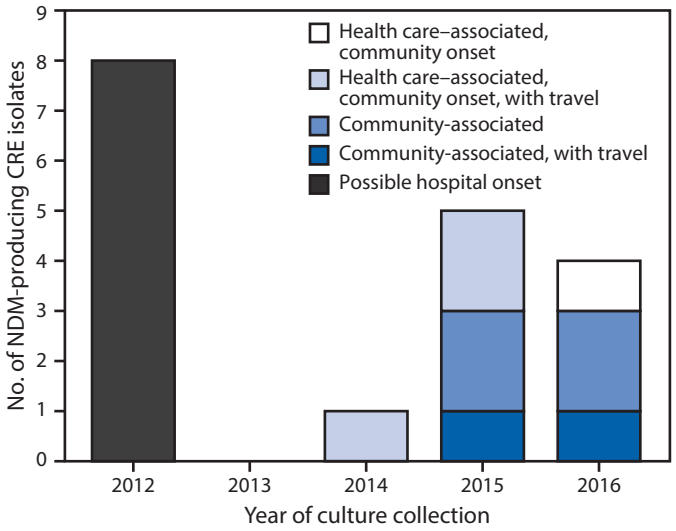
Carbapenem-resistant Enterobacteriaceae (CRE) are considered an urgent threat in the United States because they are associated with high morbidity and mortality, limited treatment options, and potential for rapid spread among patients (*1*). Carbapenemases, enzymes that confer resistance to the carbapenem class of antibiotics, are believed to contribute to increasing transmission and regional spread of CRE because the genes encoding these enzymes can reside on mobile plasmids and can be transferred among bacterial species. *Klebsiella pneumoniae* carbapenemase (KPC) is the most common carbapenemase seen in the United States, but isolates with the New Delhi metallo-ß-lactamase (NDM) are emerging. Known risk factors for carbapenemase-producing CRE, including NDM, include health care exposures such as hospitalization outside the United States, recent overnight admissions to short-stay and long-term acute care hospitals, residence in long-term care facilities, surgical procedures, and having indwelling devices. Community-associated CRE lack these health care exposures and are rare in the United States (*2*). During 2014–2016, NDM-producing CRE were isolated from patients in Colorado without known health care risk factors.

The Colorado Department of Public Health and Environment (CDPHE) has conducted statewide laboratory-based surveillance of CRE since November 2012. CRE isolates that are resistant to two or more carbapenems are tested for the KPC and NDM genes by polymerase-chain reaction at the CDPHE laboratory. As of April 2016, Colorado had reported the second highest number of NDM-producing CRE in the United States (*3*). NDM was first detected in Colorado in 2012 in eight patients during a hospital outbreak (*4*). Ten additional patients with NDM-producing CRE were identified in Colorado during 2014–2016. Among these 10 patients, the mean age was 64 years (range = 20–85 years); isolates from nine patients were from urine, and in one patient, from bile. Five patients had traveled internationally in the 2 months before specimen collection (two of whom had known hospitalizations during international travel) (Figure). In six patients, the isolate was detected from cultures collected in outpatient settings and lacked the known CRE risk factors of overnight stays in health care settings, dialysis, or surgery in the preceding 12 months, and had no invasive devices in the preceding 2 days (i.e., the isolates were community-associated).

FIGURE. Number of identified CRE isolates that produce NDM, by epidemiologic classification* — Colorado, 2012–2016



Abbreviations: CRE = carbapenem-resistant Enterobacteriaceae; NDM = New Delhi metallo-β-lactamase.

* **Community-associated**: no known health care exposures, including hospitalizations, long-term care facility residence, surgery, dialysis, or indwelling devices. **Travel:** to international areas where the prevalence of NDM is unknown. **Health care–associated:** history of hospitalization, surgery, dialysis, indwelling devices, or residence in a long-term care facility in the year preceding the first known CRE-positive culture. **Possible hospital onset:** symptoms associated with the NDM isolate had onset >3 calendar days after hospital admission. The first known CRE-positive culture was detected during hospitalization; prior CRE colonization in patients is unknown.

Among the six patients identified with community-associated, NDM-producing CRE, two patients traveled internationally: one to an unknown country in Africa and one to the Bahamas. Mean age was 61 years (range = 20–85 years). All patients received diagnoses of urinary tract infections. Medical record review indicated that three of these six patients had antibiotic exposure, two within 1 month and the other within 10 months prior to the positive culture. Three of the six patients with community-associated, NDM-producing CRE had no underlying comorbidities; one patient was pregnant at the time of her positive culture, and two patients had underlying medical conditions. One patient with underlying medical conditions reported caring for a family member in multiple health care facilities before the positive NDM culture, including an acute care hospital, a long-term acute care hospital, and an assisted living facility.

There were no known epidemiologic links among the 10 most recent patients, and no known epidemiologic links between recent patients and patients from the 2012 outbreak. Whole genome sequencing (WGS) performed at CDC on isolates from 15 patients* confirmed that the recent isolates did not share common strains or plasmids with the 2012 outbreak. Among the seven recent isolates that underwent WGS, only two *E. coli* ST167 isolates appeared to be related. These isolates were separated by only 10 single nucleotide polymorphism differences and share a common NDM allele (bla_{NDM7}) and other genetic signatures; the two patients associated with these isolates resided in the same large metropolitan area but had no known epidemiologic links. The source for the community-associated strains is unknown, but might represent transmission of multiple NDM strains outside inpatient health care settings.

The vast majority of CRE isolates previously identified in Colorado were reported from patients with recent health care exposures or indwelling devices and with underlying comorbidities. Approximately 8% of the patients with CRE reported to CDC's Emerging Infections Program, which includes the Denver metropolitan area, did not have health care risk factors documented in their medical records; 9% did not have any underlying comorbidities (*2*). Of note, identification of carbapenemase-producing CRE from healthy international travelers without health care exposure has been reported (*5*); however, only two of the six patients with community-associated, NDM-producing CRE in Colorado had this exposure. The finding that six of 10 recent NDM-producing CRE are community-associated suggests that the epidemiology of CRE could be changing. Further surveillance is required to determine whether this pattern continues.

Testing for common carbapenemases at clinical or state health laboratories can inform CRE epidemiology and guide health care facilities to implement additional infection prevention and control interventions, such as screening contacts of patients with a CRE infection or colonization (*6*). As a result of this investigation, CDPHE has now implemented patient interviews as a routine part of NDM-producing CRE case investigations to assist in determining possible risk factors and epidemiologic links.

* The 15 patients include eight from the 2012 outbreak and seven more recent patients; DNA sequences were placed in the National Center for Biotechnology Information Sequence Read Archive under BioProject accession PRJNA328506 for the 2012 outbreak, and BioProject accession PRJNA328507 for the recent isolates.

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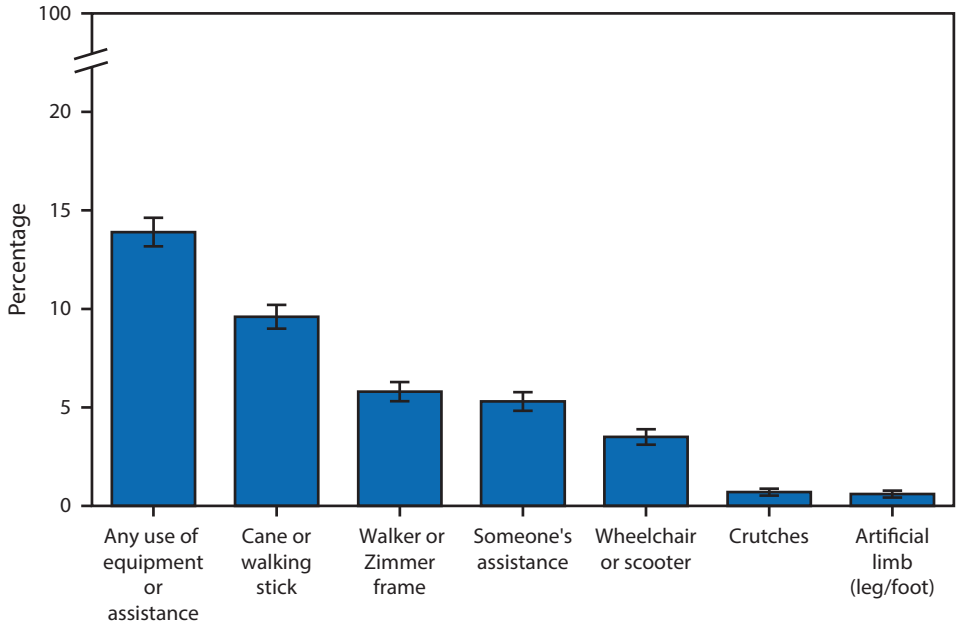
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Use of Equipment or Assistance* for Getting Around Among Persons Aged ≥50 Years — National Health Interview Survey, 2014–2015†



* Use of any equipment or assistance in response to the question, "Do you use any equipment or receive help for getting around?" Other responses were based on the follow-up question, "Do you use any of the following?" and these response categories for those who responded "yes": cane or walking stick, walker or Zimmer frame, crutches, wheelchair or scooter, artificial limb (leg/foot), someone's assistance, or other type of equipment or help. Responses were not mutually exclusive. Percentages are shown with 95% confidence intervals.

† Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population and are derived from combining the 2014 and 2015 National Health Interview Survey Sample Adult Functioning and Disability Files.

In 2014–2015, 13.9% of persons aged ≥50 years used equipment or received assistance for getting around. Specifically, 9.6% of persons aged ≥50 years used a cane or walking stick, 5.8% used a walker or Zimmer frame, and 5.3% had assistance from another person. Wheelchairs or scooters were used by 3.5%, crutches by 0.7%, and artificial limbs by 0.6%.

Source: National Health Interview Survey, 2014 and 2015 combined. http://www.cdc.gov/nchs/nhis.htm.

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