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# Prevention of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease With the 13-Valent Pneumococcal Conjugate Vaccine

**Sara Tomczyk,[1,2] Ruth Lynfield,[5] William Schaffner,[6] Arthur Reingold,[7] Lisa Miller,[8] Susan Petit,[9] Corinne Holtzman,[5] Shelley M. Zansky,[10] Ann Thomas,[11] Joan Baumbach,[12] Lee H. Harrison,[13] Monica M. Farley,[3,4] Bernard Beall,[2] Lesley McGee,[2] Ryan Gierke,[2] Tracy Pondo,[2] and Lindsay Kim[2]**

[1]Epidemic Intelligence Service, [2]Respiratory Diseases Branch, Centers for Disease Control and Prevention, [3]Emory University School of Medicine, and [4]Veterans Affairs Medical Center, Atlanta, Georgia; [5]Minnesota Department of Health, St. Paul; [6]Vanderbilt University School of Medicine, Nashville, Tennessee; [7]University of California School of Public Health, Berkeley; [8]Colorado Department of Public Health & Environment, Denver; [9]Connecticut Department of Public Health, Hartford; [10]New York State Department of Health, Albany; [11]Oregon Public Health Division, Portland; [12]New Mexico Department of Health, Santa Fe; and [13]John Hopkins University Bloomberg School of Public Health, Baltimore, Maryland

***Background.*** Antibiotic-nonsusceptible invasive pneumococcal disease (IPD) decreased substantially after the US introduction of the pediatric 7-valent pneumococcal conjugate vaccine (PCV7) in 2000. However, rates of antibiotic-nonsusceptible non-PCV7-type IPD increased during 2004–2009. In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7. We assessed the impact of PCV13 on antibiotic-nonsusceptible IPD rates.

***Methods.*** We defined IPD as pneumococcal isolation from a normally sterile site in a resident from 10 US surveillance sites. Antibiotic-nonsusceptible isolates were those intermediate or resistant to ≥1 antibiotic classes according to 2012 Clinical and Laboratory Standards Institute breakpoints. We examined rates of antibiotic nonsusceptibility and estimated cases prevented between observed cases of antibiotic-nonsusceptible IPD and cases that would have occurred if PCV13 had not been introduced.

***Results.*** From 2009 to 2013, rates of antibiotic-nonsusceptible IPD caused by serotypes included in PCV13 but not in PCV7 decreased from 6.5 to 0.5 per 100 000 in children aged <5 years and from 4.4 to 1.4 per 100 000 in adults aged ≥65 years. During 2010–2013, we estimated that 1636 and 1327 cases of antibiotic-nonsusceptible IPD caused by serotypes included in PCV13 but not PCV7 were prevented among children aged <5 years (−97% difference) and among adults aged ≥65 years (−64% difference), respectively. Although we observed small increases in antibiotic-nonsusceptible IPD caused by non-PCV13 serotypes, no non-PCV13 serotype dominated among antibiotic-nonsusceptible strains.

***Conclusions.*** After PCV13 introduction, antibiotic-nonsusceptible IPD decreased in multiple age groups. Continued surveillance is needed to monitor trends of nonvaccine serotypes. Pneumococcal conjugate vaccines are important tools in the approach to combat antibiotic resistance.

**Keywords.** antibiotic nonsusceptibility; resistance; *Streptococcus pneumoniae*; pneumococcal conjugate vaccine.

*Streptococcus pneumoniae* (pneumococcus) is a major bacterial cause of morbidity and mortality among children and adults [1–3]. Clinical syndromes include noninvasive disease, such as otitis media and nonbacteremic pneumonia, and invasive pneumococcal disease (IPD), such as meningitis and bacteremia. *S. pneumoniae* has >90 serotypes, although a relatively limited number cause the majority of IPD [4]. Pneumococcal conjugate vaccines (PCVs) are highly effective at preventing vaccine-type IPD and radiographically confirmed pneumonia in children [5–8], and widespread use in children has substantially reduced rates of IPD and pneumonia among adults [2, 9, 10]. PCVs prevent acquisition of vaccine-type pneumococci among children and, subsequently, reduce transmission to other children and adults; however, in the United States, despite widespread use of PCV in infants, an estimated 401 000 hospitalizations owing to *S. pneumoniae* occurred in 2004 and an estimated 44 000 IPD cases in 2009 [11, 12].

Antibiotic-nonsusceptible *S. pneumoniae* complicates the treatment of pneumococcal disease and has been associated with worse clinical outcomes and increased healthcare costs. According to a 2013 Centers for Disease Control and Prevention (CDC) report, antibiotic-nonsusceptible *S. pneumoniae* was deemed a serious threat, causing 19 000 excess hospitalizations, 7000 excess deaths, and $96 million in excess medical costs per year [13]. Accordingly, *Healthy People 2020*, a framework for US health indicators, set a goal to reduce antibiotic-nonsusceptible IPD from 8.3 to 6.0 cases per 100 000 among children aged <5 years and from 12.2 to 9.0 cases per 100 000 among adults aged ≥65 years in the United States [14].

Because some of the serotypes included in the 7-valent PCV (PCV7) are associated with antibiotic nonsusceptibility, PCV7 reduced antibiotic-nonsusceptible IPD. In 2000, PCV7 was

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Correspondence: S. Tomczyk, Respiratory Diseases Branch, Division of Bacterial Disease, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30329 (xdj2@cdc.gov).

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introduced in the US childhood immunization program. From 1998–1999 to 2008, rates of penicillin-nonsusceptible IPD declined 64% among children aged <5 years (12.1 to 4.4 cases per 100 000) and 45% among adults aged ≥65 years (4.8 to 2.6 cases per 100 000) [15]. Although rates of penicillin-nonsusceptible disease caused by serotypes in PCV7 decreased substantially, serotype replacement, an increase in the prevalence of nonvaccine serotypes in response to reductions in vaccine serotypes, was observed. In addition, continued antibiotic use likely contributed to increases observed in rates of antibiotic-nonsusceptible IPD [16]. In particular, serotype 19A, not included in PCV7, seemed to drive the increase in overall antibiotic-nonsusceptible IPD and penicillin-nonsusceptible IPD. From 1998–1999 to 2008, penicillin-nonsusceptible IPD caused by serotype 19A increased from 0.04 to 4.3 cases per 100 000 among children aged <5 years and from 0.1 to 2.0 cases per 100 000 among adults aged ≥65 [15].

In 2010, the 13-valent PCV (PCV13), with expanded serotype coverage that included 19A, replaced PCV7 in the US childhood immunization schedule. The objectives of this analysis were to assess the impact of PCV13 on rates of antibiotic-nonsusceptible IPD caused by all serotypes, serotypes included in PCV13 but not in PCV7, and non-PCV13 serotypes.

## METHODS

We used data from the CDC's Active Bacterial Core surveillance (ABCs) reported from January 2005 to December 2013. ABCs is an active, laboratory- and population-based surveillance system for invasive bacterial pathogens. *S. pneumoniae* surveillance is conducted in 10 US sites, including statewide surveillance in Connecticut, New Mexico, and Minnesota and selected counties in California, Colorado, Georgia, Maryland, New York, Oregon, and Tennessee [17]. The pneumococcal surveillance population is approximately 31 million persons, or 11% of the US population [18]. ABCs epidemiological and laboratory data collection were considered surveillance activities and were exempt from CDC institutional review. However, individual ABCs sites obtained institutional review when required.

Cases were defined as isolation of pneumococcus from a normally sterile site (eg, blood, cerebrospinal fluid, or pleural fluid) in a resident of the surveillance population. Laboratory audits were performed at least every 6 months to ensure completeness of reporting. For each case, clinical records were reviewed. Serotyping was performed at CDC or the Minnesota Department of Health using the Quellung method and classified according to the following: (1) PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) and serotype 6A, which is afforded cross-protection by serotype 6B [19] and (2) serotypes included in PCV13 but not in PCV7 (1, 3, 5, 7F, 19A); and (3) non-PCV13 serotypes.

Reference broth microdilution was used for antibiotic susceptibility testing at CDC, the Minnesota Department of Health, and the University of Texas Health Science Center at San Antonio, as described elsewhere [20]. An antibiotic-nonsusceptible isolate was defined as an isolate that was intermediate or resistant to ≥1 antibiotic classes according to 2012 Clinical and Laboratory Standards Institute breakpoints [21]. For penicillin, we used meningitis breakpoints for meningitis cases and nonmeningitis breakpoints for all other cases according to the Clinical and Laboratory Standards Institute standard. We included the antibiotic classes that were used to determine the *Healthy People 2020* goal for antibiotic-nonsusceptible IPD: macrolides (ie, erythromycin), cephalosporins (ie, cefotaxime, ceftriaxone, and cefuroxime), tetracyclines (ie, tetracycline), penicillins (ie, penicillin and amoxicillin), fluoroquinolones (ie, levofloxacin), and glycopeptides (ie, vancomycin). Multidrug nonsusceptibility was defined as nonsusceptibility to ≥3 antibiotic classes. Cases with missing isolates (n = 6810; 11%) were assumed to have the same distribution of serotypes and antibiotic susceptibility as cases with known data within age groups.

We described demographic and clinical characteristics among cases of antibiotic-nonsusceptible IPD during 2005–2013. To describe trends, we examined overall rates of antibiotic-nonsusceptible IPD and multidrug-nonsusceptible IPD caused by all serotypes, serotypes included in PCV13 but not in PCV7, and non-PCV13 serotypes. We also stratified these results by age and antibiotic class. Annual rates of antibiotic-nonsusceptible IPD per 100 000 persons were calculated by applying ABCs case counts and surveillance population estimates from the US Census Bureau to the proportion of antibiotic-nonsusceptible pneumococcal isolates.

To estimate the effect of PCV13 on antibiotic-nonsusceptible IPD, we used a potential outcomes modeling approach [22]. The potential outcome was the predicted number of antibiotic-nonsusceptible IPD cases between July 2010 and June 2013 if PCV13 had not been introduced. We first fit monthly case counts, during the pre-PCV13 period from July 2004 to March 2010, to a nonlinear time-series model with sinusoidal seasonality terms. We next imputed the counterfactual monthly cases for the post-PCV13 period by extending the time-series model into the July 2010 to June 2013 period. We imputed a distribution of potential outcomes at each time point by accounting for the variance of the regression coefficients. We calculated median cases prevented and the percent difference between the observed and predicted cases of antibiotic-nonsusceptible IPD with their associated 95% credible intervals (CIs) during 2010–2013. SAS software (version 9.3; SAS Institute) was used for all analyses in addition to R software (version 2.15.1; R Foundation for Statistical Computing) for the Bayesian analysis portion of the potential outcomes modeling approach.

## RESULTS

Before PCV13 introduction (2005–2009), ABCs reported 17 846 IPD cases with antibiotic susceptibility results (88.0%

**Table 1. Characteristics of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease Cases From Active Bacterial Core Surveillance in 2005–2013 (N = 8462)**

| Factor | Nonsusceptible IPD Cases, No. (%)[a] |
|---|---|
| Age, y | |
| <5 | 1130 (13.4) |
| 5–17 | 246 (2.9) |
| 18–49 | 1860 (22.0) |
| 50–64 | 2223 (26.3) |
| ≥65 | 3003 (35.5) |
| Female sex | 4227 (50.0) |
| Race | |
| White | 5247 (69.7) |
| Black or African American | 2015 (26.8) |
| American Indian or Alaska Native | 152 (2.0) |
| Asian or Pacific Islander | 119 (1.6) |
| US region[b] | |
| Northeast | 2500 (29.5) |
| Midwest | 1513 (17.9) |
| South | 2926 (34.6) |
| West | 1523 (18.0) |
| Comorbid conditions, No.[c] | |
| 0 | 3276 (38.7) |
| 1 | 2519 (29.8) |
| 2 | 1567 (18.5) |
| 3 | 747 (8.8) |
| ≥4 | 353 (4.2) |
| Syndromes | |
| Meningitis | 695 (8.2) |
| Bacteremia | 1786 (21.1) |
| Bacteremic pneumonia | 5537 (65.4) |
| Hospitalized | 7553 (89.7) |
| Duration of hospitalization, median (IQR), d | 6 (3–11) |
| Died | 920 (10.9) |
| Nonsusceptibility to antibiotic classes | |
| Macrolides | 7324 (86.6) |
| Cephalosporins | 4039 (47.7) |
| Tetracyclines | 3691 (43.6) |
| Penicillins | 2712 (32.1) |
| Fluoroquinolones | 0 (0) |
| Glycopeptides | 0 (0) |

Abbreviations: IPD, invasive pneumococcal disease; IQR, interquartile range.

[a] Data represent No. (%) unless otherwise specificed; percentages represent proportion of nonmissing values.

[b] Northeast region included Conneticut, Maryland, and New York; Midwest, Minnesota; West, California, Colorado, New Mexico, and Oregon; South, Georgia and Tennesse.

[c] Comorbid conditions included AIDS, atherosclerotic cardiovascular disease, splenectomy or asplenia, asthma, cirrhosis, cochlear implant, chronic obstructive pulmonary disease, cerebral vascular accident or stroke, diabetes mellitus, immunoglobulin deficiency, heart failure, human immunodeficiency virus, Hodgkin disease, leukemia, systemic lupus erythematosus, multiple myeloma, nephrotic syndrome, obesity, organ, other cancer, and sickle cell anemia.

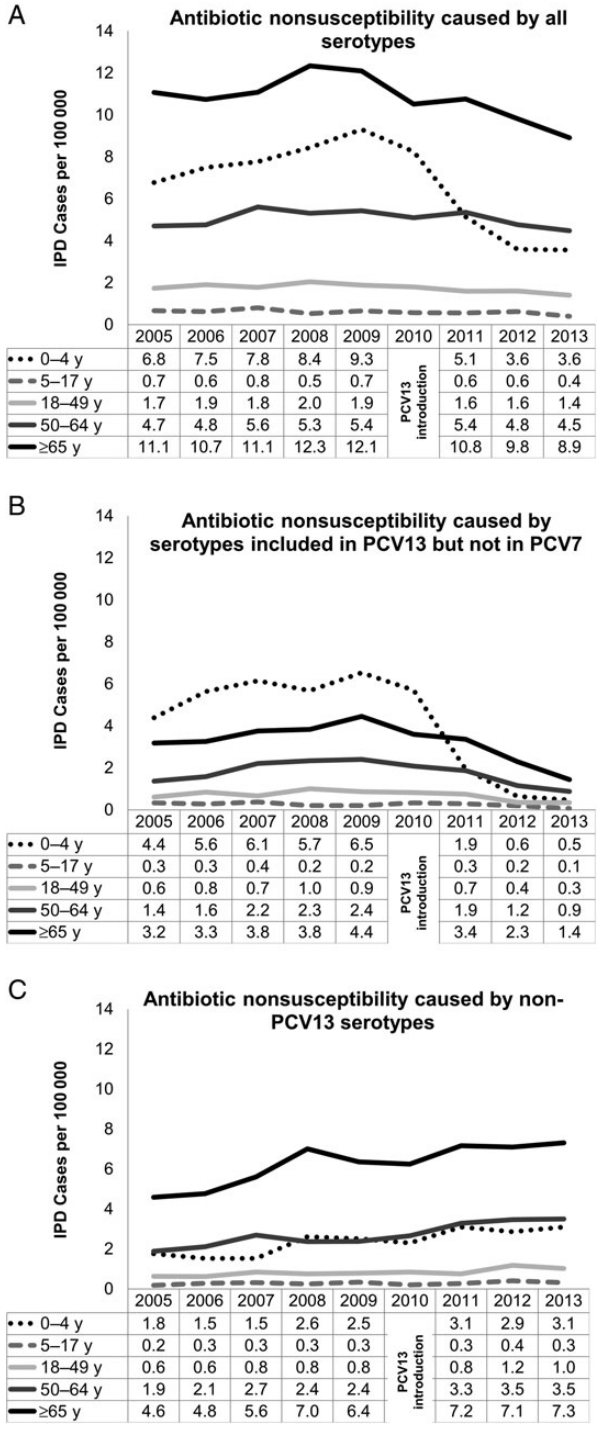


**Figure 1.** Annual rates of antibiotic-nonsusceptible invasive pneumococcal disease (IPD) caused by all serotypes (*A*), serotypes included in 13-valent pneumococcal conjugate vaccine (PCV13) but not in 7-valent pneumococcal conjugate vaccine (PCV7) (*B*), and non-PCV13 serotypes (*C*) per 100 000 persons in the United States in 2005–2013.

of 20 270 total IPD cases), and 4773 (26.7%) that were nonsusceptible to ≥1 antibiotic class. After PCV13 introduction (2010–2013), ABCs reported 12 001 cases of IPD with antibiotic susceptibility results (90.4% of 13 273 total IPD cases), and 3689 (30.7%) were nonsusceptible to ≥1 antibiotic class. Among antibiotic-nonsusceptible IPD cases, those caused by serotypes included in PCV13 but not in PCV7 decreased from 42.6% (n = 2034) to 31.1% (n = 1147), and PCV7-type cases decreased from 15.6% (n = 741) to 3.8% (n = 140) before (2005–2009) and after (2010–2013) PCV13 introduction, respectively ($P < .001$).

In contrast, cases of antibiotic-nonsusceptible IPD caused by non-PCV13 serotypes increased from 41.8% (n = 1995) to 65.0% (n = 2397) ($P < .001$). Multidrug-nonsusceptible cases decreased from 36.2% (n = 1728) to 30.3% (n = 1118) ($P < .001$) during 2005–2013. Among antibiotic-nonsusceptible IPD cases, 86.6% (n = 7324) were nonsusceptible to macrolides, 47.7% (n = 4039) to cephalosporins, 43.6% (n = 3691) to tetracyclines, and 32.1% (n = 2712) to penicillins from 2005–2013. No fluoroquinolone or glycopeptide nonsusceptibility was found (Table 1).

Overall, rates of antibiotic-nonsusceptible IPD caused by serotypes included in PCV13 but not in PCV7 decreased from 2009 (immediately before PCV13 introduction) to 2013 (6.7 to 2.2 per 100 000), largely driven by decreases in serotype 19A. Rates of antibiotic-nonsusceptible IPD caused by serotypes included in PCV13 but not in PCV7 decreased from 6.5 to 0.5 per 100 000 in children aged <5 years and from 4.4 to 1.4 per 100 000 in adults aged ≥65 years from 2009 (immediately before PCV13 introduction) to 2013 (Figure 1). Similarly, we saw large decreases from 2009 to 2013 in rates of multidrug-nonsusceptible IPD, from 5.2 to 0.8 per 100 000 in children aged <5 years and from 4.2 to 1.8 per 100 000 in adults aged ≥65 years. Less dramatic reductions in rates of antibiotic-nonsusceptible IPD were seen in those aged 5–17 or 18–49 years. Among antibiotic-nonsusceptible IPD caused by non-PCV13 serotypes, we observed increases from 2009 to 2013 among children aged <5 years (from 2.5 to 3.1 per 100 000) and among adults aged ≥65 years (from 6.4 to 7.3 per 100 000) (Figure 1). In 2013, the most frequent nonvaccine serotypes among cases with antibiotic-nonsusceptible IPD were 35B (16.2%), 33F (15.5%), 22F (12.3%), and 15A (11.7%). Among multidrug-nonsusceptible IPD, the most frequent nonvaccine serotypes were 35B (59.9%), 15A (17.8%), 6C (5.6%), and 15C (5.6%).

Macrolide-nonsusceptible IPD cases decreased from 2009 to 2013, from 8.8 to 3.3 per 100 000 in children aged <5 years and from 10.5 to 8.0 per 100 000 in adults aged ≥65 years (Table 2). Cephalosporin-nonsusceptible IPD decreased from 5.9 to 1.1 per 100 000 in children aged <5 years and 6.3 to 3.2 per 100 000 in adults aged ≥65 years. Tetracycline-nonsusceptible IPD decreased from 5.3 to 1.0 per 100 000 in children aged <5 years and from 5.7 to 2.7 per 100 000 in adults aged ≥65 years. Penicillin-nonsusceptible IPD decreased from 5.2 to 0.9 per 100 000 in children aged <5 years and from 3.7 to 1.6 per 100 000 in adults aged ≥65 years. In 2013, the proportions of IPD cases that were nonsusceptible by antibiotic class among

**Table 2. Annual Rates of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease Cases by Antibiotic Class and Age in the United States, 2005–2013**

| | Antibiotic-Nonsusceptible IPD Cases, No. per 100 000 Population | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Antibiotic Class by Age[a] | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
| Macrolides | | | | | | | | | |
| <5 y | 6.1 | 6.8 | 7.4 | 7.8 | 8.8 | 7.6 | 4.5 | 3.3 | 3.3 |
| 5–17 y | 0.6 | 0.5 | 0.7 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.4 |
| 18–49 y | 1.3 | 1.6 | 1.5 | 1.7 | 1.6 | 1.6 | 1.4 | 1.4 | 1.2 |
| 50–64 y | 3.9 | 3.8 | 4.6 | 4.3 | 4.8 | 4.4 | 4.7 | 4.3 | 3.9 |
| ≥65 y | 8.9 | 9.1 | 9.1 | 10.6 | 10.5 | 9.2 | 9.5 | 8.7 | 8.0 |
| Cephalosporins | | | | | | | | | |
| <5 y | 4.1 | 4.4 | 5.2 | 5.5 | 5.9 | 5.7 | 2.6 | 1.5 | 1.1 |
| 5–17 y | 0.4 | 0.3 | 0.5 | 0.3 | 0.3 | 0.4 | 0.3 | 0.2 | 0.1 |
| 18–49 y | 0.8 | 1.0 | 0.8 | 1.0 | 1.0 | 0.9 | 0.8 | 0.5 | 0.4 |
| 50–64 y | 2.2 | 2.4 | 2.8 | 2.6 | 2.7 | 2.1 | 2.3 | 1.7 | 1.4 |
| ≥65 y | 5.8 | 5.4 | 5.0 | 6.2 | 6.3 | 5.4 | 4.6 | 4.2 | 3.2 |
| Tetracyclines | | | | | | | | | |
| <5 y | 3.1 | 3.9 | 4.3 | 4.8 | 5.3 | 5.4 | 2.3 | 1.1 | 1.0 |
| 5–17 y | 0.3 | 0.2 | 0.4 | 0.1 | 0.3 | 0.4 | 0.2 | 0.2 | 0.2 |
| 18–49 y | 0.6 | 0.8 | 0.8 | 1.0 | 1.1 | 0.9 | 0.8 | 0.6 | 0.5 |
| 50–64 y | 1.8 | 2.3 | 2.6 | 2.6 | 2.8 | 2.6 | 2.3 | 1.6 | 1.5 |
| ≥65 y | 3.9 | 4.6 | 4.8 | 4.7 | 5.7 | 4.7 | 4.6 | 3.4 | 2.7 |
| Penicillins | | | | | | | | | |
| <5 y | 3.1 | 4.1 | 4.5 | 5.2 | 5.2 | 5.4 | 2.0 | 0.9 | 0.9 |
| 5–17 y | 0.3 | 0.3 | 0.3 | 0.2 | 0.2 | 0.3 | 0.3 | 0.2 | 0.1 |
| 18–49 y | 0.4 | 0.6 | 0.5 | 0.7 | 0.7 | 0.7 | 0.7 | 0.4 | 0.3 |
| 50–64 y | 1.4 | 1.5 | 1.8 | 1.9 | 2.0 | 1.4 | 1.8 | 1.1 | 0.9 |
| ≥65 y | 3.2 | 2.7 | 2.9 | 3.0 | 3.7 | 3.4 | 2.9 | 2.3 | 1.6 |

Abbreviation: IPD, invasive pneumococcal disease.

[a] All isolates were susceptible to fluoroquinolones or glycopeptides.

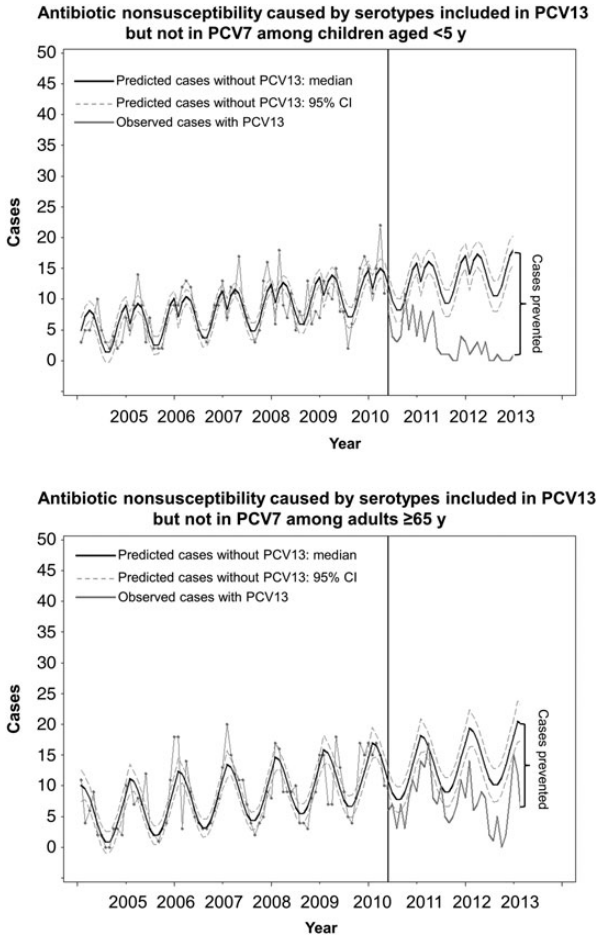


**Figure 2.** Observed (ie, with 13-valent pneumococcal conjugate vaccine [PCV13] introduction) and predicted (ie, if PCV13 were never introduced) cases of antibiotic-nonsusceptible invasive pneumococcal disease (IPD) caused by serotypes in PCV13 but not in 7-valent pneumococcal conjugate vaccine (PCV7) among children aged <5 years (*A*) and adults aged ≥65 years (*B*) in the United States, 2005–2013. Abbreviation: CI, credible interval.

children aged <18 years included 33.3% (n = 81) that were nonsusceptible to macrolides, 11.5% (n = 28) to cephalosporins, 10.7% (n = 26) to tetracyclines, and 9.9% (n = 24) to penicillins. Among adults aged ≥18 years, 27.7% (n = 718) of IPD cases were nonsusceptible to macrolides, 10.1% (n = 262) to cephalosporins, 10.5% (n = 271) to tetracyclines, and 6.1% (n = 158) to penicillins.

To make inferences about the causal effect of PCV13 on antibiotic-nonsusceptible IPD, we compared observed cases of antibiotic-nonsusceptible IPD caused by serotypes included in PCV13 but not in PCV7 and predicted the number of cases that would have occurred had PCV13 not been introduced (Figure 2). During 2010–2013, the median number of cases of antibiotic-nonsusceptible IPD caused by serotypes included in PCV13 but not in PCV7 that we estimated were prevented by PCV13 introduction were as follows, by age group: age <5 years, 1636 cases (95% CI, 1365–1900); 5–17 years, 135 (30–237); 18–49 years, 1090 (843–1324); 50–64 years, 1065 (833–1327); and ≥65 years, 1327 (996–1692). These translated to the following median percentage differences by age group: age <5 years −97% (95% CI, −97% to −96%); 5–17 years, −73% (−82% to −37%); 18–49 years, −75% (−78% to −70%); 50–64 years, −63% (−68% to −57%); and ≥65 years, −64% (−70% to −57%). We saw similar decreasing trends among rates of antibiotic-nonsusceptible IPD caused by all serotypes (data not shown).

## DISCUSSION

We found large decreases in annual rates of antibiotic-nonsusceptible IPD caused by all serotypes, serotypes included in PCV13 but not in PCV7, and multidrug-nonsusceptible IPD across all age groups after PCV13 introduction, particularly among children aged <5 years and adults aged ≥65 years. Less dramatic reductions were seen in other age groups (ie, 5–64 years), but these groups had lower baseline rates of antibiotic-nonsusceptible IPD before PCV13 introduction. The *Healthy People 2020* objectives to reduce antibiotic-nonsusceptible IPD were achieved 7 years early, after PCV13 introduction in 2013, with reported rates of 3.6 cases per 100 000 among children aged <5 years (goal: 6.0 cases per 100 000) and 8.9 cases per 100 000 among adults aged ≥65 years (goal: 9.0 cases per 100 000). The impact of PCV13 was further highlighted by the cases estimated prevented and percent differences of antibiotic-nonsusceptible IPD caused by serotypes included in PCV13 but not PCV7 in 2010–2013.

PCV13 has been shown to reduce IPD across all age groups when routinely used in the US childhood vaccination program. The incidence of IPD declined by 64% in children aged <5 years and 12%–32% in adults with the introduction of PCV13, compared with incidence expected if PCV7 alone had been continued [23]. Our study focused on the impact of PCV13 on antibiotic-nonsusceptible IPD in the setting of a mature US childhood vaccination program. Antibiotic-nonsusceptible *S. pneumoniae* and associated serotype prevalence estimates have been reported worldwide, varying from region to region in the context of different vaccine administration programs [24]. Several studies have shown that PCV7 has been effective at reducing rates of antibiotic-nonsusceptibile IPD [20, 25, 26]. In the United States, Hampton et al [20] showed that penicillin-nonsusceptible IPD rates decreased by 64% in children aged <5 years and 45% in adults aged ≥65 years after PCV7 introduction in 2000, along with similar declines in rates of IPD nonsusceptible to other antibiotics.

Concerns have also been raised about the effects of selective pressure from antibiotic use and vaccine use leading to serotype replacement with nonvaccine type antibiotic-nonsusceptible IPD. In particular, 19A-type IPD emerged to be highly associated with antibiotic nonsusceptibility in the United States [20, 27–29]. Although rates of antibiotic-nonsusceptible IPD caused

by non-PCV13 serotypes increased after PCV13 introduction, we did not find one dominant nonvaccine serotype that was highly associated with antibiotic nonsusceptibility, as we saw with 19A after PCV7 introduction. Rather, nonsusceptibility was due to several serotypes (ie, 35B, 33F, 22F, and 15A). These findings are similar to another recent report of proportional increases in replacement serotypes among antibiotic-nonsusceptible *S. pneumoniae* [30]. Continued surveillance is needed to monitor trends of nonvaccine serotypes that might emerge to be highly associated with antibiotic nonsusceptibility.

Our study has some limitations. ABCs is a population-based surveillance system in 10 geographically disparate sites across the United States; thus, the ABCs population may not be representative of the larger US population. Moreover, we did not have access to individual antibiotic use data through ABCs, so we were not able to assess how this might have influenced trends of antibiotic-nonsusceptible IPD in the United States.

We recommend sustained high use of PCV13 to continue to reduce antibiotic-nonsusceptible IPD. In addition, appropriate antibiotic use remains essential to reducing rates of antibiotic-nonsusceptible IPD. Past reports have shown that extensive antibiotic use and prescribing have contributed to the spread of antibiotic-nonsusceptible strains [13, 16, 31, 32]. In our study, despite decreases in antibiotic nonsusceptibility after PCV13 introduction, high rates of macrolide nonsusceptibility remained, which could be due to continued high rates of macrolide prescribing. Evidence has shown that macrolide use leads to emergence of macrolide resistance on the individual level [33, 34].

In conclusion, this study demonstrated that PCV13 has been effective against antibiotic nonsusceptibility. Appropriate use of antibiotics is essential to maintaining low rates of antibiotic nonsusceptibility, including through awareness initiatives [35]. Other strategies such as surveillance and development of new drugs and diagnostics have also been highlighted in the National Action Plan for Combating Antibiotic Resistant Bacteria [36]. Our study and these reports underscore the importance of using several approaches to address antibiotic nonsusceptibility, including vaccination.

## Notes

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