Impact of Childhood Vaccination on Racial Disparities in Invasive Streptococcus pneumoniae Infections

Brendan Flannery, PhD
Stephanie Schrag, DPhil
Nancy M. Bennett, MD
Ruth Lynfield, MD
Lee H. Harrison, MD
Arthur Reingold, MD
Paul R. Cieslak, MD
James Hadler, MD, MPH
Monica M. Farley, MD
Richard R. Facklam, PhD
Elizabeth R. Zell, MStat
Cynthia G. Whitney, MD, MPH

for the Active Bacterial Core Surveillance/Emerging Infections Program Network

Historically, blacks in the United States have had a higher incidence of invasive pneumococcal disease than whites, with the widest disparities occurring among children in the first 2 years of life and among adults 18 to 64 years old.1-3 Introduction of a new 7-valent pneumococcal conjugate vaccine (Prevnar; Wyeth Lederle Vaccines, Madison, NJ) for young children has led to dramatic declines in invasive disease among children younger than 2 years, as well as declines in incidence among adults and elderly individuals.4 The impact of vaccination on racial disparities in incidence of pneumococcal disease has not been examined.

For editorial comment see p 2253.

Context Historically, incidence of pneumococcal disease in the United States has been higher among blacks than among whites. Following recommendation of a new 7-valent pneumococcal conjugate vaccine for children in October 2000, the incidence of invasive pneumococcal disease has declined dramatically, but the impact of vaccination on racial disparities in incidence of pneumococcal disease is unknown.

Objective To assess the effect of conjugate vaccine introduction on rates of pneumococcal disease among whites and blacks in the United States.

Design, Setting, and Patients Analysis of data from the Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network, an active, population-based surveillance system in 7 states. Patients were 15,923 persons with invasive pneumococcal disease occurring between January 1, 1998, and December 31, 2002.

Main Outcome Measures Age- and race-specific pneumococcal disease incidence rates (cases per 100,000 persons), rate ratios, and rate differences.

Results Between 1998 and 2002, annual incidence rates for invasive pneumococcal disease decreased from 19.0 to 12.1 cases per 100,000 among whites and from 54.9 to 26.5 among blacks. Due to these declines, 14,730 fewer cases occurred among whites and 8780 fewer cases occurred among blacks in the United States in 2002, compared with 2 prevaccine years, 1998 and 1999. Before vaccine introduction, incidence among blacks was 2.9 times higher than among whites (95% confidence interval [CI], 2.7-3.0); in 2002, the black-white rate ratio had been reduced to 2.2 (95% CI, 2.0-2.4). Incidence among black children younger than 2 years went from being 3.3 times higher (95% CI, 3.0-3.7) than among white children in the prevaccine period to 1.6 times higher (95% CI, 1.1-2.2) in 2002. By 2002, 74% of white children and 68% of black children aged 19 to 35 months in the 7 states had received at least 1 dose of pneumococcal conjugate vaccine; 43% of white and 39% of black children received 3 or more doses.

Conclusion Although blacks remain at higher risk of invasive pneumococcal disease, introduction of childhood pneumococcal vaccination has reduced the racial disparity in incidence of pneumococcal disease.

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In October 2000, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination for all children younger than 2 years and for children aged 2 to 4 years with certain chronic illnesses. For newborns, the ACIP recommended 3 doses given at 2, 4, and 6 months of age with a fourth dose given between the ages of 12 and 15 months. Fewer doses were recommended for children who began the series later. For unvaccinated children aged 2 to 4 years with certain chronic conditions, the ACIP recommended 2 doses given 2 months apart. Among healthy unvaccinated children aged 2 to 4 years, the ACIP recommended a single dose of vaccine, with priority given to children of Alaska Native, American Indian, or African American descent. The pneumococcal conjugate vaccine is one of a few vaccines for which certain minority populations have been targeted for priority vaccination and was the first to specifically list children of African American descent as a high-risk group.

Eliminating racial disparities in disease incidence is a main objective set forth in Healthy People 2010. The goal of eliminating disparities requires meeting Healthy People 2010 targets for pneumococcal disease in all racial and ethnic minority populations. The Healthy People 2010 targets for invasive pneumococcal disease are to reduce incidence to 46 cases per 100000 children younger than 5 years and to 42 per 100000 adults aged 65 years or older.

We measured progress toward these goals using data from the US Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance (ABCs) system. This analysis examined the impact of childhood vaccination on disease incidence and pneumococcal serotype distribution among whites and blacks. For comparison with trends in disease incidence, we analyzed vaccination coverage by racial group measured in 2 National Immunization Surveys.

METHODS

Between January 1, 1998, and December 31, 2002, the ABCs system continuously monitored invasive pneumococcal infections in San Francisco, Calif; the state of Connecticut; the Atlanta, Ga, metropolitan area; the Baltimore, Md, metropolitan area; Minneapolis and St Paul, Minn; Rochester, NY; and Portland, Ore. The total population under surveillance in 2002 was 16.5 million persons (6% of the US population). According to the 2000 US Census, the surveillance population was 78% white, 17% black, and 5% Asian or Pacific Islander, with 6% Hispanic ethnicity. Compared with the US population, the surveillance areas have a higher percentage of persons of black race and a lower percentage of those of Hispanic ethnicity. Data from all sites were combined because trends by race were similar across sites.

Cases of invasive pneumococcal disease were identified through active, laboratory-based surveillance. All clinical laboratories serving the residents of the surveillance population were contacted regularly and audited to identify cases. A case of invasive pneumococcal disease was defined as isolation of Streptococcus pneumoniae from a normally sterile body fluid (eg, blood or cerebrospinal, peritoneal, joint, or pleural fluid) obtained from a resident of the surveillance area during 1998 through 2002. Case-patient race and ethnicity were identified by review of medical records and reported to the CDC on a standardized questionnaire. Completeness of information on race ranged from 97% in Maryland to 68% in Oregon, and on ethnicity from 92% in New York to 17% in Connecticut. Pneumococcal vaccination status of case-patients was not determined as part of routine surveillance. In 5 sites (excluding Georgia and New York), data on human immunodeficiency virus (HIV) infection and AIDS were obtained from the patient’s medical records.

Pneumococcal isolates were sent to reference laboratories for serotyping using the Quellung reaction. Serotypes in the 7-valent conjugate vaccine include types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F.

Annual cumulative incidence rates were calculated for 1998 through 2002 using population estimates from the US Census Bureau for each year. Race was defined according to the US Census prior to 2000. Race-specific incidence rates for 2000 through 2002 were calculated using bridged census files to maintain consistent race categories. The calculation of incidence rates in 1998 and 1999 for persons of Hispanic ethnicity used the population estimate from the 2000 US Census. To calculate race-specific disease rates, we redistributed case-patients with missing race information (12% of case-patients) according to the distribution of those with known race by site and age group. Case-patients for whom ethnicity was not reported were assumed to be non-Hispanic. Rate ratios were calculated comparing age- and race-specific incidence in 2001 or 2002 with a baseline “prevaccine” rate defined as the average of 1998 and 1999 incidence rates to account for variability in prevaccine years. Confidence intervals (CIs) for rate ratios were calculated using Poisson regression with terms for race and time period. We tested the significance of a race × time interaction term in the model to assess the difference between the black-white rate ratios in the 2 time periods. For national projections of cases, we applied age- and race-specific rates of disease from the surveillance areas to the age and racial distribution of the US population for the corresponding year. We defined the excess number of cases among blacks in each period as the difference in rates between blacks and whites, projected to the US black population. The above analyses were conducted using SAS version 8.0 (SAS Institute Inc, Cary, NC). Significance was defined as P<.05, 2-tailed.

To estimate pneumococcal conjugate vaccination coverage in the surveillance areas, we analyzed data from the 2001 and 2002 National Immunization...
Children program.\textsuperscript{8} Children included widely available through the Vaccines for Children introduced for all populations in 2001 (n=3576) and 2002 (n=3597), identified through random-digit dialing. Children included in the 2001 survey were born between February 1998 and May 2000, and would have been between 5 and 32 months of age in October 2000, when the conjugate vaccine became widely available through the Vaccines for Children program.\textsuperscript{8} Children included in the 2002 survey were born between February 1999 and May 2001.\textsuperscript{9} We calculated survey means and CIs, or medians and interquartile ranges, accounting for the complex survey design using SAS-callable SUDAAN version 8.0 software (Research Triangle Institute, Research Triangle Park, NC).\textsuperscript{10}

A shortage of vaccine was reported between August 2001 and May 2003.\textsuperscript{11,12} During this time, clinicians were asked to withhold vaccine from all healthy children aged 2 to 4 years and to defer the fourth dose of vaccine for healthy infants.\textsuperscript{13}

RESULTS

Patient Characteristics

From 1998 through 2002, 15923 cases of invasive pneumococcal disease were reported from the 7 geographic sites. Among 14025 (88%) case-patients with known race, 8754 (62%) were white, 4911 (35%) were black, and 363 (3%) were Asian/Pacific Islander or American Indian/Alaskan Native; 4% (669/15923) of all case-patients were of Hispanic ethnicity. In 5 sites where HIV status was routinely collected, HIV infection or AIDS was identified in 11% (1191/10706) of case-patients and was strongly associated with black race: 27% (773/2872) of black case-patients were identified as HIV-infected vs 5% (283/6006) of white case-patients, 3% (8/308) of Asian/Pacific Islander or American Indian/Alaskan Native case-patients, and 8% (127/1520) of case-patients with unknown race.

Illness Presentation

The proportion of case-patients hospitalized varied by age but not by race: 33% of children younger than 5 years were hospitalized vs 90% of patients aged 5 to 64 years and 95% of patients aged 65 years or older. White case-patients were more likely than black patients to have been diagnosed with pneumonia (64% vs 57%) and less likely to have had bacteremia without a focus identified (27% vs 34%); meningitis was diagnosed in 5% of all case-patients with no difference by race. The case-fatality rate was 11% for cases with known outcome (1745 deaths/15785 cases), with the highest case-fatality rate (25%) among case-patients aged 80 years or older. Case-fatality proportions by age category did not differ between white and black case-patients.

Trends by Race and Ethnicity

Incidence rates of invasive pneumococcal disease were lower after vaccine introduction for all populations included in surveillance. Prevaccine rates were 19.0 cases per 100000 population for whites, 54.9 for blacks, and 13.7 for other racial groups. In 2002, the rates were 12.1 for whites, 26.5 for blacks, and 5.6 for other racial groups. Due to these declines, 14730 fewer cases occurred among whites and 8780 fewer cases occurred among blacks in 2002, compared with 1998-1999. Among persons of Hispanic ethnicity, incidence per 100000 decreased from 13.6 in 1998-1999 to 10.5 in 2002. Among children younger than 5 years, incidence of invasive disease fell below the target set by Healthy People 2010 for whites, Asian/Pacific Islanders, and Hispanics in 2001, and for blacks in 2002 (FIGURE 1).

Compared with the prevaccine period, incidence of invasive pneumococcal disease was lower for whites and blacks in every age category in 2001 and 2002 (TABLE 1). The greatest reductions were among children younger than 2 years. In 2002, incidence was 77% (95% CI, 72%-81%) lower among white children younger than 2 years and 89% (95% CI, 85%-92%) lower among black children younger than 2 years, compared with 1998-1999 averages. The ratio of black-white incidence was significantly lower in 2001 and 2002 than during the prevaccine period, and in 2002 was approaching equality (Table 1). Among children aged 2 to 4 years, incidence in 2002 was 51% (95% CI, 36%-63%) lower among whites and 66% (95% CI, 50%-76%) lower among blacks than in the prevaccine period. The black-white rate ratio among children aged 2 to 4 years was lower in 2002 than in 1998-1999, although the difference was not significant.

Overall, the ratio of black-white incidence of invasive pneumococcal disease fell from 2.89 in 1998-1999 to 2.19 in 2002 (Table 1). While blacks experienced significantly higher rates than whites in almost every age category, the difference between rates for blacks and whites fell 60%, from 35.9 cases per 100000 in the prevaccine period to 14.4 in 2002. To examine black-white disparities among adults separate from the influence of HIV infection, we repeated the analyses using only 5 sites that routinely collected information on
HIV status and removed 1191 case-patients with known HIV infection. With HIV-infected case-patients removed from the analysis, rates among black adults aged 18 to 34 years were still 4.6 times higher than rates among whites in the prevaccine period and 4.2 times higher in 2002 \((P=.77)\). Among those aged 35 to 49 years, black-white rate ratios were 5.2 in the prevaccine period \(vs 3.4\) in 2002 \((P=.02)\).

Projecting standardized incidence rates to the US population, an estimated 29190 cases occurred among whites and 10250 cases occurred among blacks in 2002 (TABLE 2). Among blacks, 6480 of 10250 cases (63%) could be considered “excess cases” with respect to incidence among whites. This number of excess cases in the black population was substantially lower than the comparable figure for the prevaccine period, when the annual excess was estimated at 13220 of 19030 cases (69%) in the US black population. The reduction in excess cases in children younger than 2 years accounted for 47% of the decrease in excess cases among blacks during the time period.

Among persons aged 65 years or older, rates in 2002 were close to meeting the Healthy People 2010 target: incidence was 42.2 per 100000 among whites and 57.5 among blacks. This age group accounted for a small percentage (17%) of pneumococcal disease among blacks vs 50% of all cases among whites. In 2002, adults aged 18 to 49 years accounted for 44% of black vs 24% of white case-patients, while adults aged 50 to 64 years accounted for 24% of black and 20% of white case-patients.

### Serotype Distribution
Serotype was analyzed for 7827 isolates (89%) from white case-patients and 4449 isolates (91%) from black case-patients. Between the prevaccine period and 2002, the incidence of disease caused by the 7 vaccine serotypes declined 87% (95% CI, 83%-90%) among white children younger than 5 years, from 58.0 to 7.4 cases per 100000, and 92% (95% CI, 89%-94%) among black children, from 180.3 to 14.5 cases per 100000. There were no significant differences between the percentage reductions among black and white children in the incidence of disease caused by individual vaccine serotypes. The incidence of nonvaccine serotype disease increased among white children younger than 5 years, from 5.6 to 8.7 cases per 100000 \((P=.004)\), and did not change significantly among black children younger than 5 years \(9.7\) vs 9.3 cases per 100000, \(P=.90)\).

Declines in incidence of vaccine-serotype disease among young children and adults changed the serotype distribution of invasive pneumococcal disease. In 2002, serotypes in the 7-valent vaccine accounted for 36% of isolates from white children younger than 5 years and 44% of isolates from black children, as opposed to 81% and 84%, respectively, in the prevaccine period. Among whites, rates of vaccine serotypes for adults aged 18 to 64 years decreased 51% (95% CI, 44%-57%), from 5.5 to 2.7 cases per 100000; among blacks, the corresponding rates decreased 69% (95% CI, 64%-73%), from 27.8 to 8.6. Among white persons aged 65 years or older, rates of conjugate vaccine serotypes decreased 46% (95% CI, 38%-53%), from 33.3 to 18.1 cases per 100000; among black persons of the same age, the corresponding rates decreased 47% (95% CI, 25%-62%). Rates of the remaining 16 serotypes in the 23-valent polysaccharide vaccine did not change significantly (from 13.0 to 13.3 per 100000 among whites \([P=.83]\) and from 16.2 to 12.4 per 100000 among blacks \([P=.33]\)). In 2002, the 7 conjugate vaccine serotypes accounted for 39% and 37% of isolates from white and black adults aged 18 to 64 years and 43% and 45% of isolates from white and black adults aged 65 years or older. Serotypes included in the 23-valent polysaccharide vaccine accounted for 80% and 73% of isolates from white and black adults aged 65 years or older in 2002.
Vaccine Coverage

In the 7 states with ABCs sites, receipt of 1 or more doses of pneumococcal conjugate vaccine among children aged 19 to 35 months increased nearly 2-fold, from 38% to 73% between the 2001 and 2002 National Immunization Surveys, and receipt of 3 or more doses increased from 7% to 43%. Vaccine coverage among black children aged 19 to 35 months lagged behind levels among white children in the 2002 survey, although the difference was not significant (FIGURE 2). In each survey, the youngest age group had the highest levels of immunization: 55% of both white and black children aged 19 to 23 months during the 2001 survey had received 1 or more doses of conjugate vaccine; in 2002, 83% of white and 82% of black children in this age group had received 1 or more doses. In the 2001 survey, 79% (95% CI, 65%-92%) of black children and 52% (95% CI, 43%-61%) of white children aged 30 to 35 months had received their first dose of vaccine after their second birthday. In the 2002 survey, only 8% of black children and 7% of white children aged 30 to 35 months had received their first dose after their second birthday.

COMMENT

The incidence of invasive pneumococcal disease fell sharply among all racial/ethnic groups during the first 2 years of widespread vaccination with the 7-valent conjugate vaccine, resulting in substantial reductions in excess incidence among black Americans. The Healthy People 2010 target for incidence among children younger than 5 years was met for all racial/ethnic groups in 2002. These findings are especially encouraging considering that a vaccine shortage occurred in the second half of 2001 through early 2003.11

Surprisingly, declines in incidence were greater among black children than among white children, despite similar vaccination coverage. The observation in 2001 that a higher percentage of black vs white children received vaccine after their second birthday suggests that some race-based targeting of older children occurred. This might account for the larger declines in incidence among black vs white children aged 2 to 4 years, but the greater reductions were observed in children younger than 2 years. A contributing factor was the increase in nonvaccine serotype disease among white children that was not observed among black children. In addition, rates among black children were much higher than among white children in the prevaccine period and declines may flatten out at

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lower incidence. We speculate that the ability of the vaccine to induce herd immunity\textsuperscript{1,14} may have interrupted transmission to a greater extent among blacks than among whites.

Herd immunity is also the best explanation for the reduced incidence of pneumococcal disease observed among adults following vaccination of children.\textsuperscript{4,14} Some adults would have received the 23-valent pneumococcal polysaccharide vaccine, which is recommended for all persons aged 65 years or older and has been available since 1983.\textsuperscript{8} However, coverage with the 23-valent polysaccharide vaccine remains well below the Healthy People 2010 target of 90% vaccination among persons aged 65 years or older\textsuperscript{6} and has been especially low in minority populations.\textsuperscript{15} The 23-valent vaccine contains all 7 serotypes included in the conjugate vaccine. Among persons aged 65 years or older, we observed declines in incidence of disease caused by conjugate vaccine serotypes but not by other serotypes in the 23-valent polysaccharide vaccine. This suggests that changes in adult disease were due to decreased transmission of conjugate vaccine-serotype pneumococci from children to adults,\textsuperscript{4} consistent with previous studies showing reduced carriage of vaccine serotypes in children receiving a pneumococcal conjugate vaccine.\textsuperscript{16,17}

Differences in the age distributions of pneumococcal disease among white and black adults have been previously described.\textsuperscript{1} The observation that 83% of disease among black adults occurred before age 65 years suggests that current immunization policy may not be optimal for black adults. Although the polysaccharide vaccine is recommended for persons younger than 65 years with underlying medical conditions,\textsuperscript{18} only 27% of persons aged 50 to 64 years with medical indications had received the polysaccharide vaccine in 2001. Among blacks with medical indications, the percentage was only 13%.\textsuperscript{16} Recent analyses suggest that vaccination of such "high-risk" individuals aged 50 to 64 years would be cost-effective, especially for blacks.\textsuperscript{15} Equally important are strategies to decrease the prevalence of diabetes, HIV infection, and other underlying conditions that increase the risk of pneumococcal disease and disproportionately affect minority populations.

This analysis presents for the first time the incidence of invasive pneumococcal disease for Hispanics in the ABCs areas. Although Hispanics make up 6.3% of the ABCs population (compared with 12.2% of the US population),\textsuperscript{19} previous analyses have had too few case-patients identified as Hispanic to produce stable estimates of incidence. Using 2000 US Census estimates for the size of the Hispanic population in the prevaccine period, we found that the rates of invasive pneumococcal disease among Hispanics were similar to rates among whites. As the Hispanic population increases, specific health information about Hispanics will be increasingly important.

The current analysis has limitations. Race and ethnicity of case-patients were abstracted from medical records and may differ from self-reported race and ethnicity. We assumed that information on race was missing at random within each ABCs site and redistributed patients with missing information on race in order to improve estimates of race-specific pneumococcal disease incidence. If analyses were limited to patients with known race, the black-white rate difference among children younger than 2 years and the estimate of excess cases in black children younger than 2 years would have been 7% lower in 2001 and 8% lower in 2002. For case-patients with missing ethnicity information, 87% had race identified. We assumed that Hispanic case-patients were more likely to have ethnicity identified than were non-Hispanics, and therefore cases missing ethnicity were not redistributed. Therefore, rates presented for the Hispanic population should be interpreted as lower bounds for the true incidence of pneumococcal disease in this population.

This study did not investigate reasons for the higher risk of pneumococcal disease among blacks. Among children younger than 5 years, one study found that black race was not an independent risk factor when day care attendance, underlying disease, and breastfeeding were taken into account.\textsuperscript{20} Among adults, previous studies have identified both individual risk factors (eg, smoking and underlying diseases including HIV\textsuperscript{3}) and community-level risk factors (eg, prevalence of AIDS and poverty\textsuperscript{21}) that explain some but not all of the increased risk among blacks. Our analysis did show that removing case-patients with known HIV infection reduced somewhat the apparent excess risk of disease among black adults in the ABCs system. Because not all case-patients were tested for HIV, the contribution of HIV infection to the observed disparity may be even greater than we measured. In addition, data on socioeconomic status and other possible risk factors were not available.

The full potential of the ACIP race-based recommendations was not realized due to limitations in vaccine supply, yet they focused attention on the disparities between blacks and whites in incidence of pneumococcal disease. While the cause of the excess pneumococcal disease burden observed in black Americans remains unclear, the use of pneumococcal conjugate vaccine is clearly an important tool for reducing this excess risk.

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Study concept and design: Flannery, Schrag, Reingold, Cieslak, Zell, Whitney.

Acquisition of data: Bennett, Lynfield, Reingold, Hadler, Farley, Facklam, Whitney.

Analysis and interpretation of data: Flannery, Schrag, Lynfield, Harrison, Reingold, Cieslak, Hadler, Farley, Facklam, Whitney.

Drafting of the manuscript: Flannery, Schrag.

Critical revision of the manuscript for important intellectual content: Schrag, Bennett, Lynfield, Harrison, Reingold, Cieslak, Hadler, Farley, Facklam, Zell, Whitney.

Statistical expertise: Flannery, Zell.

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Administrative, technical, or material support: Bennett, Reingold, Cieslak, Hadler, Farley.

Study supervision: Schrag, Reingold, Cieslak, Farley, Facklam, Whitney.
RACIAL DISPARITIES IN CHILDHOOD VACCINATION

Members of the ABCs/Emerging Infections Program Network: California Emerging Infections Program: Pam Daily, MPH; Suzanne Phelps, MPH; Art Reingold, MD, Duc Vugia, MD, MPH; Connecticut Emerging Infections Program: Nancy L. Barrett, MS, MPH, Susan Petit, MPH, M. Zachariah Fraser, Patricia Mshar, MPH, Robert Howard, MS, Jim Hadler, MD, MPH; Georgia Emerging Infections Program: Patricia Martell-Clear, MS, Alicia McDonald, MPH, James Howgate, MPH, Suzanne Segler, MPH, Matthew Johns, Wendy Baughman, MSPH, David S. Stephens, MD, Monica Farley, MD, Maryland Emerging Infections Program: Laurie Thompson Sanza, RN, BS, CIC, Lee Harrison, MD; Minnesota Emerging Infections Program: Catherine Lexau, RN, MPH, Lori Triden, Miriam Shapiro, Brenda Jewell, Billie Juni, MS, Ruth Lynfield, MD; New York Emerging Infections Program: Bridget Anderson, PhD, Shelley Zansky, PhD, Glenda Smith, Nancy Bennett, MD; Oregon Emerging Infections Program: Eileen Lorber, MD, DMD, Linda Duke, RRA, Karen Stefonek, RN, MPH, Holly Conwell, RN, Paul Cieslak, MD; University of Texas Health Sciences Center at San Antonio: James Jorgensen, PhD; US Centers for Disease Control and Prevention (EIDC): Anne Schuchat, MD, Chris Van Beneden, MD, MPH, Tami Hilger Skoff, MS, Carolyn Wright, Tamar Pilishvili, MPH, Richard Facklam, PhD, Elizabet Zell, MStat, Cynthia Whitney, MD, MPH.

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