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UNDERSTANDING POST-VACCINE PNEUMOCOCCAL EVOLUTION AND ANTIMICROBIAL RESISTANCE IN THE UNITED STATES

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By

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B.S. in Biology

Hope College

2007

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ABSTRACT

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By Kyu Han Lee

Purpose: *S. pneumoniae* is a leading cause of pneumonia, meningitis, and bacteremia in children under five years of age worldwide and is responsible for an estimated 1.6 million deaths per year in all ages. Two serotype-specific pneumococcal vaccines, PCV7 and PCV13, were introduced in the United States for routine immunization in children under two years of age in 2000 and 2010, respectively. The purpose of this study was to examine changes in invasive pneumococci following the introduction of these vaccines in the US.

Methods: We used laboratory and demographic data of 13,383 cases of IPD collected by the Active Bacterial Core surveillance program from eight surveillance areas in 1998-1999, 2009, and 2012 to estimate rates and antimicrobial resistance in IPD

Results: The overall rates of invasive disease fell from 21.9 to 12.8 cases per 100,000 persons following PCV7 and continued to drop to 9.2 cases per 100,000 persons following PCV13. These declines in rate were due to substantial drops in IPD caused by vaccine-type serotypes and were observed across all age groups. PCV7-serotype IPD dropped from 13.8 to 0.5 cases per 100,000 persons post-PCV7 and PCV13-serotype IPD dropped from 6.5 to 2.6 cases per 100,000 persons post-PCV13. A noticeable increase from 8.2 to 12.3 cases per 100,000 persons was observed in non-PCV7-serotype IPD following PCV7 with 19A as the predominant serotype. No significant increase was seen in non-PCV13-serotype IPD following PCV13. Though overall incidence decreased, the proportion of strains showing antimicrobial resistance to 7 antimicrobial drugs rose dramatically by 9 years following PCV7 but dropped or remained the same for 13 antimicrobial drugs following PCV13. MDR proportion followed a similar pattern.

Conclusions: PCV7 led to a substantial reduction in IPD both in young children and non-vaccinated children. However, we saw indications of serotype replacement following PCV7, characterized by increased drug-resistance largely due to the expansion of highly-resistant strains, particularly within serotype 19A. Targeting of these serotypes by PCV13 has led to a continued decline in invasive disease and antimicrobial resistance. Though serotype replacement was not detected following PCV13, a longer follow-up may reveal the expansion of non-PCV13 serotypes.

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ABBREVIATIONS

ABCs	Active Bacterial Core surveillance
CC	Clonal complex
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
IPD	Invasive pneumococcal disease
MDR	Multidrug resistance
MIC	Minimum inhibitory concentration
MLST	Multilocus sequence typing
NVT	Non-vaccine-type
PCR	Polymerase chain reaction
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PMEN	Pneumococcal Molecular Epidemiology Network
SAS	Statistical Analysis System
SNP	Single-nucleotide polymorphism
ST	Sequence type
VT	Vaccine-type
WGS	Whole-genome sequencing

BACKGROUND AND SIGNIFICANCE

Streptococcus pneumoniae, the pneumococcus, is a leading cause of pneumonia, meningitis, bacteremia, and otitis media worldwide [1-3] and is responsible for an estimated 1.6 million deaths each year, including 700,000 to 1 million deaths in children [3, 4]. The respiratory pathogen is primarily a commensal that colonizes the nasopharynx [5] and causes invasive pneumococcal disease (IPD) when it invades normally sterile sites such as the blood, cerebrospinal fluid or pleural fluid [6]. Asymptomatic colonization by at least one serotype is common in most healthy children and is an essential precursor for transmission and pathogenesis. However, the mechanisms behind translocation of the pneumococcus from the nasopharyngeal to other sites to cause respiratory or systemic diseases is not yet fully understood and thought to be a multifactorial process [7, 8].

The burden of IPD is greatest in children <5 years in developing countries, in children <2 years and adults ≥65 years in developed countries, and in immunocompromised individuals [3]. *S. pneumoniae* leads to an estimated 15 cases of IPD per 100,000 persons per year [9]. In the US alone, an estimated 50,000 cases of bacteremia and 3,000 cases of meningitis were attributed to *S. pneumoniae* each year prior to the introduction of pneumococcal vaccines [10]. Although IPD can be prevented through vaccination and mostly treated with antibiotics such as penicillin and other β-lactams [11], the genetic diversity and adaptability of this highly recombinant pathogen has led to a rise in antimicrobial resistance and the evolution of mechanisms for vaccine evasion [12].

There are currently >90 identified serotypes of *S. pneumoniae*, universally characterized through antisera tests that immunologically target variations in the bacterial polysaccharide capsule [13, 14]. The capsule is a crucial structure that prevents clearance by mucous secretion, restricts autolysis, and protects against phagocytosis [15]. In addition, the capsule is the primary virulence determinant as different serotypes are associated with different propensities of invasive potential, carriage, and antimicrobial resistance [16-19].

In February 2000, a 7-valent pneumococcal conjugate vaccine (PCV7, Prevnar®) was introduced for routine immunization in the US for all children <2 years and children at high risk [9]. PCV7 contained antigens that targeted the seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) that were most commonly associated with IPD in the US [12] and commonly characterized by penicillin resistance and multidrug resistance with exception to serotypes 4 and 18C [11, 20]. The introduction of PCV7 resulted in a substantial drop in the incidence of IPD both in children as well as non-vaccinated adults, through herd immunity, reducing the incidence rate from an estimated 23.7 cases per 100,000 persons between 1996-1999 to 12.6 cases per 100,000 persons in 2004 [6]. The efficacy of PCV7 has been attributed to its ability to dramatically reduce carriage of PCV7 serotypes [21], which consequently reduces the incidence of IPD as all invasive strains originate from homologous strains in the nasopharynx [22].

Nevertheless, a small increase in the incidence of non-PCV7 serotype IPD has been observed with 19A emerging as a predominant cause of IPD commonly characterized by MDR [6, 23-25] This post-vaccine shift in serotype prevalence can be attributed to serotype replacement, which refers to the expansion of a non-vaccine

serotype into the ecological niche previously dominated by vaccine serotypes, and capsule switching, where a strain changes its serotype through alterations or exchange of the *cps* locus [12, 26]. From 2005-2007, 86.7-87.3% of all serotype 19A isolates were identified as one of three 19A clonal complexes (CC199, CC320/271 or C695) [27]. Studies suggest that the increase in prevalence of 19A in the US is primarily due to the expansion of existing clones rather than the emergence of new clones [24, 28]. However, clonal complexes (CC) such as CC320/271, predominant in many Asian countries, and CC695, characterized by simultaneous transfer of the *cps* locus and adjacent *pbp2x* and *pbp1a* genes, have been implicated with potential "vaccine escape" capsular switch events and have contributed to the increase in drug-resistant IPD [27-29]. Though the increase in non-PCV7 serotypes is relatively small, these phenomena bring to question the long-term benefits of the vaccine.

With the majority of pneumococcal infections treated empirically, resistance to antibiotics including β-lactams (penicillins and second or third generation cephalosporins) and macrolides has become a major public health concern [1, 30-33]. Furthermore, antimicrobial resistance to other drug classes such as fluoroquinolones has also been recognized worldwide [15]. Drug-resistant, particularly multidrug-resistant (MDR), infections often require treatment with second or third-line drugs that may be less effective, more toxic, or more costly [34]. In the US alone, there are approximately 1.2 million drug-resistant pneumococcal infections per year which result in an estimated $96 million in excess medical costs [35]. As antimicrobial resistance is closely associated with serotype [36], routine immunization with PCV7 has substantially reduced the rising prevalence of penicillin-nonsusceptible and MDR IPD, which were primarily caused by

PCV7 pneumococci, but has also led to the emergence and increased prevalence of MDR non-PCV7 serotype clones [6, 17, 20]. The Pneumococcal Molecular Epidemiology Network (PMEN) collaboration (www.sph.emory.edu/PMEN) has shown that multidrug-resistant infections can be driven by a small number of highly successful clones [19, 36]. Understanding the factors behind the emergence and spread of these clones is critical in tackling the resurgence of antimicrobial resistance.

In February 2010, PCV7 was replaced by a 13-valent pneumococcal conjugate vaccine (PCV13, Prevnar®) which targets six serotypes (1, 3, 5, 6A, 7F, and 19A) in addition to the original PCV7 serotypes [37]. Continuous surveillance is necessary to understand the epidemiological effect of PCV13 on the pneumococcal population.

The present study utilizes data from the Active Bacterial Core surveillance (ABCs) program of the Centers for Disease Control and Prevention (CDC) to examine changes in the ecology and evolution of invasive pneumococcus in the United States following the introduction of PCV7 in 2000 and PCV13 in 2010.

METHODS

Surveillance Data

The ABCs program (www.cdc.gov/abcs) is a core component of the CDC's Emerging Infections Program (EIP) Network which actively tracks invasive infections in the United States caused by a number of important public health pathogens, including *S. pneumoniae.* This study used isolates of *S. pneumoniae* from 8 EIP sites during 1998-1999, 2009, and 2012. A case of IPD was defined as the isolation of *S. pneumoniae* from a normally sterile site including the blood, cerebrospinal fluid, or pleural fluid from a

resident of the surveillance area. The sites for 1998 included: California (San Francisco County), Connecticut, Georgia (Atlanta area, 20 counties), Maryland (Baltimore area, 6 counties), Minnesota (Twin Cities area, 7 counties), New York (Rochester areas, 7 counties), Oregon (Portland area, 3 counties), and Tennessee (5 urban counties). In 1999, New York was expanded to include 8 additional counties in the Albany area. In 2009, the surveillance area was expanded to include all counties in Minnesota and 6 additional urban counties were added to Tennessee. In 2012, Tennessee was expanded to include a total of 20 counties. Populations of surveillance sites were estimated using data from the US Census Bureau for 1998-1999 and the National Center for Health Statistics for 2009 and 2012. The surveillance areas used in this study represent 17,382,322 persons as of 1998, 18,550,681 persons as of 1999, 24,532,185 persons as of 2009, and 25,524,903 persons as of 2012.

The following data were available for each isolate: patient age, surveillance site (state level), serotype, antimicrobial susceptibility test results for 14 antibiotics, and clinical syndromes. Patient age was stratified into ≤2 years, 3-5 years, 6-64 years, and ≥65 years. Serotyping was performed using latex agglutination and confirmed with positive Quellung reactions. Antimicrobial susceptibility testing of isolates were conducted using broth microdilutions for the following antibiotics: amoxicillin, penicillin, cefuroxime, chloramphenicol, clindamycin, trimethroprim/sulfamethoxazole, erythromycin, levofloxacin, meropenem, rifampin, quinupristin-dalfopristin, tetracycline, and vancomycin. Susceptibility results were categorized as resistant or nonsusceptible/susceptible according to the 2013 definitions of the Clinical and Laboratory Standards Institute (CLSI) [38]. MDR was defined as resistance to ≥3 drugs.

Ethics

All bacterial isolates in this study were de-identified with no link to patients. IRB approval was waived by the Emory Institutional Review Board as this study did not meet the definition of research with "human subjects" as set forth in institutional guidelines .

Statistical Analysis

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc). IPD incidence rates were calculated by year, surveillance site, and age group. In addition, serotype-specific incidence rates were calculated for children ≤2 years of age. For each stratum, the mean rate in1998 and 1999 (pre-PCV7) was subtracted from the rate in 2009 (post-PCV7) and the post-PCV7 rate was subtracted from the rate in 2012 (post-PCV13) to calculate the change in rate following the introduction of PCV7 and PCV13, respectively. Percent change with 95% confidence intervals (CI) was calculated for each comparison. The chi-square test or Fisher's exact test was used to test for significance between the proportions the population with invasive cases between each sequential period of time. In additionally, the Cochran-Armitage trend test was used to test for significance in trend in proportions from 1998-1999, 2009, and 2012.

Overall AMR and serotype-specific AMR proportions and rates were estimated for each of the 14 antibiotics by period of time. To estimate MDR proportion, all β-lactams (penicillin, amoxicillin, cefotaxime, cefuroxime, or meropenem) were placed in a new variable that was categorized as resistant if the isolate was resistant to at least one β-

lactam. A p-value <0.05 were considered statistically significant for all comparisons of proportion.

RESULTS

A total of 13,383 cases of IPD were identified in 8 surveillance sites during 1998-1999, 2009, and 2012. General characteristics of isolates are summarized on Table 1. The majority of isolates were cultured from blood (≥95.0%) and the most commonly reported clinical syndrome for cases was pneumonia (>55.0%) in all three periods of time.

Overall US Rates

The estimated rates of IPD across all sites and age groups were 21.9, 12.8, and 9.2 cases per 100,000 persons for 1998-1999 (mean rate), 2009, and 2012, respectively (Table 2). A significant decline was observed between 1998-1999 and 2009 (-41.6%, p<0.0001) (Figure 1) as well as between 2009 and 2012 (-28.2%, p<0.0001) (Figure 2). Test for trend was significant across all three periods of time (p<0.0001).

State-specific Rates

State-specific rates of IPD ranged from 17.0 to 34.4, 10.5 to 15.9, and 8.0 to 11.7 cases per 100,000 persons in 1998-1999, 2009, and 2012, respectively (Table 2). A significant decline in rate was observed in each state post-PCV7 (range: [-61.5%, -15.4%], p-value range: [<0.0001, 0.0188]) and post-PCV13 (range: [-44.7%, -20.9%], p-value range: [<0.0001, 0.0483]) (Figure 3). Significance in trend was observed in each state (p<0.0001). Percent change was greatest in California post-PCV7 (-61.5%) and in Maryland post-PCV13 (-44.7%).

Age-specific Rates

The ranges of age-specific rates were 12.4-124.3, 8.9-34.5, and 4.8-27 cases per 100,000 persons in 1998-1999, 2009, and 2012, respectively (Table 3). Rates decreased significantly for each age group following PCV7 (range: [-76.1%, -28.1%], p-value range: [<0.0001, ≤0.0003]) and PCV13 (range: [-58.7%, -21.9%], p<0.0001) (Figure 4). Test of trend suggests a significant change in rate in each age group (p<0.0001). The greatest percent change was observed in children ≤2 years for both post-PCV7 (-76.3%) and post-PCV13 (-58.9%) comparisons.

PCV7 and Non-PCV7 Serotypes

A dramatic reduction from 13.8 to 0.5 cases per 100,000 persons was observed for PCV7-serotype IPD following the introduction of PCV7 (-96.5%, p<0.0001) (Table 4). Between 92.5%-98.3% reduction was seen in state-specific rates (Figure 5) and between 93.9%-99.6% reduction was seen in age-specific rates (Figure 6). P-values were <0.0001 for each state-specific and age-specific rate comparison between 1998-1999 and 2009. The greatest change in state-specific and age-specific rates were in Georgia (-98.3%) and in children ≤2 years (-99.6%), respectively.

A significant increase from 8.2 cases per 100,000 persons in 1998-1999 to 12.3 cases per 100,000 persons in 2009 was observed for non-PCV7-serotype IPD (including 6 additional serotypes in PCV13) following PCV7 (50.4%, p<0.0001) (Table 5). With exception to California (-27.5%, p=0.007), state-specific rates increased significantly for each state post-PCV7 (range: [26.6%, 114.3%], p<0.0001) (Figure 5) and a significant increase in rate was observed in each age group (range: [42.2%, 134.0%], p<0.0001)

(Figure 6).The greatest increase in state-specific and age-specific rates were seen in New York (114.3%) and in children >2 and ≤5 years (134.0%), respectively.

PCV13 and Non-PCV13 Serotypes

The rate of PCV13-serotype IPD decreased substantially from 6.5 to 2.6 cases per 100,000 persons following the introduction of PCV13 (-61.0%, p<0.0001) (Table 6). Significant declines in rate were observed in every state (range: [-67.9%, -44.7%], p<0.0001) and age group ([-90.7, -46.5%], p<0.0001) (Table 7). The greatest reduction in state-specific and age-specific rates were seen in Maryland (-67.9%) (Figure 7) and in children ≤2 years (-90.7%) (Figure 8), respectively.

There was no significant change in the overall rate of non-PCV13 serotype IPD (p=0.2013) following PCV13 (Table 6). However, a significant increase was observed in state-specific rates for Georgia (22%, p=0.0162) and Minnesota (16.8%, p=0.0487) and a significant decline in rate was observed in Maryland (-20.4%, p=0.0283). There were no significant changes in age-specific rates (Table 7).

Children ≤2 Years

Overall rates of IPD in children ≤2 years were 124.3, 29.4, and 12.1 cases per 100,000 persons in 1998-1999, 2009, and 2012, respectively (Table 3). The change in IPD rate was significant for both post-PCV7 and post-PCV13 comparisons (p<0.0001).

PCV7 and Non-PCV7 Serotypes following PCV7

A dramatic decline was observed in the overall rate of PCV7-serotype IPD, dropping from 103.9 to 0.4 cases per 100,000 persons following PCV7 ($p<0.0001$) (Table 5). Serotype-specific rates were reduced by -100.0% to -98.5% for PCV7 serotypes (Figure 9). There were no reported cases with serotypes 6B, 9V, 14, or 18C in 2009 (Table 8). The overall rate of non-PCV7-serotype IPD (including 6 additional serotypes in PCV13) increased significantly from 20.4 to 29.0 cases per 100,000 persons following the introduction of PCV7($p<0.0001$) (Table 5). Serotype-specific rates show substantial declines in serotype 1 (-100%, $p=0.0075$), 6A (-100%, $p<0.0001$), 9A (-100.0%, $p=0.0015$), 12F (-70.4%, $p=0.0206$), and 18B (-100.0%, $p=0.0466$) and increases in serotype 7F (301.8%, $p<0.0001$), 19A (321.5%, $p<0.0001$), 15A (788.1%, $p=0.0197$), and 33F (171.4%, $p=0.0037$) following the introduction of PCV7 (Figures 10 and 11). There were no other non-PCV7 serotypes with a significant change in rate (Table 8).

PCV13 and Non-PCV13 Serotypes following PCV13

A dramatic drop in overall PCV13-serotype IPD (including PCV7 serotypes) was observed following PCV13 in children ≤ 2 years with the rate falling from 18.4 to 1.7 cases per 100,000 persons ($p<0.0001$) (Table 7). Serotype-specific rates of the original PCV7 serotypes either did not show significant change or could not be tested for significance due to low numbers of cases in both 2009 and 2012 (Table 8). For serotypes newly added in PCV13, significant declines were observed in rate for serotype 7F (-97.2%, $p<0.0001$) and 19A (-91.8%, $p<0.0001$) following PCV13. No significant change in rate was observed in overall non-PCV13-serotype IPD following PCV13 ($p=0.4397$) (Table 7). The only non-PCV13 serotype with significant post-PCV13 change in rate was 33F (-56.2%, $p=0.0320$) (Table 8). Test of significance for post-PCV13 comparison

could not be conducted for serotype 1, 5, 9A or 18B as both 2009 and 2012 did not report any cases with these serotypes.

Serogroup

For serogroup-specific rate across all age groups, substantial reductions ($p<0.0001$) were observed in serogroups 6 (-66.0%), 9 (-80.8%), 18 (-57.3%), and 23 (-64.3%) and increases were observed in 7 (321.5%) and 19 (34.2%) following PCV7. Significant reductions ($p<0.0001$) in rate were observed for serogroups 6 (-35.2%), 7 (-69.2%), and 19 (-62.6%).

Clinical Syndrome

Figure 12 illustrates the change in IPD rate by major clinical syndromes. A significant decline was observed in the rate of pneumococcal bacteremia, dropping from 3.7 to 2.5 cases per 100,000 persons following PCV7 (-33.5%, $p<0.0001$) and reaching 1.6 cases per 100,000 persons after PCV13 (-37.2%, $p<0.0001$) (Table 10). A significant decline was also observed in pneumococcal bacteremic pneumonia from 12.1 to 8.9 cases per 100,000 persons (-26.1%, $p<0.0001$) following PCV7 and dropping to 6.3 cases per 100,000 persons following PCV13 (-29.6%, $p<0.0001$). Change in rate of pneumococcal meningitis cases was significant post-PCV7 (-40.0%, $p<0.0001$) but not post-PCV13 ($p=0.5831$). Trend tests showed significant change in all three clinical syndromes over all three periods of time ($p<0.0001$).

Antimicrobial Resistance

Figure 13 depicts the change in proportion and rate of isolates resistant to 14 different antibiotic drugs in pneumococcal isolates for all ages. Significant increases in both proportion and rate of resistant isolates were observed in amoxicillin (+4.3%, p<0.0001; +0.2 cases per million persons, p<0.0024), penicillin (+2.8%, p<0.0001; +0.2 cases per million persons), clindamycin (+10.4%, p<0.0001; +1.0 cases per million persons, p<0.0001), and tetracycline (+8.9%, p<0.0001; p<0.0001) after PCV7 introduction (Table 11). Proportion of resistant strains increased but rate decreased in erythromycin (+9.1%, p<0.0001, -0.4 cases per million people, p<0.0045) and meropenem (+2.1%, p=0.0007; -0.5 cases per million, p<0.0001). Chloramphenicol only showed significant increase in proportion resistant (+1.7%, p<0.0001) while quinupristin-dalfopristin showed only increase in rate (+<0.1 cases per million, p=0.0465). Significant declines in both proportion and rate were observed in cefuroxime (-4.1%, p<0.0001; -2.3 cases per million persons, p<0.0001), trimethoprim/sulfamethoxazole (-7.9%, p<0.0001; -3.3 cases per million persons, p<0.0001), and rifampin (-0.3%, p=0.0010; -0.5 cases per million persons) following PCV7.

Significant declines in proportion and rate of resistance to amoxicillin (-3.2%, p<0.0001; -0.6 cases per million, p<0.0001), penicillin (-2.0%, p<0.0001; -0.3 cases per million, p<0.0001), cefuroxime (-3.0%, p=0.0015; -0.8 cases per million persons, p<0.0001), cefotaxime (-0.9%, p=0.0101; -0.01 cases per million persons, p<0.0001), clindamycin (-4.0%, p<0.0001; -0.9 cases per million persons, p<0.0001),

trimethoprim/sulfamethoxazole (-6.0%, p<0.0001; -1.2 cases per million persons, p<0.0001), meropenem (-4.0%, p<0.0001; -0.8 cases per million persons, p<0.0001), and tetracycline (-3.8%, p<0.0001; -0.9 cases per million persons, p<0.0001) were observed following PCV13. Significant increases in proportion and decrease in rate were seen in erythromycin (+3.3%, p=0.0075; -0.7 cases per million persons, p<0.0001) and only significant decrease in rate was observed in chloramphenicol-resistant cases (-0.1 cases per million, p=0.0429) following PCV13. No pneumococcal isolates were resistant to rifampin and quinopristin-dalfopristin in 2009 and 2012 and to vancomycin in all three periods of time.

PCV7 Serotypes

Overall proportion of antimicrobial resistance in PCV7 serotypes increased in cefuroxime (+8.3%, p=0.0654), chloramphenicol (+5.8%, p=0.0046), clindamycin (+12.7%, p<0.0001), trimethoprim-sulfamethoxazole (+10.9%, p=0.0120), erythromycin (+14.9%, p=0.0001), levofloxacin (+1.5%, p=0.0330), and tetracycline (+17.8%, p<0.0001) following the introduction of PCV7 (Tables 12.1-12.13). The rate of resistant PCV7-serotype IPD decreased in each drug (p≤0.0625) which reflects the overall trend of decreasing PCV7-serotypes. No significant change in resistance proportion was observed post-PCV13 for each antimicrobial drug. However, we did observe continued decrease in rate for cefuroxime (p<0.0002), chloramphenicol (p<0.0001), clindamycin (p<0.0082), trimethoprim-sulfamethoxazole (p<0.0003), erythromycin (p<0.0001), and tetracycline (p,0.0017).

Serotype 4 was characterized with significant increases in resistance to trimethroprim-sulfamethoxazole following PCV7 (+17.2%, p<0.0001) and to erythromycin (+20.0%, p=0.0498) following PCV13. Significant increases in resistance to cefuroxime (+39.5%, p=0.0004), chloramphenicol (+13.9%, p=0.0004), clindamycin (13.0%, p=0.0042), trimethoprim-sulfamethoxazole (40.6%, p=0.0002), and erythromycin (51.4%, p<0.0001) were observed in serotype 9V following PCV7. However, there was no significant change in antimicrobial resistance following PCV13 for 9V. Significant increases in resistance to chloramphenicol (+14.3%, p=0.0183), trimethoprim-sulfamethoxazole (+27.3%, p=0.0058), and tetracycline (+28.1%, p=0.0017) were observed in serotype 18C following PCV7. However, there was no significant change in antimicrobial resistance following PCV13 for 18C.

Serotype 19F was characterized by an increase in resistance to amoxicillin (+19.5%, p<0.0001), cefuroxime (+20.3%, p=0.0236), clindamycin (+34.7%, p<0.0001), erythromycin (+36.7%, p<0.0001), meropenem (+26.0%, p=0.0007), and tetracycline (+31.1%, p=0.0004) following PCV7. This increase was followed by declines in resistance to cefuroxime (-36.0%, p=0.0021), clindamycin (-31.6%, p=0.0039), trimethoprim-sulfamethoxazole (-26.2%, p=0.0272), erythromycin (-41.8%, p=0.0010), meropenem (-27.9%, p=0.0089), and tetracycline (-50.4%, p=0.0010) after the introduction of PCV13. Significant increase in clindamycin (+29.2%, p=0.0258), erythromycin (+40.3%, p=0.0175), levofloxacin (+12.3%, p=0.0278), and tetracycline (+55.2%, p=0.0013) resistance was observed in serotype 23F but there was no significant change in antimicrobial resistance following PCV13. A significant increase in resistance

to tetracycline was observed in serotype 14 (+31.8%, p=0.0013) post-PCV7. There was no significant change in resistance for serotype 6B both post-PCV7 and post-PCV13.

Serotypes New in PCV13

Overall proportion of antimicrobial resistance in PCV13 serotypes (newly targeted in PCV13) was elevated in amoxicillin (+16.3%, p<0.0001), penicillin (7.0%, p<0.0001), cefuroxime (11.7%, p<0.0001), cefotaxime (+3.2%, p<0.0001), chloramphenicol (+3.4%, p<0.0001), clindamycin (+19.4%, p<0.0001), trimethoprim-sulfamethoxazole (+3.7%, p=0.0223), erythromycin (+14.2%, p<0.0001), meropenem (+18.5%, p<0.0001), and tetracycline (+18.7%, p<0.0001) following the introduction of PCV7 (Tables 12.1-12.13). Increases in chloramphenicol (+8.5%, p<0.0001), clindamycin (+4.1%, p=0.0068), erythromycin (+5.3%, p=0.0061), and tetracycline (+9.8%, p<0.0001) resistance was observed in serotype 3 following PCV7. Increase in rate of resistant cases was observed in all drugs (p<0.0001) except levofloxacin, rifampin, and quinupristin-dalfopristin following PCV7. No significant change was observed following PCV13. Declines in rate were observed in all drugs post-PCV13 ($p \leq 0.0019$) except for chloramphenicol and levofloxacin. No cases were resistant to rifampin, quinupristin-dalfopristin, and vancomycin in 2009 or 2012.

Serotype 6A was characterized by decreases in resistance to cefuroxime (-23.6%, p=0.0009) and trimethoprim-sulfamethoxazole (36.0%, p<0.0001) and an increase in resistance to erythromycin (+43.1%, p<0.0001) following PCV7 introduction. Significant increases in resistance to amoxicillin (+40.4%, p<0.0001), penicillin (+18.5%, p<0.0001), cefuroxime (+44.2%, p<0.0001), cefotaxime (+8.1%, p<0.0001), chloramphenicol

(+4.7%, p=0.0047), clindamycin (+40.5%, p<0.0001), trimethoprim-sulfamethoxazole (+20.7%, p<0.0001), erythromycin (+39.3%, p<0.0001), meropenem (+45.9%, p<0.0001), and tetracycline (+41.6%, p<0.0001) was seen in serotype 19A following PCV7. Additional increases in resistance to amoxicillin (+8.7%, p=0.0264) and chloramphenicol (+4.9%, p=0.0217) were observed following PCV13. A significant decline in resistance to tetracycline (-2.4%, p=0.0052) was observed in serotype 7F. There was no significant change in resistance for serotypes 1 and 5 for both post-PCV7 and post-PCV13 comparisons.

Non-PCV13 Serotypes

Overall proportion of antimicrobial resistance in non-PCV13 serotypes (all other serotypes) increased for penicillin (+0.8%, p=0.0014), cefuroxime (+2.9%, p=0.0003), chloramphenicol (+4.5%, p<0.0001), clindamycin (+7.7%, p<0.0001), trimethoprim-sulfamethoxazole (+2.6%, p=0.0014), erythromycin (+18.3%, p<0.0001), and tetracycline (+6.7%, p<0.0001) following PCV7 (Tables 12.1-12.13). Increase in rate of cases resistant to penicillin (p=0.0029), cefuroxime (p=0.0032), chloramphenicol (p<0.0001), clindamycin (p<0.0001), trimethroprim-sulfamethoxazole (p=0.0117), erythromycin (p<0.0001), and tetracycline (p<0.0001) were observed post-PCV7. Following PCV13, increases in rate were observed in cefuroxime (p=0.0051), erythromycin (p<0.0001), and meropenem (p=0.0134) while the rate of clindamycin=resistant cases dropped (p<0.0134).

Increases in cefuroxime (+19.3%, p=0.0149) and trimethoprim-sulfamethoxazole (+25.5%, p=0.0027) resistance were observed in serotype 6C. In addition, significant

increases in erythromycin resistance were observed both post-PCV7 (+17.8%, p=0.0268) and post-PCV13 (+17.1%, p=0.0022) in 6C. Serotype 9N was characterized by a decline in resistance to trimethoprim-sulfamethoxazole (-4.7%, p=0.0426) and an increase in resistance to erythromycin (+9.4%, p=0.0044) following PCV7. Erythromycine resistance dropped in 9N following PCV13 (-8.0%, p=0.0272). Increases in resistance to trimethoprim-sulfamethoxazole (+8.7, p=0.0188) and erythromycin (+12.1%, p=0.0010) following PCV7 and to erythromycin (+20.3%, p=0.0027) following PCV13 were observed in serotype 11A. Serotype 12F showed increased post-PCV7 resistance proportion for chloramphenicol (+7.9%, p=0.0131) and erythromycin (+11.2%, p=0.0148) resistance.

Significant increases in resistance to chloramphenicol (+34.9%, p=0.0073), clindamycin (+77.0%, p<0.0001), erythromycin (+79.8, p<0.0001), and tetracycline (+79.8%, p<0.0001) was observed in serotype 15A following PCV7. Increased resistance to erythromycin (+19.4%, p<0.0001) was observed in serotypes 15B/C/F post-PCV7 and to erythromycin (+20.0%, p=0.0054) and tetracycline (+14.5%, p=0.0095) post-PCV13. Serotype 18C was characterized by an increase in tetracycline resistance (+28.1%, p=0.0017) following PCV7. Increases in resistance to erythromycin was observed in 22F both post-PCV7 (8.1%, p=0.0001) and post-PCV13 (+12.7%, p=0.0002) in addition to an increase to chloramphenicol (+5.8%, p=0.0078) post-PCV13.

Increases in resistance to clindamycin (+14.9%, p=0.0201), erythromycin (+22.3%, p=0.0030), and tetracycline (+14.9%, p=0.0201) were observed in serotype 23A following PCV7 and to erythromycin (+12.5%, p=0.0418) following PCV13. Resistance to erythromycin increased significantly following PCV7 (+55.0%, p<0.0001)

and PCV13 (+29.8%, p<0.0001) in serotype 33F. Post-PCV7 (+38.5%, p<0.0001) and post-PCV13 (+28.9%, p=0.0003) increases in erythromycin resistance were seen in 35B.

Multidrug Resistance

The proportion of multidrug resistance in all serotypes increased significantly from 13.8% to 17.4% after the introduction of PCV7 (p<0.0001) and decreased significantly to 11.8% after PCV13 (p<0.0001) (Figure 14). Significant drops in MDR cases were observed across all three periods of (p<0.0001 for both comparisons) (Table 13)

Overall MDR proportion in PCV7 serotypes increased from 18.9% to 35.0% post-PCV7 (p<0.0001) but post-PCV13 decline was not considered significant (p=0.0654). The rate of MDR PCV7 serotypes dropped across all three periods of time (p<0.0001 for both comparisons). Significant increases in serotype-specific MDR proportion were observed in serotypes 9V (+53.1%, p<0.0001), 18C (+14.3%, p=0.0183), 19F (+31.5%, p=0.0003), and 23F (+39.3%, p=0.0210) following PCV7. A significant reduction was only observed in serotype 19F (-43.5%, p=0.0003) following PCV13.

Overall MDR proportion in PCV13-serotypes (only those newly targeted by PCV13) increased from 9.4% to 22.9% post-PCV7 (p<0.0001) but did not change post-PCV13 (p=0.8170). The rate was characterized by a substantial increase post-PCV7 (p<0.0001) followed by a decline post-PCV13 (p<0.0001). Significant increases in MDR proportion and rate were observed in serotype 3 (+5.2%, p=0.0044; p<0.0001) and 19A (+44.1%, p<0.0001; p<0.0001). A decline in proportion was observed in serotype 6A (-

21.1%, p=0.0023). There was no significant change in serotype-specific MDR proportion following PCV13.

Overall MDR proportion in non-PCV13 serotypes (all other serotypes) increased from 2.0% in 1998-1999 to 10.9% in 2009 ($p<0.0001$) and then dropped down to 7.7% in 2012 ($p=0.0017$). A similar pattern was observed in the rate of MDR cases with a post-PCV7 increase ($p<0.0001$) and post-PCV13 decrease ($p=0.0094$). Substantial increases in MDR proportion and rate were observed in serotypes 15A (+77%, $p<0.0001$; $p<0.0001$) and 23A (+13.8%, $p=0.0205$; $p<0.0001$) following PCV7. Rate dropped post-PCV13 for 15 ($p=0.0039$).

DISCUSSION

The purpose of this study was to examine changes in the pneumococcal population in the US following the introduction of conjugate vaccines in 2000 and 2010. Unlike most countries, a systematic reporting of IPD cases and a detailed census database allows for the estimation of changes in incidence rates and antimicrobial resistance in *S. pneumoniae* in the US. Routine immunization of young children and infants with PCV7 led to a substantial decrease in IPD with the overall rate dropping from 21.9 to 12.8 cases per 100,000 persons in the US. This decline is mainly due to a drastic reduction in cases caused by PCV7 serotypes which reflects the results of previously conducted randomized clinical trials [39, 40] as well as population-based studies [41-44]. The greatest change in IPD was observed in children ≤2 years where nearly all PCV7-serotype IPD cases were eliminated after the introduction of PCV7. The rate of IPD continued to drop in the US

across all surveillance sites and age groups following the introduction of a higher valency vaccine, PCV13. This drop in IPD supports the results of studies that examined the efficacy of PCV13 [45, 46] and is due to a substantial reduction of PCV13-serotype IPD. The greatest change was seen PCV13-serotype IPD in children ≤2 years, particularly in serotype 7F and 19A. Though we observed an emergence of serogroups 7 and 19 following PCV7, we now see declining rates in both serogroups.

A reduction in vaccine-type (VT) serotypes has often been associated with a significant increase in non-vaccine-type (NVT) following the introduction of pneumococcal vaccines. This phenomenon, known as serotype replacement, has been observed in both nasopharyngeal carriage [47-49] and IPD [47, 48]. We observed a similar shift in the distribution of serotypes in IPD cases following PCV7. As all invasive infections originate from a homologous strain in the nasopharynx [22], a similar transition may be occurring in carriage populations. Though there is evidence of capsular switching [12, 29], the expansion of pre-existing sequence types has been recognized as the primary mechanism of serotype replacement [49]. Contrary to PCV7, we did not observe notable serotype replacement following the introduction of PCV13. However, the two-year period between PCV13 introduction and the post-PCV13 cases used in this study may be an insufficient period of time to detect serotype replacement.

Though routine vaccination has only been recommended for children under two years of age and individuals at increased risk for IPD [9], we observed dramatic declines of IPD across all age groups following the introduction of PCV7 and PCV13, which provides support for herd immunity in non-vaccinated individuals [8]. As nasopharyngeal colonization is associate with age, targeting carriage in children through vaccination leads

to a reduction in pneumococcal transmission to non-vaccinated adults [22]. Our results show that targeting high risk individuals is an effect method of preventing disease in the entire population. Nevertheless, non-uniform decreases in IPD rate across the eight surveillance states suggests that, though nationwide vaccination was promoted, other factors, such as state-specific coverage, may be influencing the impact of vaccines.

Antimicrobial resistance is an emerging global public health threat. Following the introduction PCV7 in the US, we observed significant increases in proportion of isolates resistant to amoxicillin, penicillin, chloramphenicol, clindamycin, erythromycin, meropenem, and tetracycline even after a drastic reduction in IPD by PCV7 serotypes, which have been previously characterized as the cause of most antimicrobial-resistant infections (excluding 18C and 4) [6]. In addition to the effects of changes in antimicrobial use [1, 32], the increase in AMR can be attributed to the expansion of non-PCV7 serotypes where the proportion of resistance increased significantly against all antimicrobial drugs except for levofloxacin, rifampin, quinupristin-dalfopristin, and vancomycin. Among non-PCV7 serotypes, 19A emerged as a dominant serotype following PCV7 rising from 3.1 to 13.0 cases per 100,000 persons in children $\leq$2 years and was characterized by substantial increases in resistance to 10 different antimicrobial drugs and MDR proportion. Similar trends of increased AMR have been previously described in several studies [6, 23, 24, 28, 50]. This may be due to the expansion of highly antimicrobial-resistant clones within CC320/271, a clonal complex undetected prior to PCV7 [28]. An interesting observation was the acquisition of chloramphenicol resistance in serotype 3 following PCV7. Further molecular studies may contribute to understanding the underlying biological mechanism.

Overall, the introduction of PCV13 led to a reduction or no significant change in AMR to each antimicrobial with exception to erythromycin. This may be due to the drastic reduction in serotype 19A IPD, which was newly targeted by PCV13. Based on our current post-PCV13 data, the new vaccine appears to be slowing the emergence of resistant and multidrug-resistant pneumococcal clones. However, we highlight the emergence of macrolide resistance in multiple serotypes, particularly NVT, as it continues to expand following the introduction of both vaccines.

STRENGTHS AND WEAKNESSES

Strengths

The data analyzed in this study originates from the ABCs program, which has conducted continuous population-based surveillance since 1998 from sites that compose a good geographic representation of the US. In addition, possessing both a large number of IPD cases and comprehensive molecular and demographic information in the database allows for analysis that would otherwise be less reliable due to inadequate statistical power.

Weaknesses

One limitation is the expansion of the surveillance area between 1998, 1999, 2009, and 2012. Though no new states were included in the analysis, a few counties were added to the surveillance population each year. We assumed IPD cases in the new counties carried the same distribution of characteristics as cases in their respective states.

A limitation in analysis of AMR was the substantial decrease in the number of IPD cases following both PCV7 and PCV13, which resulted in a loss of statistical power for analysis.

PUBLIC HEALTH IMPLICATIONS

As a leading cause of death in young children and infants worldwide, implementing appropriate interventions for the prevention and treatment of pneumococcal infections is critical for improving public health particularly in developing countries. This study strongly encourages the introduction of cost-effective and cost-saving [51-53] pneumococcal conjugate vaccines in countries which have not yet done so by highlighting the high efficacy of pneumococcal conjugate vaccines in reducing IPD-associated morbidity and mortality.

In addition, this study emphasizes the importance of examining the underlying pneumococcal population and understanding the ecological and evolutionary changes that occur as a result of serotype-specific vaccines and changes in antimicrobial use. Understanding these changes is a step towards the development of future vaccines that prevent emerging invasive serotypes and the promotion of antimicrobial stewardship.

FUTURE DIRECTION

Using the well-defined collection of invasive disease isolates from the US ABCs surveillance, a random selection of 2,000 isolates (pre and post vaccine introductions)

have been selected for inclusion in the Global Pneumococcal Sequencing (GPS) project. This project aims to sequence 20,000 pneumococcal genomes, primarily from the developing world to study the evolution of pneumococci due to pressures of antibiotic use and vaccine introduction. The 2,000 strains from ABCs will serve as a baseline of comparison for strains from the developing world. Currently, data on genotyping through MLST sequence data are available on the web (www.mlst.net). Similarly, web based tools are currently being developed in this project to provide open access to whole-genome sequencing data from approximately 20,000 global strains which will allow further pneumococcal research. This shared network of data will promote the understanding of global transmission, capsule type switching, antibiotic resistance acquisition and virulence determinants.

TABLES

Table 1. Characteristics of Observed Invasive Pneumococcal Disease Cases, 1998-1999, 2009, and 2012.

	All Isolates		1998-1999		2009		2012	
	N=13,383	(%)	N=7,887	(%)	N=3,145	(%)	N=2,351	(%)
Age Group* (Years)								
≤2	2261	(16.9)	1851	(23.5)	296	(9.4)	114	(4.8)
>2 and ≤5	372	(2.8)	228	(2.9)	97	(3.1)	47	(2.0)
>5 and ≤64	6642	(49.6)	3580	(45.4)	1754	(55.8)	1308	(55.6)
≥65	4106	(30.7)	2226	(28.2)	998	(31.7)	882	(37.5)
State								
CA	704	(5.3)	514	(6.5)	108	(3.4)	82	(3.5)
CT	2083	(15.6)	1365	(17.3)	422	(13.4)	296	(12.6)
GA	2775	(20.7)	1794	(22.7)	556	(17.7)	425	(18.1)
MD	1950	(14.6)	1291	(16.4)	421	(13.4)	238	(10.1)
MN	2158	(16.1)	1036	(13.1)	639	(20.3)	483	(20.5)
NY	1128	(8.4)	557	(7.1)	316	(10.0)	255	(10.8)
OR	845	(6.3)	466	(5.9)	224	(7.1)	155	(6.6)
TN	1740	(13.0)	864	(11.0)	459	(14.6)	417	(17.7)
Source								
Blood	12801	(95.7)	7570	(96.0)	2998	(95.3)	2233	(95.0)
CSF	337	(2.5)	193	(2.4)	79	(2.5)	66	(2.8)
Pleural Fluid	110	(0.8)	57	(0.7)	30	(1.0)	23	(1.0)
Other	135	(1.0)	67	(0.8)	38	(1.2)	29	(1.2)
Clinical Syndrome								
Bacteremia	3846	(28.7)	2836	(36.0)	611	(19.4)	399	(17.0)
Meningitis	787	(5.9)	422	(5.4)	173	(5.5)	192	(8.2)
Pneumonia	8140	(60.8)	4344	(55.1)	2191	(69.7)	1605	(68.3)

*2 cases with missing age variable in 1999

Table 2. Change in Estimated Rate of Invasive Pneumococcal Disease Cases, by State, 1998-1999, 2009, and 2012.

	Rate*			Rate Difference (95% CI)*				% Change in Rate (95% CI)*				P-value†		
State	1998/9	2009	2012	PCV7		PCV13		PCV7		PCV13		PCV7	PCV13	Trend
All	21.9	12.8	9.2	-9.1	(-9.8, -8.5)	-3.6	(-3.6, -3.6)	-41.6%	(-44.6, -38.6)	-28.2%	(-28.4, -27.9)	<.0001	<.0001	<.0001
CA	34.4	13.2	9.9	-21.2	(-25.1, -17.3)	-3.3	(-4.5, -2.2)	-61.5%	(-72.8, -50.3)	-25.0%	(-33.7, -16.4)	<.0001	0.0483	<.0001
CT	20.8	12.0	8.2	-8.8	(-10.4, -7.2)	-3.8	(-4.0, -3.5)	-42.4%	(-50.0, -34.8)	-31.3%	(-33.3, -29.2)	<.0001	<.0001	<.0001
GA	23.6	10.5	8.0	-13.1	(-14.5, -11.7)	-2.4	(-2.6, -2.3)	-55.5%	(-61.6, -49.8)	-23.4%	(-24.6, -21.6)	<.0001	<.0001	<.0001
MD	26.4	15.9	8.8	-10.5	(-12.6, -8.4)	-7.1	(-7.5, -6.8)	-39.8%	(-47.6, -31.7)	-44.7%	(-47.1, -42.5)	<.0001	<.0001	<.0001
MN	20.4	12.1	9.0	-8.3	(-9.9, -6.7)	-3.2	(-3.3, -3.0)	-40.7%	(-48.2, -33.0)	-25.8%	(-27.4, -24.6)	<.0001	<.0001	<.0001
NY	17.5	14.8	11.7	-2.7	(-4.8, -0.5)	-3.1	(-3.6, -2.6)	-15.4%	(-27.7, -2.7)	-20.9%	(-24.1, -17.7)	0.0188	0.0052	<.0001
OR	17.0	13.6	9.2	-3.4	(-5.7, -1.0)	-4.4	(-5.0, -3.8)	-20.0%	(-33.9, -6.1)	-32.6%	(-36.6, -28.3)	0.006	0.0002	<.0001
TN	19.7	14.4	10.8	-5.3	(-7.2, -3.4)	-3.6	(-3.9, -3.3)	-26.9%	(-36.4, -17.5)	-25.2%	(-27.2, -23.2)	<.0001	<.0001	<.0001

*Per 100,000 persons

†Calculated by chi-square test or Fisher's exact test for PCV7 and PCV13; calculated by Cochran-Armitage test for trend.

Table 3. Change in Estimated Rate of Invasive Pneumococcal Disease Cases, by Age Group, 1998-1999, 2009, and 2012.

Age Group‡	Rate*			Rate Difference (95% CI)*				% Change in Rate (95% CI)				P-value†		
(Years)	1998/9	2009	2012	PCV7		PCV13		PCV7		PCV13		PCV7	PCV13	Trend
All	21.9	12.8	9.2	-9.1	(-9.8, -8.5)	-3.6	(-4.2, -3.0)	-41.6%	(-44.6, -38.6)	-28.2%	(-32.7, -23.6)	<.0001	<.0001	<.0001
≤2	124.3	29.4	12.1	-94.9	(-101.4, -88.3)	-17.3	(-21.3, -13.3)	-76.3%	(-81.6, -71.0)	-58.7%	(-72.4, -45.1)	<.0001	<.0001	<.0001
>2 and ≤5	15.2	9.8	4.8	-5.4	(-8.2, -2.6)	-5.0	(-7.4, -2.6)	-35.4%	(-53.7, -17.1)	-50.9%	(-75.3, -26.6)	0.0003	<.0001	<.0001
>5 and ≤64	12.4	8.9	6.4	-3.5	(-4.1, -2.9)	-2.5	(-3.0, -2.0)	-28.1%	(-32.8, -23.4)	-28.0%	(-34.1, -21.9)	<.0001	<.0001	<.0001
≥65	54.2	34.5	27.0	-19.7	(-22.9, -16.6)	-7.6	(-10.3,-4.8)	-36.4%	(-42.1, -30.7)	-21.9%	(-30.0, -13.8)	<.0001	<.0001	<.0001

*Per 100,000 persons

†Calculated by chi-square test or Fisher's exact test for PCV7 and PCV13; calculated by Cochran-Armitage test for trend.

‡2 cases with missing age variable in 1999

Table 4. Change in Estimated Rate of Invasive Pneumococcal Cases following PCV7 Introduction, by State, PCV7 and Non-PCV7 Serotype Groups, 1998-1999 and 2009.

		Rate*		Rate Difference		% Change in Rate		
Serotype	**State**	1998/9	2009	**(95% CI)***		**(95% CI)***		**P-value†**
PCV7	All	13.8	0.5	-13.3	(-13.7, -12.9)	-96.4%	(-99.3, -93.6)	<.0001
	CA	18.0	1.3	-16.7	(-19.0, -14.4)	-92.5%	(-105.3, -79.8)	<.0001
	CT	12.9	0.3	-12.6	(-13.5, -11.7)	-97.8%	(-104.7, -90.9)	<.0001
	GA	15.6	0.3	-15.3	(-16.2, -14.4)	-98.3%	(-104.1, -92.5)	<.0001
	MD	17.9	0.9	-17.0	(-18.2, -15.8)	-94.9%	(-101.9, -88.0)	<.0001
	MN	12.3	0.4	-11.9	(-12.9, -10.9)	-96.8%	(-104.7, -88.8)	<.0001
	NY	10.8	0.6	-10.3	(-11.4, -9.1)	-94.8%	(-105.8, -83.8)	<.0001
	OR	10.4	0.4	-10.0	(-11.2, -8.7)	-95.9%	(-107.9, -83.9)	<.0001
	TN	11.7	0.7	-11.1	(-12.1, -10.0)	-94.4%	(-103.4, -85.4)	<.0001
Non-	All	8.2	12.3	4.1	(3.6, 4.7)	50.4%	(43.9, 56.9)	<.0001
PCV7	CA	16.4	11.9	-4.5	(-7.7, -1.4)	-27.5%	(-46.6, -8.4)	0.007
	CT	7.9	11.7	3.8	(2.5, 5.1)	47.6%	(31.0, 64.3)	<.0001
	GA	8.1	10.2	2.1	(1.1, 3.2)	26.6%	(13.4, 39.9)	<.0001
	MD	8.5	15.0	6.5	(4.8, 8.2)	77.1%	(57.2, 97.0)	<.0001
	MN	8.1	11.7	3.6	(2.4, 4.8)	44.8%	(29.8, 59.8)	<.0001
	NY	6.6	14.2	7.6	(5.8, 9.4)	114.3%	(86.7, 141.8)	<.0001
	OR	6.6	13.1	6.6	(4.6, 8.6)	99.5%	(69.3, 129.8)	<.0001
	TN	8.0	13.7	5.8	(4.2, 7.3)	72.1%	(52.9, 91.3)	<.0001

*Per 100,000 persons

†Calculated by chi-square test or Fisher's exact test

Table 5. Change in Estimated Rate of Invasive Pneumococcal Cases following PCV7 Introduction, by Age Group, PCV7 and Non-PCV7 Serotype Groups, 1998-1999 and 2009.

	Age Group‡	Rate*		Rate Difference		% Change in Rate		
Serotype	(Years)	1998/9	2009	(95% CI)*		(95% CI)		P-value†
PCV7	All	13.8	0.5	-13.3	(-13.7, -12.9)	-96.4%	(-99.3, -93.6)	<.0001
	≤2	103.9	0.4	-103.5	(-108.7, -98.3)	-99.6%	(-104.6, -94.6)	<.0001
	>2 and ≤5	11.1	0.3	-10.8	(-12.6, -9.1)	-97.3%	(-112.7, -81.8)	<.0001
	>5 and ≤64	6.9	0.4	-6.4	(-6.7, -6.1)	-93.9%	(-98.5, -89.3)	<.0001
	≥65	30.5	1.1	-29.4	(-31.1, -27.7)	-96.5%	(-102.2, -90.8)	<.0001
Non-PCV7	All	8.2	12.3	4.1	(3.6, 4.7)	50.5%	(44.0, 56.9)	<.0001
	≤2	20.4	29.0	8.6	(4.6, 12.7)	42.2%	(22.4, 62.0)	<.0001
	>2 and ≤5	4.1	9.5	5.5	(3.3, 7.6)	134.0%	(80.5, 187.6)	<.0001
	>5 and ≤64	5.6	8.5	2.9	(2.5, 3.4)	53.0%	(44.2, 61.8)	<.0001
	≥65	23.8	33.4	9.6	(7.1, 12.2)	40.6%	(29.7, 51.4)	<.0001

*Per 100,000 persons

†Calculated by chi-square test or Fisher's exact test

‡2 cases with missing age variable in 1999

Table 6. Change in Estimated Rate of Invasive Pneumococcal Disease Cases, by State following PCV13 Introduction, by State, PCV13 and Non-PCV13 Serotype Groups, 2009 and 2012.

		Rate*		Rate Difference		% Change in Rate		
Serotype	**State**	2009	2012	**(95% CI)***		**(95% CI)**		**P-value†**
PCV13	All	6.5	2.6	-3.9	(-3.9, -3.9)	-61.0%	(-60.4, -59.7)	<.0001
	CA	6.1	3.4	-2.7	(-3.5, -2.0)	-44.7%	(-56.8, -32.7)	0.0108
	CT	5.7	3.0	-2.8	(-2.9, -2.6)	-48.3%	(-51.2, -45.5)	<.0001
	GA	5.5	2.0	-3.5	(-3.6, -3.4)	-63.2%	(-65.0, -61.3)	<.0001
	MD	8.2	2.6	-5.5	(-5.8, -5.3)	-67.9%	(-70.8, -64.9)	<.0001
	MN	6.5	2.4	-4.1	(-4.2, -4.0)	-62.7%	(-64.4, -61.0)	<.0001
	NY	7.3	3.4	-3.9	(-4.2, -3.6)	-53.8%	(-57.9, -49.7)	<.0001
	OR	6.8	2.5	-4.4	(-4.7, -4.0)	-63.7%	(-69.0, -58.5)	<.0001
	TN	6.9	2.7	-4.2	(-4.4, -4.0)	-61.3%	(-63.9, -58.6)	<.0001
Non-	All	6.3	6.6	0.3	(0.3, 0.3)	4.6%	(4.1, 5.0)	0.2013
PCV13	CA	7.1	6.5	-0.6	(-1.5, 0.3)	-8.1%	(-20.5, 4.3)	0.6558
	CT	6.3	5.3	-1.0	(-1.2, -0.8)	-15.8%	(-18.7, -12.8)	0.0828
	GA	4.9	6.0	1.1	(1.0, 1.2)	22.2%	(19.7, 24.7)	0.0162
	MD	7.8	6.2	-1.6	(-1.9, -1.3)	-20.4%	(-23.9, -16.9)	0.0283
	MN	5.6	6.5	0.9	(0.8, 1.1)	16.8%	(14.5, 19.1)	0.0487
	NY	7.5	8.4	0.8	(0.5, 1.2)	10.8%	(6.0, 15.6)	0.3432
	OR	6.7	6.7	0.0	(-0.5, 0.4)	-0.6%	(-7.0, 5.8)	0.9620
	TN	7.5	8.1	0.6	(0.4, 0.8)	7.7%	(4.8, 10.7)	0.3861

*Per 100,000 persons

†Calculated by chi-square test or Fisher's exact test

Table 7. Change in Estimated Rate of Invasive Pneumococcal Disease Cases following PCV13 Introduction, by Age Group, PCV13 and Non-PCV13 Serotype Groups, 2009 and 2012.

	Age Group‡	Rate*		Rate Difference		% Change in Rate		
Serotype	(Years)	2009	2012	(95% CI)*		(95% CI)*		P-value†
PCV13	All	6.5	2.6	-3.9	(-4.3, -3.5)	-60.1%	(-65.8, -54.3)	<.0001
	≤2	18.4	1.7	-16.7	(-19.5, -13.9)	-90.7%	(-105.8, -75.6)	<.0001
	>2 and ≤5	7.4	1.5	-5.9	(-7.7, -4.0)	-79.2%	(-104.4, -54.0)	<.0001
	>5 and ≤64	4.7	1.9	-2.8	(-3.2, -2.5)	-60.1%	(-67.7, -52.5)	<.0001
	≥65	14.3	7.7	-6.7	(-8.4, -5.0)	-46.5%	(-58.2, -34.9)	<.0001
Non-PCV13	All	6.3	6.6	0.3	(-0.2, 0.7)	4.6%	(-2.5, 11.6)	0.2013
	≤2	11.0	10.4	-0.6	(-3.5, 2.3)	-5.4%	(-31.8, 21.0)	0.6887
	>2 and ≤5	2.4	3.3	0.9	(-0.6, 2.3)	35.0%	(-26.6, 96.5)	0.2647
	>5 and ≤64	4.2	4.6	0.3	(-0.1, 0.7)	7.5%	(-2.2, 17.2)	0.1302
	≥65	20.2	19.3	-0.9	(-3.1, 1.3)	-4.3%	(-15.4, 6.7)	0.4397

*Per 100,000 persons
†Calculated by chi-square test or Fisher's exact test
‡2 cases with missing age variable in 1999

Table 8. Change in Estimated Rate of Invasive Pneumococcal Disease Cases among Children ≤2 years, by Serotype, 1998-1999, 2009, and 2012.

	Cases			Rate*			Rate Difference (95% CI)*				% Change in Rate (95% CI)				P-value†	
Serotype	1998/9	2009	2012	1998/9	2009	2012	PCV7		PCV13		PCV7		PCV13		PCV7	PCV13
PCV7																
4	132	1	1	8.9	0.1	0.1	-8.8	(-10.3, -7.2)	0.0	(-0.3, 0.3)	-98.9%	(-116.1, -81.7)	7.1%	(-280.1, 294.4)	<.0001	1.0000
6B	208	0	0	14.0	0.0	0.0	-14.0	(-15.9, -12.1)	0.0	(0.0, 0.0)	-100.0%	(-113.6, -86.4)		-	<.0001	-
9V	113	0	0	7.6	0.0	0.0	-7.6	(-9.0, -6.2)	0.0	(0.0, 0.0)	-100.0%	(-118.4, -81.6)		-	<.0001	-
14	613	0	0	41.2	0.0	0.0	-41.2	(-44.4, -37.9)	0.0	(0.0, 0.0)	-100.0%	(-107.9, -92.1)		-	<.0001	-
18C	153	0	1	10.3	0.0	0.1	-10.3	(-11.9, -8.6)	0.1	(-0.1, 0.3)	-100.0%	(-115.8, -84.2)		-	<.0001	0.4827
19F	200	2	0	13.4	0.2	0.0	-13.2	(-15.1, -11.3)	-0.2	(-0.5, 0.1)	-98.5%	(-112.5, -84.5)	-100.0%	(-248.5, 48.5)	<.0001	0.5006
23F	128	1	0	8.6	0.1	0.0	-8.5	(-10.0, -7.0)	-0.1	(-0.3, 0.1)	-98.8%	(-116.3, -81.4)	-100.0%	(-310.0, 110.0)	<.0001	1.0000
New in PCV13																
1	10	0	0	0.7	0.0	0.0	-0.7	(-1.1, -0.3)	0.0	(0.0, 0.0)	-100.0%	(-162.0, -38.0)		-	0.0075	-
3	7	10	3	0.5	1.0	0.3	0.5	(-0.2, 1.2)	-0.7	(-1.4, 0.1)	111.5%	(-39.1, 262.0)	-67.9%	(-142.4, 6.7)	0.1199	0.0948
5	1	2	0	0.1	0.2	0.0	0.1	(-0.2, 0.4)	-0.2	(-0.5, 0.1)	196.0%	(-258.7, 650.7)	-100.0%	(-248.5, 48.5)	0.5692	0.5006
6A	91	0	0	6.1	0.0	0.0	-6.1	(-7.4, -4.9)	0.0	(0.0, 0.0)	-100.0%	(-120.5, -79.5)		-	<.0001	-
7F	14	38	1	0.9	3.8	0.1	2.8	(1.5, 4.1)	-3.7	(-5.0, -2.4)	301.8%	(163.7, 439.8)	-97.2%	(-131.6, -62.7)	<.0001	<.0001
19A	46	131	10	3.1	13.0	1.1	9.9	(7.5, 12.3)	-12.0	(-14.4, -9.5)	321.5%	(243.8, 399.3)	-91.8%	(-110.8, -72.9)	<.0001	<.0001
Non-PCV13‡																
9A	15	0	0	1.0	0.0	0.0	-1.0	(-1.5, -0.5)	0.0	(0.0, 0.0)	-100.0%	(-150.6, -49.4)		-	0.0015	-
12F	20	4	7	1.3	0.4	0.7	-0.9	(-1.7, -0.2)	0.3	(-0.3, 1.0)	-70.4%	(-123.0, -17.8)	87.5%	(-79.3, 254.3)	0.0182	0.3740
15A	1	6	5	0.1	0.6	0.5	0.5	(0.0, 1.0)	-0.1	(-0.7, 0.6)	788.1%	(50.9, 1525.3)	-10.7%	(-123.3, 101.9)	0.0197	1.0000
18B	7	0	0	0.5	0.0	0.0	-0.5	(-0.8, -0.1)	0.0	(0.0, 0.0)	-100.0%	(-174.1, -25.9)		-	0.0466	-
33F	12	22	9	0.8	2.2	1.0	1.4	(0.4, 2.4)	-1.2	(-2.4, -0.1)	171.4%	(44.6, 298.1)	-56.2%	(-108.3, -4.0)	0.0037	0.0320

*Per 100,000 persons

†Calculated by chi-square test or Fisher's exact test

‡Only includes non-PCV7 serotypes with at least one comparison with p-value <0.05

Table 9. Change in Estimated Rate of Invasive Pneumococcal Disease Cases across All Age Groups, by Serogroup of Interest, 1998-1999, 2009, and 2012.

	Cases			Rate*			Rate Difference (95% CI)*				% Change in Rate (95% CI)				P-value†	
Serogroup	1998/9	2009	2012	1998/9	2009	2012	PCV7		PCV13		PCV7		PCV13		PCV7	PCV13
6	953	221	149	2.7	0.9	0.6	-1.8	(-1.9, -1.6)	-0.3	(-0.4, -0.2)	-66.0%	(-70.9, -62.1)	-35.2%	(-43.8, -26.6)	<.0001	<.0001
7	204	587	188	0.6	2.4	0.7	1.8	(1.7, 1.9)	-1.7	(-1.8, -1.5)	321.5%	(302.7, 340.2)	-69.2%	(-73.9, -64.5)	<.0001	<.0001
9	856	112	106	2.4	0.5	0.4	-1.9	(-2.0, -1.8)	0.0	(-0.1, 0.0)	-80.8%	(-84.7, -77.0)	-9.0%	(-22.0, 3.9)	<.0001	0.4844
18	400	9	4	1.1	0.0	0.0	-1.1	(-1.1, -1.0)	0.0	(0.0, 0.0)	-96.7%	(-101.8, -91.6)	-57.3%	(-96.9, -17.7)	<.0001	0.1447
19	691	633	246	1.9	2.6	1.0	0.7	(0.5, 0.8)	-1.6	(-1.7, -1.5)	34.2%	(27.6, 40.7)	-62.6%	(-67.3, -58.0)	<.0001	<.0001
23	627	153	146	1.7	0.6	0.6	-1.1	(-1.2, -1.0)	-0.1	(-0.1, 0.0)	-64.3%	(-69.2, -59.3)	-8.3%	(19.4, 2.8)	<.0001	0.4545

*Per 100,000 persons

†Calculated by chi-square test

Table 10. Change in Estimated Rate of Invasive Pneumococcal Cases, by Clinical Syndrome, 1998-1999, 2009, and 2012.

Clinical	Rate*			Rate Difference (95% CI)*				% Change in Rate (95% CI)				P-value†		
Syndrome	1998/9	2009	2012	PCV7		PCV13		PCV7		PCV13		PCV7	PCV13	Trend
Bacteremia	3.7	2.5	1.6	-1.3	(-1.6, -0.9)	-0.9	(-0.9, -0.9)	-33.5%	(-42.9, -24.1)	-37.2%	(-37.9, -36.6)	<.0001	<.0001	<.0001
Meningitis	1.2	0.7	0.8	-0.5	(-0.5, -0.6)	0.0	(0.0, 0.1)	-40.0%	(-53.0, -26.9)	6.7%	(5.3, 8.0)	<.0001	0.5381	<.0001
Pneumonia	12.1	8.9	6.3	-3.2	(-3.2, -3.7)	-2.6	(-2.7, -2.6)	-26.1%	(-30.4, -21.8)	-29.6%	(-29.9, -29.3)	<.0001	<.0001	<.0001

*Per 100,000 persons

†Calculated by chi-square test for PCV7 and PCV13; calculated by Cochran-Armitage test for trend

Table 11. Change in Proportion and Rate in Antimicrobial-Resistant *S. pneumoniae* Isolates in the US, by Antimicrobial, 1998-1999, 2009, and 2012.

	Resistance						Change				P-value‡			
	Proportion*			Rate†			Proportion*		Rate†		Proportion*		Rate	
Antimicrobial Drug	1998/9	2009	2012	1998/9	2009	2012	PCV7	PCV13	PCV7	PCV13	PCV7	PCV13	PCV7	PCV13
Amoxicillin	3.8%	8.1%	4.9%	0.8	1.0	0.4	4.3%	-3.2%	0.2	-0.6	<0.0001	<0.0001	0.0024	<.0001
Penicillin	1.5%	4.3%	2.3%	0.3	0.6	0.2	2.8%	-2.0%	0.2	-0.3	<0.0001	<0.0001	<0.0001	<0.0001
Cefuroxime	19.3%	15.2%	12.2%	4.2	1.9	1.1	-4.1%	-3.0%	-2.3	-0.8	<0.0001	0.0015	<0.0001	<0.0001
Cefotaxime	2.1%	1.9%	1.0%	0.5	0.2	0.1	-0.2%	-0.9%	-0.2	-0.1	0.4676	0.0101	<0.0001	<0.0001
Chloramphenicol	3.5%	5.2%	5.7%	0.8	0.7	0.5	1.7%	0.5%	-0.1	-0.1	<0.0001	0.3809	0.1319	0.0429
Clindamycin	3.5%	13.9%	9.8%	0.8	1.8	0.9	10.4%	-4.0%	1.0	-0.9	<0.0001	<0.0001	<0.0001	<0.0001
Trimethoprim/sulfamethoxazole	24.6%	16.7%	10.7%	5.4	2.1	1.0	-7.9%	-6.0%	-3.3	-1.2	<0.0001	<0.0001	<0.0001	<0.0001
Erythromycin	17.7%	26.7%	30.0%	3.9	3.4	2.8	9.1%	3.3%	-0.4	-0.7	<0.0001	0.0075	0.0054	<0.0001
Levofloxacin	0.2%	0.3%	0.4%	0.0	0.0	0.0	0.1%	0.1%	0.0	0.0	0.3659	0.3797	0.7592	0.8863
Meropenem	8.5%	10.5%	6.5%	1.9	1.3	0.6	2.1%	-4.0%	-0.5	-0.8	0.0007	<0.0001	<0.0001	<0.0001
Rifampin	0.3%	0.0%	0.0%	0.1	0.0	0.0	-0.3%	0.0%	-0.1	0.0	0.0010	-	<0.0001	-
Quinupristin-dalfopristin	0.1%	0.0%	0.0%	0.0	0.0	0.0	-0.1%	0.0%	0.0	0.0	0.2029	-	0.0465	-
Tetracycline	7.2%	16.0%	12.2%	1.6	2.1	1.1	8.9%	-3.8%	0.5	-0.9	<0.0001	<0.0001	<0.0001	<0.0001
Vancomycin	0.0%	0.0%	0.0%	0.0	0.0	0.0	0.0%	0.0%	0.0	0.0	-	-	-	-

*Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as available data

†Per 100,000 persons

‡Calculated by chi-square test or Fisher's exact test

Table 12.1 Change in Proportion and Rate of Amoxicillin-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	281	4816	5.8%	7.8	7	120	5.8%	0.3	4	64	6.3%	0.2	0.9995	1.0000	<.0001	0.3657
4	1	811	0.1%	0.0	0	33	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	1.0000	-
6B	25	554	4.5%	0.7	1	11	9.1%	0.0	0	4	0.0%	0.0	0.4072	1.0000	0.0001	0.4901
9V	0	673	0.0%	0.0	0	21	0.0%	0.0	0	5	0.0%	0.0	-	-	-	-
14	192	1405	13.7%	5.3	0	13	0.0%	0.0	1	5	20.0%	0.0	0.2363	0.2778	<.0001	1.0000
18C	0	364	0.0%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	-	-	-	-
19F	12	445	2.7%	0.3	6	27	22.2%	0.2	3	33	9.1%	0.1	<.0001	0.2756	0.5317	0.3348
23F	51	564	9.0%	1.4	0	8	0.0%	0.0	0	4	0.0%	0.0	1.0000	-	<.0001	-
New in PCV13	6	1203	0.5%	0.2	247	1473	16.8%	10.1	105	595	17.6%	4.1	<.0001	0.6303	<.0001	<.0001
1	0	146	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	1	289	0.3%	0.0	0	240	0.0%	0.0	0	207	0.0%	0.0	1.0000	-	1.0000	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	4	336	1.2%	0.1	0	42	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	0.1518	-
7F	0	189	0.0%	0.0	0	559	0.0%	0.0	0	158	0.0%	0.0	-	-	-	-
19A	1	232	0.4%	0.0	247	606	40.8%	10.1	105	212	49.5%	4.1	0.0000	0.0264	<.0001	<.0001
Non-PCV◊	1	1632	0.1%	0.0	1	1552	0.1%	0.0	5	1682	0.3%	0.2	1.0000	0.2206	1.0000	0.2187

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as available

‡Per 1,000,000 persons

◊Serotype-specific proportion and rate were not included as no significant change was observed in any non-PCV13 serotype

§Calculated by chi-square test or Fisher's exact test

Table 12.2 Change in Proportion and Rate of Penicillin-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	105	4941	2.1%	2.9	2	120	1.7%	0.1	3	64	4.7%	0.1	0.7302	0.3437	<.0001	1.0000
4	0	834	0.0%	0.0	0	33	0.0%	0.0	0	10	0.0%	0.0	-	-	-	-
6B	13	563	2.3%	0.4	0	11	0.0%	0.0	0	4	0.0%	0.0	1.0000	-	0.0029	-
9V	5	686	0.7%	0.1	0	21	0.0%	0.0	0	5	0.0%	0.0	1.0000	-	0.0851	-
14	29	1443	2.0%	0.8	1	13	7.7%	0.0	0	5	0.0%	0.0	0.2380	1.0000	<.0001	0.4901
18C	1	375	0.3%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	1.0000	-	1.0000	-
19F	17	453	3.8%	0.5	0	27	0.0%	0.0	3	33	9.1%	0.1	0.6142	0.2449	0.0007	0.2503
23F	40	587	6.8%	1.1	1	8	12.5%	0.0	0	4	0.0%	0.0	0.4371	1.0000	<.0001	0.4901
New in PCV13	13	1247	1.0%	0.4	118	1473	8.0%	4.8	38	598	6.4%	1.5	<.0001	0.1955	<.0001	<.0001
1	0	151	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	0	301	0.0%	0.0	0	240	0.0%	0.0	0	207	0.0%	0.0	-	-	-	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	11	352	3.1%	0.3	1	42	2.4%	0.0	0	10	0.0%	0.0	1.0000	1.0000	0.0348	0.4901
7F	0	194	0.0%	0.0	0	559	0.0%	0.0	0	160	0.0%	0.0	-	-	-	-
19A	2	238	0.8%	0.1	117	606	19.3%	4.8	38	213	17.8%	1.5	<.0001	0.6383	<.0001	<.0001
Non-PCV◊	3	1699	0.2%	0.1	16	1552	1.0%	0.7	13	1689	0.8%	0.5	0.0014	0.4301	0.0029	0.5775
15A	0	17	0.0%	0.0	6	107	5.6%	0.2	3	75	4.0%	0.1	1.0000	0.7384	0.0045	0.3348

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Serotype-specific proportion and rate were not included as no significant change was observed in any non-PCV13 serotype

§Calculated by chi-square test or Fisher's exact test

Table 12.3 Change in Proportion and Rate of Cefuroxime-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	1321	4940	26.7%	36.8	42	120	35.0%	1.7	14	64	21.9%	0.5	0.0439	0.0654	<.0001	0.0002
4	7	834	0.8%	0.2	0	33	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	0.0465	-
6B	171	563	30.4%	4.8	5	11	45.5%	0.2	3	4	75.0%	0.1	0.3254	0.5692	<.0001	0.4997
9V	317	686	46.2%	8.8	18	21	85.7%	0.7	3	5	60.0%	0.1	0.0004	0.2357	<.0001	0.0008
14	476	1443	33.0%	13.2	3	13	23.1%	0.1	3	5	60.0%	0.1	0.5634	0.2682	<.0001	1.0000
18C	1	375	0.3%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	1.0000	-	1.0000	-
19F	126	453	27.8%	3.5	13	27	48.1%	0.5	4	33	12.1%	0.2	0.0236	0.0021	<.0001	0.0235
23F	223	586	38.1%	6.2	3	8	37.5%	0.1	1	4	25.0%	0.0	1.0000	1.0000	<.0001	0.3654
New in PCV13	127	1247	10.2%	3.5	323	1473	21.9%	13.2	113	595	19.0%	4.4	<.0001	0.1383	<.0001	<.0001
1	0	151	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	5	301	1.7%	0.1	0	240	0.0%	0.0	0	207	0.0%	0.0	0.0693	-	0.0851	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	100	352	28.4%	2.8	2	42	4.8%	0.1	1	10	10.0%	0.0	0.0009	0.4805	<.0001	0.6177
7F	1	194	0.5%	0.0	0	559	0.0%	0.0	0	158	0.0%	0.0	0.2576	-	1.0000	-
19A	21	238	8.8%	0.6	321	606	53.0%	13.1	112	212	52.8%	4.4	<.0001	0.9719	<.0001	<.0001
Non-PCV◊	72	1694	4.3%	2.0	112	1552	7.2%	4.6	158	1682	9.4%	6.2	0.0003	0.0253	0.0032	0.0051
6C	4	38	10.5%	0.1	50	168	29.8%	2.0	47	135	34.8%	1.8	0.0149	0.3487	<.0001	0.6171
9A	20	39	51.3%	0.6	0	0	-	0.0	0	0	-	0.0	-	-	0.0002	-

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Only serotypes with significant change in serotype-specific proportion or rate are individually listed below

§Calculated by chi-square test or Fisher's exact test

Table 12.4 Change in Proportion and Rate of Cefotaxime-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	158	4941	3.2%	4.4	3	120	2.5%	0.1	2	64	3.1%	0.1	1.0000	1.0000	<.0001	1.0000
4	1	834	0.1%	0.0	0	33	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	1.0000	-
6B	10	563	1.8%	0.3	0	11	0.0%	0.0	0	4	0.0%	0.0	1.0000	-	0.0074	-
9V	7	686	1.0%	0.2	1	21	4.8%	0.0	0	5	0.0%	0.0	0.2153	1.0000	0.1540	0.4901
14	28	1443	1.9%	0.8	0	13	0.0%	0.0	0	5	0.0%	0.0	1.0000	-	<.0001	-
18C	0	375	0.0%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	-	-	-	-
19F	8	453	1.8%	0.2	2	27	7.4%	0.1	2	33	6.1%	0.1	0.1038	1.0000	0.2174	1.0000
23F	104	587	17.7%	2.9	0	8	0.0%	0.0	0	4	0.0%	0.0	0.3620	-	<.0001	-
New in PCV13	6	1247	0.5%	0.2	54	1473	3.7%	2.2	20	598	3.3%	0.8	<.0001	0.7209	<.0001	<.0001
1	0	151	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	0	301	0.0%	0.0	0	240	0.0%	0.0	0	207	0.0%	0.0	-	-	-	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	4	352	1.1%	0.1	0	42	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	0.1518	-
7F	0	194	0.0%	0.0	0	559	0.0%	0.0	0	160	0.0%	0.0	-	-	-	-
19A	2	238	0.8%	0.1	54	606	8.9%	2.2	20	213	9.4%	0.8	<.0001	0.8339	<.0001	<.0001
Non-PCV◊	1	1699	0.1%	0.0	2	1552	0.1%	0.1	2	1689	0.1%	0.1	0.6087	1.0000	1.0000	1.0000

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Serotype-specific proportion and rate were not included as no significant change was observed in any non-PCV13 serotype

§Calculated by chi-square test or Fisher's exact test

Table 12.5 Change in Proportion and Rate of Chloramphenicol-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	249	4941	5.0%	6.9	13	120	10.8%	0.5	3	64	4.7%	0.1	0.0046	0.1588	<.0001	<.0001
4	3	834	0.4%	0.1	1	33	3.0%	0.0	2	10	20.0%	0.1	0.1440	0.1301	0.6512	1.0000
6B	69	563	12.3%	1.9	2	11	18.2%	0.1	0	4	0.0%	0.0	0.6343	1.0000	<.0001	0.2402
9V	3	686	0.4%	0.1	3	21	14.3%	0.1	0	5	0.0%	0.0	0.0004	1.0000	0.6920	0.1177
14	21	1443	1.5%	0.6	0	13	0.0%	0.0	0	5	0.0%	0.0	1.0000	-	0.0002	-
18C	0	375	0.0%	0.0	1	7	14.3%	0.0	0	3	0.0%	0.0	0.0183	1.0000	0.4057	0.4901
19F	47	453	10.4%	1.3	3	27	11.1%	0.1	1	33	3.0%	0.0	0.7532	0.3179	<.0001	0.3654
23F	106	587	18.1%	2.9	3	8	37.5%	0.1	0	4	0.0%	0.0	0.1661	0.4909	<.0001	-
New in PCV13	15	1247	1.2%	0.4	68	1473	4.6%	2.8	56	595	9.4%	2.2	<.0001	<.0001	<.0001	0.2812
1	0	151	0.0%	0.0	1	23	4.3%	0.0	0	8	0.0%	0.0	0.1322	1.0000	0.4057	0.4901
3	7	301	2.3%	0.2	26	240	10.8%	1.1	30	207	14.5%	1.2	<.0001	0.2439	<.0001	0.6994
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	4	352	1.1%	0.1	1	42	2.4%	0.0	1	10	10.0%	0.0	0.4326	0.3507	0.6545	1.0000
7F	0	194	0.0%	0.0	1	559	0.2%	0.0	1	158	0.6%	0.0	1.0000	0.3924	0.4057	1.0000
19A	4	238	1.7%	0.1	39	606	6.4%	1.6	24	212	11.3%	0.9	0.0047	0.0217	<.0001	0.0406
Non-PCV◊	13	1694	0.8%	0.4	82	1552	5.3%	3.3	75	1682	4.5%	2.9	<.0001	0.2757	<.0001	0.5764
12F	9	327	2.8%	0.3	6	56	10.7%	0.2	5	80	6.3%	0.2	0.0131	0.3596	0.9640	0.7134
15A	2	17	11.8%	0.1	50	107	46.7%	2.0	28	74	37.8%	1.1	0.0073	0.2350	<.0001	0.0077
22F	0	234	0.0%	0.0	3	213	1.4%	0.1	18	290	6.2%	0.7	0.1074	0.0078	0.0668	0.0015
23A	0	33	0.0%	0.0	7	94	7.4%	0.3	3	95	3.2%	0.1	0.1888	0.2127	0.0018	0.2181

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Only serotypes with significant change in serotype-specific proportion or rate are individually listed below

§Calculated by chi-square test or Fisher's exact test

Table 12.6 Change in Proportion and Rate of Clindamycin-Resistant in Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	239	4941	4.8%	6.7	21	120	17.5%	0.9	7	64	10.9%	0.3	<.0001	0.2379	<.0001	0.0082
4	4	834	0.5%	0.1	0	33	0.0%	0.0	1	10	10.0%	0.0	1.0000	0.2326	0.1518	1.0000
6B	91	563	16.2%	2.5	2	11	18.2%	0.1	1	4	25.0%	0.0	0.6950	1.0000	<.0001	0.6177
9V	9	686	1.3%	0.3	3	21	14.3%	0.1	0	5	0.0%	0.0	0.0042	1.0000	0.3819	0.1177
14	59	1443	4.1%	1.6	2	13	15.4%	0.1	1	5	20.0%	0.0	0.1001	1.0000	<.0001	0.6177
18C	0	375	0.0%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	-	-	-	-
19F	27	453	6.0%	0.8	11	27	40.7%	0.4	3	33	9.1%	0.1	0.0000	0.0039	0.1445	0.0269
23F	49	587	8.3%	1.4	3	8	37.5%	0.1	1	4	25.0%	0.0	0.0258	1.0000	<.0001	0.3654
New in PCV13	17	1246	1.4%	0.5	278	1473	18.9%	11.3	124	595	20.8%	4.9	<.0001	0.3061	<.0001	<.0001
1	0	151	0.0%	0.0	1	23	4.3%	0.0	0	8	0.0%	0.0	0.1322	1.0000	0.4057	0.4901
3	4	301	1.3%	0.1	13	240	5.4%	0.5	18	207	8.7%	0.7	0.0068	0.1736	0.0026	0.4308
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	5	351	1.4%	0.1	1	42	2.4%	0.0	2	10	20.0%	0.1	0.4948	0.0910	0.4117	1.0000
7F	1	194	0.5%	0.0	0	559	0.0%	0.0	0	158	0.0%	0.0	0.2576	-	1.0000	-
19A	7	238	2.9%	0.2	263	606	43.4%	10.7	104	212	49.1%	4.1	<.0001	0.1540	<.0001	<.0001
Non-PCV◊	18	1694	1.1%	0.5	137	1552	8.8%	5.6	99	1683	5.9%	3.9	<.0001	0.0013	<.0001	0.0134
15A	2	17	11.8%	0.1	95	107	88.8%	3.9	62	74	83.8%	2.4	0.0000	0.3760	<.0001	0.0039
23A	0	33	0.0%	0.0	14	94	14.9%	0.6	13	95	13.7%	0.5	0.0201	0.8122	<.0001	0.7676

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Only serotypes with significant change in serotype-specific proportion or rate are individually listed below

§Calculated by chi-square test or Fisher's exact test

Table 12.7 Change in Proportion and Rate of Trimethoprim-Sulfamethoxazole-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	1603	4941	32.4%	44.6	52	120	43.3%	2.1	21	64	32.8%	0.8	0.0120	0.1647	<.0001	0.0003
4	8	834	1.0%	0.2	6	33	18.2%	0.2	4	10	40.0%	0.2	0.0000	0.2056	0.8618	0.5414
6B	237	563	42.1%	6.6	3	11	27.3%	0.1	3	4	75.0%	0.1	0.3738	0.2352	<.0001	1.0000
9V	342	686	49.9%	9.5	19	21	90.5%	0.8	4	5	80.0%	0.2	0.0002	0.4885	<.0001	0.0013
14	601	1443	41.6%	16.7	5	13	38.5%	0.2	3	5	60.0%	0.1	0.8164	0.6078	<.0001	0.4997
18C	5	375	1.3%	0.1	2	7	28.6%	0.1	0	3	0.0%	0.0	0.0058	1.0000	0.7084	0.2402
19F	142	453	31.3%	4.0	12	27	44.4%	0.5	6	33	18.2%	0.2	0.1567	0.0272	<.0001	0.1340
23F	268	587	45.7%	7.5	5	8	62.5%	0.2	1	4	25.0%	0.0	0.4798	0.5455	<.0001	0.1179
New in PCV13	262	1247	21.0%	7.3	364	1473	24.7%	14.8	133	595	22.4%	5.2	0.0223	0.2558	<.0001	<.0001
1	2	151	1.3%	0.1	0	23	0.0%	0.0	2	8	25.0%	0.1	1.0000	0.0602	0.5178	0.5002
3	6	301	2.0%	0.2	2	240	0.8%	0.1	1	207	0.5%	0.0	0.3104	1.0000	0.4862	
5	1	11	9.1%	0.0	0	3	0.0%	0.0	0	0	-	0.0	1.0000	-	1.0000	-
6A	160	352	45.5%	4.5	4	42	9.5%	0.2	2	10	20.0%	0.1	<.0001	0.3245	<.0001	0.4443
7F	2	194	1.0%	0.1	1	559	0.2%	0.0	0	158	0.0%	0.0	0.1646	1.0000	1.0000	0.4901
19A	91	238	38.2%	2.5	357	606	58.9%	14.6	128	212	60.4%	5.0	<.0001	0.7083	<.0001	<.0001
Non-PCV◊	74	1694	4.4%	2.1	108	1552	7.0%	4.4	96	1682	5.7%	3.8	0.0014	0.1437	0.0117	0.4008
6C	5	38	13.2%	0.1	65	168	38.7%	2.6	50	135	37.0%	2.0	0.0027	0.7682	<.0001	0.1070
9N	6	128	4.7%	0.2	0	91	0.0%	0.0	1	101	1.0%	0.0	0.0426	1.0000	0.0877	1.0000
11A	4	127	3.1%	0.1	9	76	11.8%	0.4	8	92	8.7%	0.3	0.0188	0.5009	0.0353	0.7457

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Only serotypes with significant change in serotype-specific proportion or rate are individually listed below

§Calculated by chi-square test or Fisher's exact test

Table 12.8 Change in Proportion and Rate of Erythromycin-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				Proportion P-value§		Rate P-value§	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	1116	4940	22.6%	31.1	45	120	37.5%	1.8	20	64	31.3%	0.8	0.0001	0.3982	<.0001	<.0001
4	16	834	1.9%	0.4	0	33	0.0%	0.0	2	10	20.0%	0.1	1.0000	0.0498	0.0009	0.5002
6B	181	563	32.1%	5.0	4	11	36.4%	0.2	3	4	75.0%	0.1	0.7523	0.2821	<.0001	0.7215
9V	105	686	15.3%	2.9	14	21	66.7%	0.6	3	5	60.0%	0.1	0.0000	1.0000	<.0001	0.0060
14	562	1443	38.9%	15.6	4	13	30.8%	0.2	2	5	40.0%	0.1	0.5471	1.0000	<.0001	0.4443
18C	3	375	0.8%	0.1	1	7	14.3%	0.0	1	3	33.3%	0.0	0.0716	1.0000	0.6512	1.0000
19F	119	453	26.3%	3.3	17	27	63.0%	0.7	7	33	21.2%	0.3	<.0001	0.0010	<.0001	0.0325
23F	130	586	22.2%	3.6	5	8	62.5%	0.2	2	4	50.0%	0.1	0.0175	1.0000	<.0001	0.2799
New in PCV13	192	1247	15.4%	5.3	436	1473	29.6%	17.8	165	595	27.7%	6.5	<.0001	0.3969	<.0001	0.0019
1	2	151	1.3%	0.1	1	23	4.3%	0.0	0	8	0.0%	0.0	0.3482	1.0000	1.0000	0.4901
3	9	301	3.0%	0.3	20	240	8.3%	0.8	20	207	9.7%	0.8	0.0061	0.6237	0.0018	0.9002
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	125	352	35.5%	3.5	33	42	78.6%	1.3	5	10	50.0%	0.2	<.0001	0.1094	<.0001	<.0001
7F	1	194	0.5%	0.0	4	559	0.7%	0.2	2	158	1.3%	0.1	1.0000	0.6180	0.1656	0.4443
19A	55	238	23.1%	1.5	378	606	62.4%	15.4	138	212	65.1%	5.4	<.0001	0.4803	<.0001	<.0001
Non-PCV◊	83	1694	4.9%	2.3	360	1551	23.2%	14.7	518	1682	30.8%	20.3	<.0001	<.0001	<.0001	<.0001
6C	5	38	13.2%	0.1	52	168	31.0%	2.1	518	1682	48.1%	20.3	0.0268	0.0022	<.0001	0.3234
9A	14	39	35.9%	0.4	0	0	-	0.0	0	0	-	0.0	-	-	0.0020	-
9N	2	128	1.6%	0.1	10	91	11.0%	0.4	3	101	3.0%	0.1	0.0044	0.0272	0.0051	0.0441
11A	3	127	2.4%	0.1	11	76	14.5%	0.4	32	92	34.8%	1.3	0.0010	0.0027	0.0038	0.0021
12F	22	327	6.7%	0.6	10	56	17.9%	0.4	16	80	20.0%	0.6	0.0148	0.7545	0.2828	0.2820
13	0	22	0.0%	0.0	0	7	0.0%	0.0	3	9	33.3%	0.1	-	0.2125	-	0.2503
15A	2	17	11.8%	0.1	98	107	91.6%	4.0	64	74	86.5%	2.5	0.0000	0.2709	<.0001	0.0035
15B/C/F	0	80	0.0%	0.0	14	72	19.4%	0.6	39	99	39.4%	1.5	<.0001	0.0054	<.0001	0.0010
22F	3	234	1.3%	0.1	20	212	9.4%	0.8	64	290	22.1%	2.5	0.0001	0.0002	<.0001	<.0001
23A	0	33	0.0%	0.0	21	94	22.3%	0.9	34	95	35.8%	1.3	0.0030	0.0418	<.0001	0.1082
23B	1	7	14.3%	0.0	6	51	11.8%	0.2	4	47	8.5%	0.2	1.0000	0.7427	0.0204	0.5414
31	0	39	0.0%	0.0	5	44	11.4%	0.2	8	55	14.5%	0.3	0.0572	0.6414	0.0110	0.4468
33F	6	66	9.1%	0.2	66	103	64.1%	2.7	93	99	93.9%	3.6	<.0001	<.0001	<.0001	0.0586
35B	0	45	0.0%	0.0	25	65	38.5%	1.0	64	95	67.4%	2.5	0.0000	0.0003	<.0001	<.0001

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Only serotypes with significant change in serotype-specific proportion or rate are individually listed below

§Calculated by chi-square test or Fisher's exact test

Table 12.9 Change in Proportion and Rate of Levofloxacin-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	10	4816	0.2%	0.3	2	120	1.7%	0.1	1	64	1.6%	0.0	0.0330	1.0000	0.0209	1.0000
4	0	811	0.0%	0.0	0	33	0.0%	0.0	0	10	0.0%	0.0	-	-	-	-
6B	2	554	0.4%	0.1	0	11	0.0%	0.0	0	4	0.0%	0.0	1.0000	-	0.5178	-
9V	2	673	0.3%	0.1	1	21	4.8%	0.0	0	5	0.0%	0.0	0.0882	1.0000	1.0000	0.4901
14	2	1405	0.1%	0.1	0	13	0.0%	0.0	1	5	20.0%	0.0	1.0000	0.2778	0.5178	1.0000
18C	1	364	0.3%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	1.0000	-	1.0000	-
19F	2	445	0.4%	0.1	0	27	0.0%	0.0	0	33	0.0%	0.0	1.0000	-	0.5178	-
23F	1	564	0.2%	0.0	1	8	12.5%	0.0	0	4	0.0%	0.0	0.0278	1.0000	1.0000	0.4901
New in PCV13	1	1203	0.1%	0.0	2	1473	0.1%	0.1	2	595	0.3%	0.1	1.0000	0.3266	1.0000	1.0000
1	0	146	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	0	289	0.0%	0.0	0	240	0.0%	0.0	0	207	0.0%	0.0	-	-	-	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	1	336	0.3%	0.0	0	42	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	1.0000	-
7F	0	189	0.0%	0.0	0	559	0.0%	0.0	1	158	0.6%	0.0	-	0.2204	-	1.0000
19A	0	232	0.0%	0.0	2	606	0.3%	0.1	1	212	0.5%	0.0	1.0000	1.0000	0.1646	0.6177
Non-PCV◊	4	1632	0.2%	0.1	5	1551	0.3%	0.2	7	1682	0.4%	0.3	0.7480	0.6613	1.0000	0.5637

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Serotype-specific proportion and rate were not included as no significant change was observed in any non-PCV13 serotype

§Calculated by chi-square test or Fisher's exact test

Table 12.10 Change in Proportion and Rate of Meropenem-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	619	4941	12.5%	17.2	15	120	12.5%	0.6	8	64	12.5%	0.3	0.9927	1.0000	<.0001	0.1444
4	3	834	0.4%	0.1	0	33	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	0.2767	-
6B	50	563	8.9%	1.4	1	11	9.1%	0.0	1	4	25.0%	0.0	1.0000	0.4762	<.0001	1.0000
9V	59	686	8.6%	1.6	1	21	4.8%	0.0	1	5	20.0%	0.0	1.0000	0.3538	<.0001	1.0000
14	330	1443	22.9%	9.2	1	13	7.7%	0.0	2	5	40.0%	0.1	0.3193	0.1716	<.0001	1.0000
18C	0	375	0.0%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	-	-	-	-
19F	50	453	11.0%	1.4	10	27	37.0%	0.4	3	33	9.1%	0.1	0.0007	0.0089	0.0002	0.0441
23F	127	587	21.6%	3.5	2	8	25.0%	0.1	1	4	25.0%	0.0	0.6859	1.0000	<.0001	0.6177
New in PCV13	20	1247	1.6%	0.6	296	1473	20.1%	12.1	105	595	17.6%	4.1	<.0001	0.2024	<.0001	<.0001
1	0	151	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	3	301	1.0%	0.1	0	240	0.0%	0.0	0	207	0.0%	0.0	0.2582	-	0.2767	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	10	352	2.8%	0.3	0	42	0.0%	0.0	1	10	10.0%	0.0	0.6088	0.1923	0.0074	1.0000
7F	0	194	0.0%	0.0	0	559	0.0%	0.0	0	158	0.0%	0.0	-	-	-	-
19A	7	238	2.9%	0.2	296	606	48.8%	12.1	104	212	49.1%	4.1	<.0001	0.9577	<.0001	<.0001
Non-PCV◊	28	1694	1.7%	0.8	20	1552	1.3%	0.8	39	1682	2.3%	1.5	0.3904	0.0288	0.2482	0.0134
9A	7	39	17.9%	0.2	0	0	0.0%	0.0	0	0	0.0%	0.0	-	-	0.0465	-
35B	13	45	28.9%	0.4	15	65	23.1%	0.6	35	95	36.8%	1.4	0.4914	0.0650	0.1613	0.0072

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Serotype-specific proportion and rate were not included as no significant change was observed in any non-PCV13 serotype

§Calculated by chi-square test or Fisher's exact test

Table 12.11 Change in Proportion and Rate of Rifampin-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	20	4939	0.4%	0.6	0	120	0.0%	0.0	0	64	0.0%	0.0	1.0000	-	<.0001	-
4	9	833	1.1%	0.3	0	33	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	0.0135	-
6B	0	563	0.0%	0.0	0	11	0.0%	0.0	0	4	0.0%	0.0	-	-	-	-
9V	0	686	0.0%	0.0	0	21	0.0%	0.0	0	5	0.0%	0.0	-	-	-	-
14	4	1442	0.3%	0.1	0	13	0.0%	0.0	0	5	0.0%	0.0	1.0000	-	0.1518	-
18C	1	375	0.3%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	1.0000	-	1.0000	-
19F	4	453	0.9%	0.1	0	27	0.0%	0.0	0	33	0.0%	0.0	1.0000	-	0.1518	-
23F	2	587	0.3%	0.1	0	8	0.0%	0.0	0	4	0.0%	0.0	1.0000	-	0.5178	-
New in PCV13	2	1247	0.2%	0.1	0	1473	0.0%	0.0	0	597	0.0%	0.0	0.2101	-	0.5000	-
1	0	151	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	1	301	0.3%	0.0	0	240	0.0%	0.0	0	207	0.0%	0.0	1.0000	-	1.0000	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	1	352	0.3%	0.0	0	42	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	1.0000	-
7F	0	194	0.0%	0.0	0	559	0.0%	0.0	0	160	0.0%	0.0	-	-	-	-
19A	0	238	0.0%	0.0	0	606	0.0%	0.0	0	212	0.0%	0.0	-	-	-	-
Non-PCV◊	5	1693	0.3%	0.1	0	1552	0.0%	0.0	0	1682	0.0%	0.0	0.0635	-	0.0625	-

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Serotype-specific proportion and rate were not included as no significant change was observed in any non-PCV13 serotype

§Calculated by chi-square test or Fisher's exact test

Table 12.12 Change in Proportion and Rate of Quinupristin-Dalfopristin-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	5	4938	0.1%	0.1	0	120	0.0%	0.0	0	64	0.0%	0.0	1.0000	-	0.0625	-
4	0	833	0.0%	0.0	0	33	0.0%	0.0	0	10	0.0%	0.0	-	-	-	-
6B	0	563	0.0%	0.0	0	11	0.0%	0.0	0	4	0.0%	0.0	-	-	-	-
9V	1	686	0.1%	0.0	0	21	0.0%	0.0	0	5	0.0%	0.0	1.0000	-	1.0000	-
14	0	1442	0.0%	0.0	0	13	0.0%	0.0	0	5	0.0%	0.0	-	-	-	-
18C	0	374	0.0%	0.0	0	7	0.0%	0.0	0	3	0.0%	0.0	-	-	-	-
19F	4	453	0.9%	0.1	0	27	0.0%	0.0	0	33	0.0%	0.0	1.0000	-	0.1518	-
23F	0	587	0.0%	0.0	0	8	0.0%	0.0	0	4	0.0%	0.0	-	-	-	-
New in PCV13	2	1247	0.2%	0.1	0	1473	0.0%	0.0	0	596	0.0%	0.0	0.2101	-	0.5000	-
1	0	151	0.0%	0.0	0	23	0.0%	0.0	0	8	0.0%	0.0	-	-	-	-
3	0	301	0.0%	0.0	0	240	0.0%	0.0	0	207	0.0%	0.0	-	-	-	-
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	1	352	0.3%	0.0	0	42	0.0%	0.0	0	10	0.0%	0.0	1.0000	-	1.0000	-
7F	0	194	0.0%	0.0	0	559	0.0%	0.0	0	160	0.0%	0.0	-	-	-	-
19A	1	238	0.4%	0.0	0	606	0.0%	0.0	0	211	0.0%	0.0	0.2820	-	1.0000	-
Non-PCV◊	0	1694	0.0%	0.0	0	1551	0.0%	0.0	0	1677	0.0%	0.0	-	-	-	-

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Serotype-specific proportion and rate were not included as no significant change was observed in any non-PCV13 serotype

§Calculated by chi-square test or Fisher's exact test

Table 12.13 Change in Proportion and Rate of Tetracycline-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value§			
													Proportion		Rate	
Serotype	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	Resistant	Total*	%Resistant†	Rate‡	PCV7	PCV13	PCV7	PCV13
PCV7	477	4938	9.7%	13.3	33	120	27.5%	1.3	12	64	18.8%	0.5	<.0001	0.1885	<.0001	0.0017
4	15	833	1.8%	0.4	0	33	0.0%	0.0	1	10	10.0%	0.0	1.0000	0.2326	0.0014	1.0000
6B	106	563	18.8%	2.9	2	11	18.2%	0.1	1	4	25.0%	0.0	1.0000	1.0000	<.0001	0.6177
9V	30	686	4.4%	0.8	3	21	14.3%	0.1	1	5	20.0%	0.0	0.0694	1.0000	0.0002	0.3654
14	97	1441	6.7%	2.7	5	13	38.5%	0.2	2	5	40.0%	0.1	0.0013	1.0000	<.0001	0.2799
18C	2	375	0.5%	0.1	2	7	28.6%	0.1	0	3	0.0%	0.0	0.0017	1.0000	1.0000	0.2402
19F	111	453	24.5%	3.1	15	27	55.6%	0.6	5	33	15.2%	0.2	0.0004	0.0010	<.0001	0.0201
23F	116	587	19.8%	3.2	6	8	75.0%	0.2	2	4	50.0%	0.1	0.0013	0.5475	<.0001	0.1716
New in PCV13	43	1247	3.4%	1.2	326	1473	22.1%	13.3	150	595	25.2%	5.9	<.0001	0.1322	<.0001	<.0001
1	2	151	1.3%	0.1	1	23	4.3%	0.0	2	8	25.0%	0.1	0.3482	0.1557	1.0000	1.0000
3	12	301	4.0%	0.3	33	240	13.8%	1.3	36	207	17.4%	1.4	<.0001	0.2880	<.0001	0.8442
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	9	352	2.6%	0.3	1	42	2.4%	0.0	2	10	20.0%	0.1	1.0000	0.0910	0.0566	1.0000
7F	5	194	2.6%	0.1	1	559	0.2%	0.0	0	158	0.0%	0.0	0.0052	1.0000	0.4117	0.4901
19A	15	238	6.3%	0.4	290	606	47.9%	11.8	110	212	51.9%	4.3	<.0001	0.3121	<.0001	<.0001
Non-PCV◊	44	1694	2.6%	1.2	145	1552	9.3%	5.9	124	1681	7.4%	4.9	<.0001	0.0431	<.0001	0.2004
9A	12	39	30.8%	0.3	0	0	0.0%	0.0	0	0	0.0%	0.0	-	-	0.0023	-
15A	2	17	11.8%	0.1	98	107	91.6%	4.0	61	74	82.4%	2.4	0.0000	0.0638	<.0001	0.0014
15B/C/F	2	80	2.5%	0.1	5	72	6.9%	0.2	21	99	21.4%	0.8	0.2567	0.0095	0.1281	0.0024
23A	0	33	0.0%	0.0	14	94	14.9%	0.6	13	95	13.7%	0.5	0.0201	0.8122	<.0001	0.7676
NT	3	21	14.3%	0.1	5	20	25.0%	0.2	0	14	0.0%	0.0	0.4537	0.0629	0.2832	0.0283

*Total number of isolates excluding those with missing susceptibility test data

†Estimated based on assumption that isolates with missing susceptibility test data carried the same distribution of resistance as those with

‡Per 1,000,000 persons

◊Only serotypes with significant change in serotype-specific proportion or rate are individually listed below

§Calculated by chi-square test or Fisher's exact test

Table 13. Change in Proportion and Rate of Multidrug-Resistant Invasive *S. pneumoniae* Isolates in the US, by Serotype, 1998-1999, 2009, and 2012.

	1998/9				2009				2012				P-value*			
													Proportion		Rate	
Serotype	MDR	Total	% MDR	Rate†	MDR	Total	% MDR	Rate†	MDR	Total	% MDR	Rate†	PCV7	PCV13	PCV7	PCV13
ALL	1086	7887	13.8%	30.2	548	3145	17.4%	22.3	278	2351	11.8%	10.9	<.0001	<.0001	<.0001	<.0001
PCV7	935	4941	18.9%	26.0	42	120	35.0%	1.7	14	64	21.9%	0.5	<.0001	0.0654	<.0001	<.0001
4	7	834	0.8%	0.2	0	33	0.0%	0.0	1	10	10.0%	0.0	1.0000	0.2326	0.0465	1.0000
6B	157	563	27.9%	4.4	3	11	27.3%	0.1	3	4	75.0%	0.1	1.0000	0.2352	<.0001	1.0000
9V	93	686	13.6%	2.6	14	21	66.7%	0.6	3	5	60.0%	0.1	0.0000	1.0000	<.0001	0.0060
14	433	1443	30.0%	12.1	4	13	30.8%	0.2	2	5	40.0%	0.1	1.0000	1.0000	<.0001	0.4443
18C	0	375	0.0%	0.0	1	7	14.3%	0.0	0	3	0.0%	0.0	0.0183	1.0000	0.4057	0.4901
19F	109	453	24.1%	3.0	15	27	55.6%	0.6	4	33	12.1%	0.2	0.0003	0.0003	<.0001	0.0090
23F	136	587	23.2%	3.8	5	8	62.5%	0.2	1	4	25.0%	0.0	0.0210	0.5455	<.0001	0.1179
New in PCV13	117	1247	9.4%	3.3	337	1473	22.9%	13.7	134	598	22.4%	5.2	<.0001	0.8170	<.0001	<.0001
1	0	151	0.0%	0.0	1	23	4.3%	0.0	0	8	0.0%	0.0	0.1322	1.0000	0.4057	0.4901
3	7	301	2.3%	0.2	18	240	7.5%	0.7	19	207	9.2%	0.7	0.0044	0.5207	0.0014	0.9651
5	0	11	0.0%	0.0	0	3	0.0%	0.0	0	0	-	0.0	-	-	-	-
6A	91	352	25.9%	2.5	2	42	4.8%	0.1	2	10	20.0%	0.1	0.0023	0.1625	<.0001	1.0000
7F	0	194	0.0%	0.0	0	559	0.0%	0.0	0	160	0.0%	0.0	-	-	-	-
19A	19	238	8.0%	0.5	316	606	52.1%	12.9	113	213	53.1%	4.4	<.0001	0.8198	<.0001	<.0001
Non-PCV13‡	34	1699	2.0%	0.9	169	1552	10.9%	6.9	130	1689	7.7%	5.1	<.0001	0.0017	<.0001	0.0094
6C	4	38	10.5%	0.1	36	168	21.4%	1.5	26	135	19.3%	1.0	0.1250	0.6418	<.0001	0.1537
9A	14	39	35.9%	0.4	0	0	0.0%	0.0	0	0	0.0%	0.0	-	-	0.0020	-
15A	2	17	11.8%	0.1	95	107	88.8%	3.9	62	75	82.7%	2.4	<.0001	0.2379	<.0001	0.0039
23A	0	33	0.0%	0.0	13	94	13.8%	0.5	13	95	13.7%	0.5	0.0205	1.0000	<.0001	0.9194
NT	4	22	18.2%	0.1	5	20	25.0%	0.2	0	15	0.0%	0.0	0.7139	0.0570	0.4998	0.0283

*Calculated by chi-square test or Fisher's exact test for PCV7 and PCV13

†Per 1,000,000 persons

‡Only serotypes with significant change in serotype-specific proportion or rate are individually listed below

FIGURES

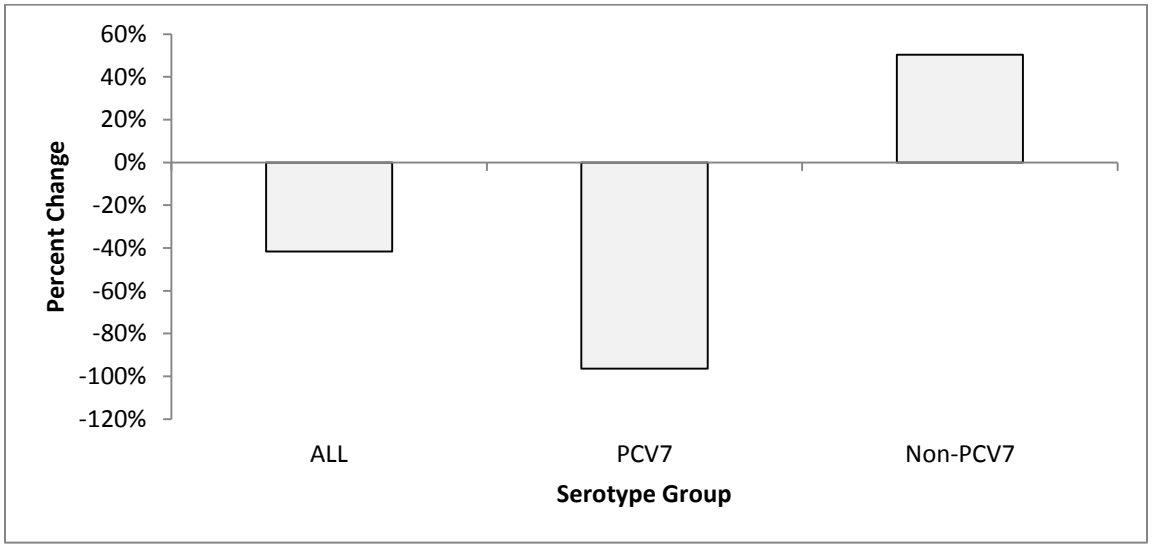

Figure 1. Percent Change in Invasive Pneumococcal Disease in the US following Introduction of PCV7, 1998-1999 and 2009.

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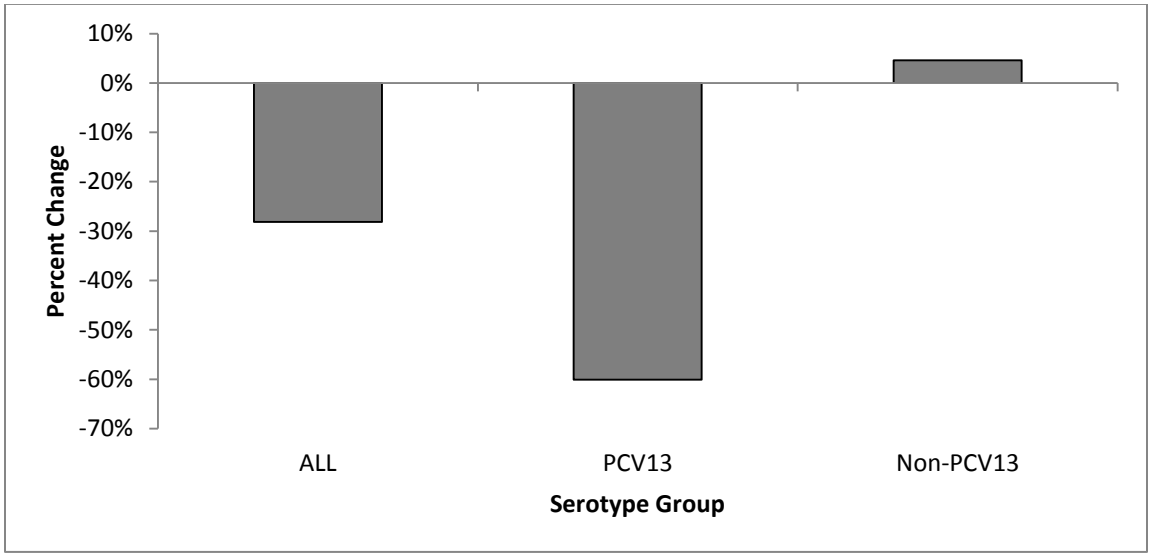

Figure 2. Percent Change in Invasive Pneumococcal Disease in the US following Introduction of PCV13, 2009 and 2012.

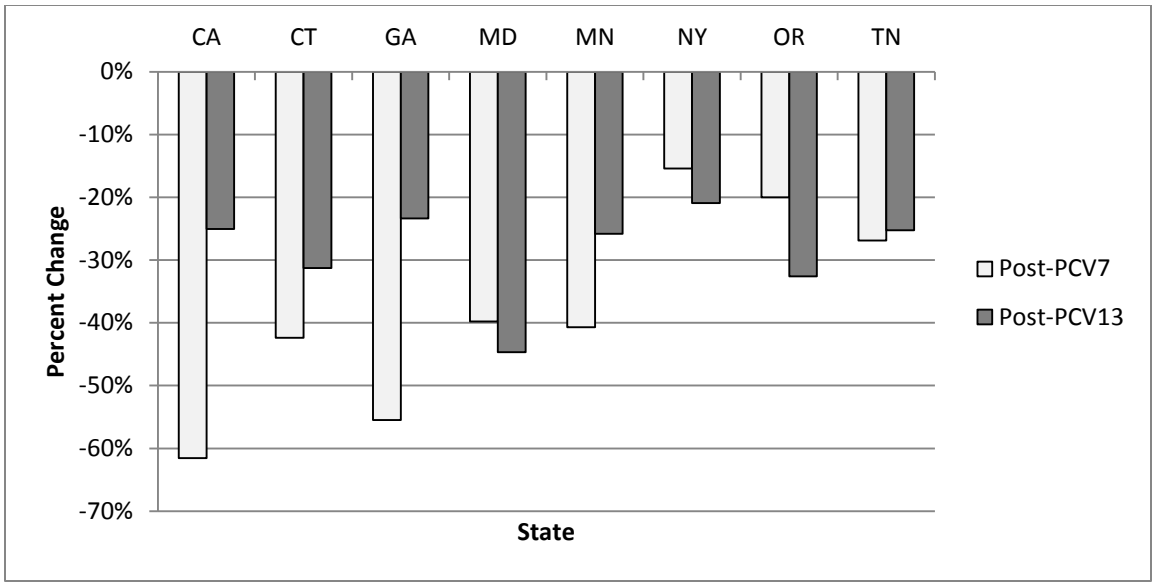

Figure 3. Percent Change in Invasive Pneumococcal Disease in the US, by State, 1998-1999, 2009, and 2012.

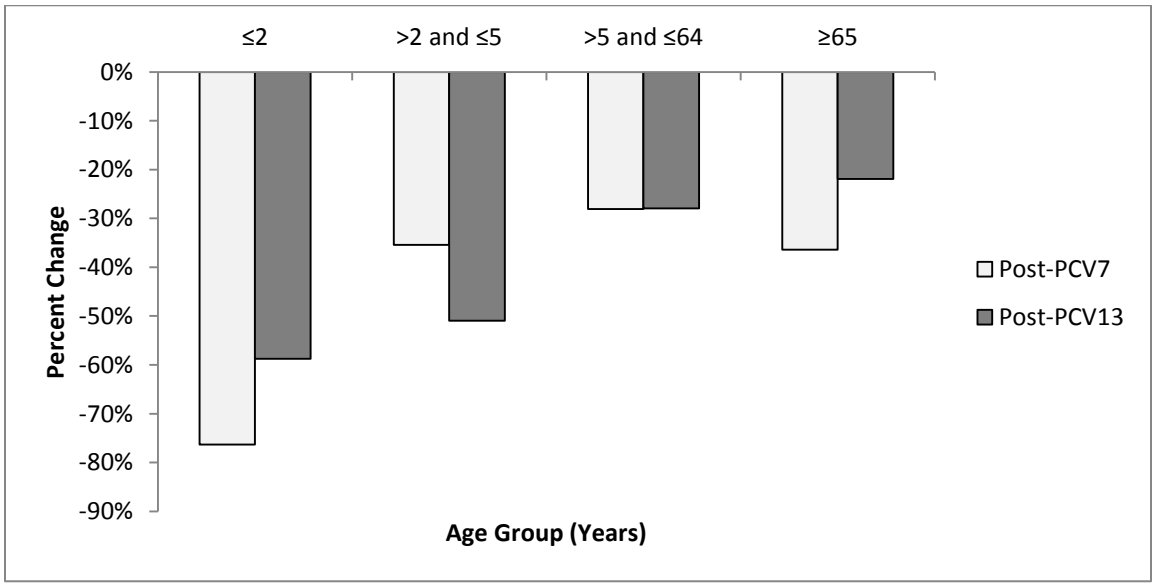

Figure 4. Percent Change in Invasive Pneumococcal Disease in the US, by Age Group, 1998-1999, 2009, and 2012.

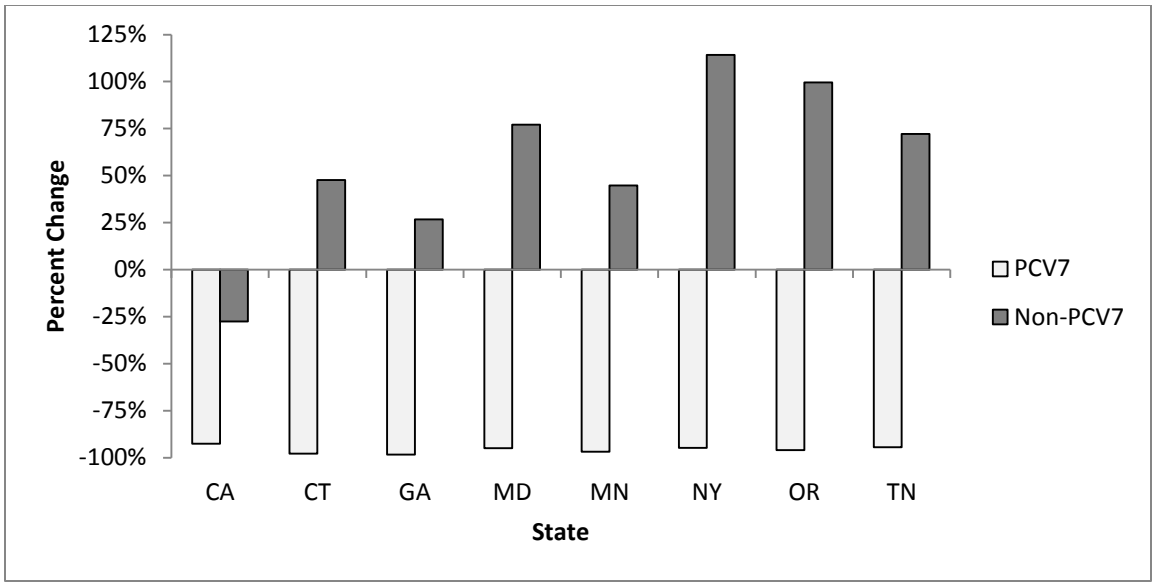

Figure 5. Percent Change in Invasive Pneumococcal Disease in the US following PCV7 Introduction, by State, PCV7 and Non-PCV7 Serotypes, 1998-1999 and 2009.

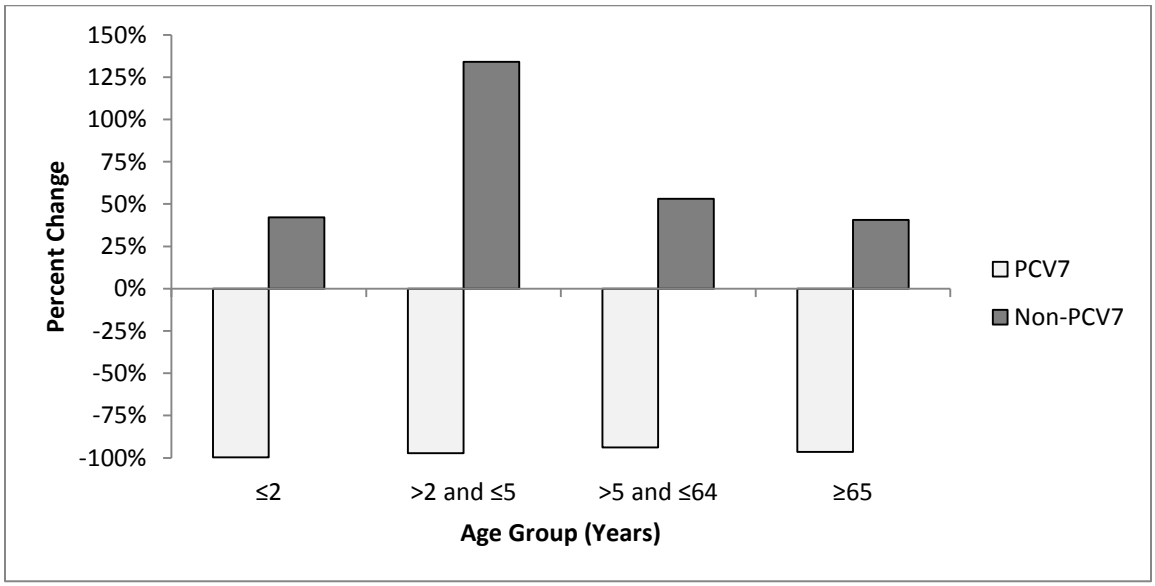

Figure 6. Percent Change in Invasive Pneumococcal Disease in the US following PCV7 Introduction, by Age Group, PCV7 and Non-PCV7 Serotypes, 1998-1999 and 2009.

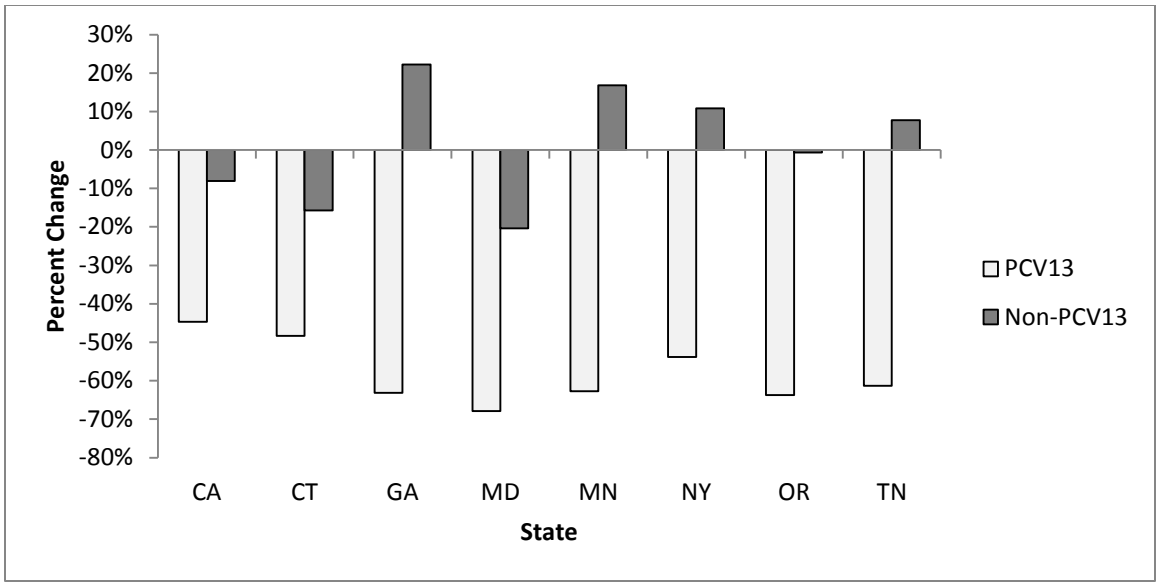

Figure 7. Percent Change in Invasive Pneumococcal Disease in the US following PCV13 Introduction, by State, PCV13 and Non-PCV13 Serotypes.

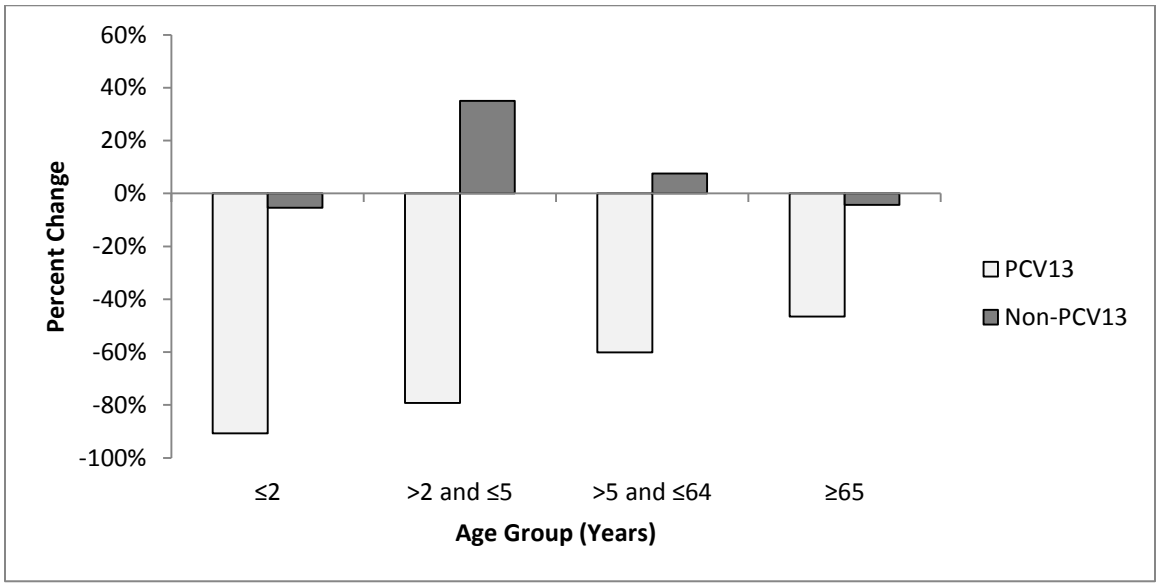

Figure 8. Percent Change in Invasive Pneumococcal Disease in the US following PCV13 Introduction, by Age Group, PCV13 and Non-PCV13 Serotypes, 2009 and 2012.

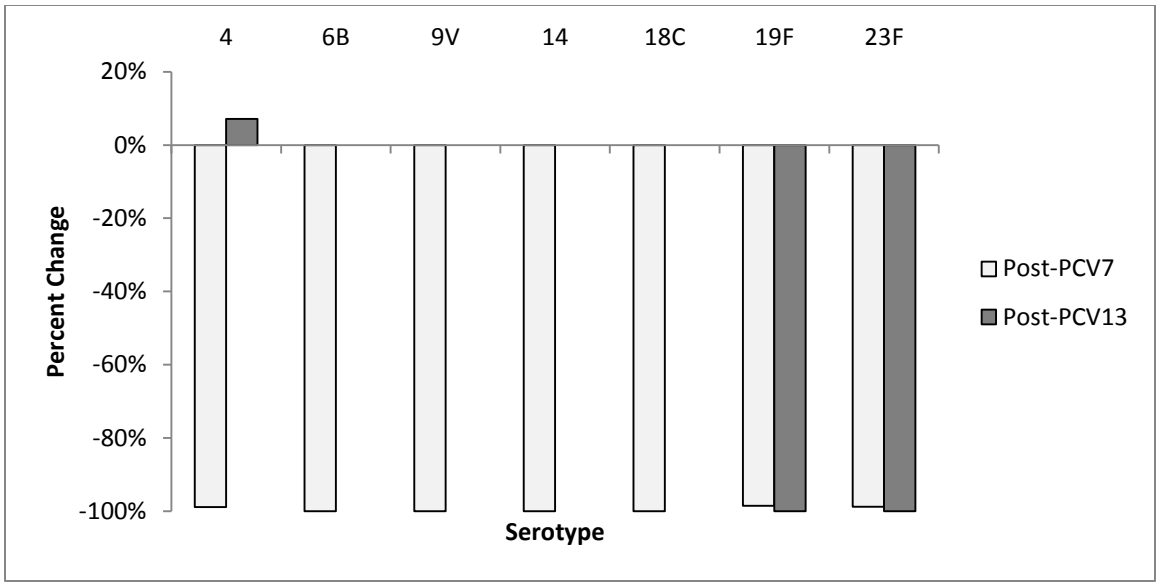

Figure 9. Percent Change in Invasive Pneumococcal Disease in the US for Children ≤2 years, by PCV7 Serotype, 1998-1999, 2009, and 2012.

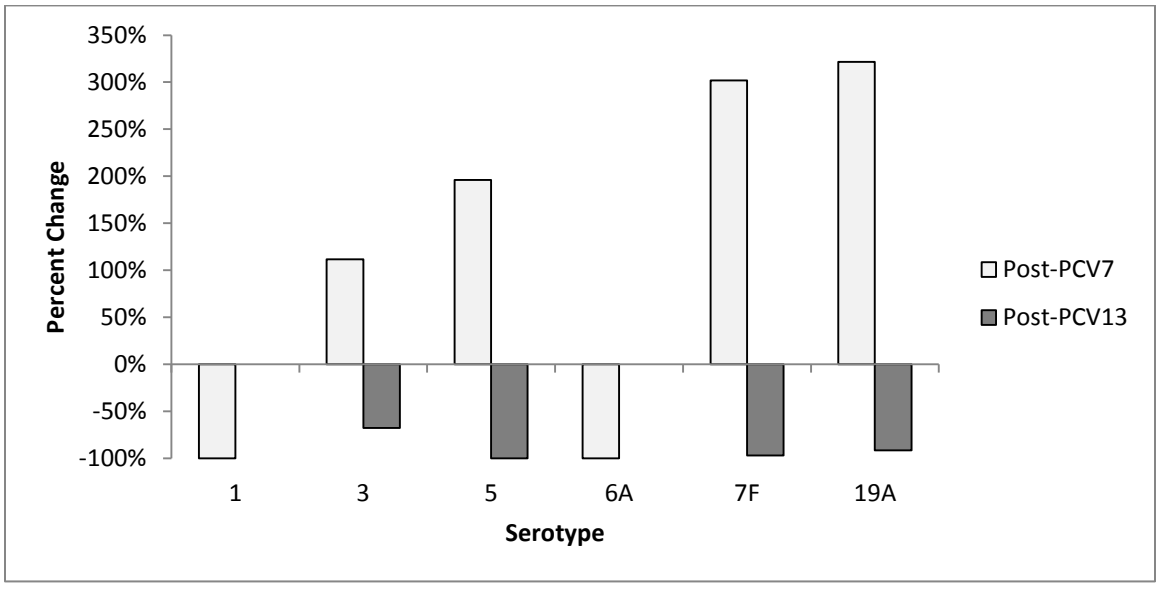

Figure 10. Percent Change in Invasive Pneumococcal Disease in the US, by Serotype New in PCV13, 1998-1999, 2009, and 2012.

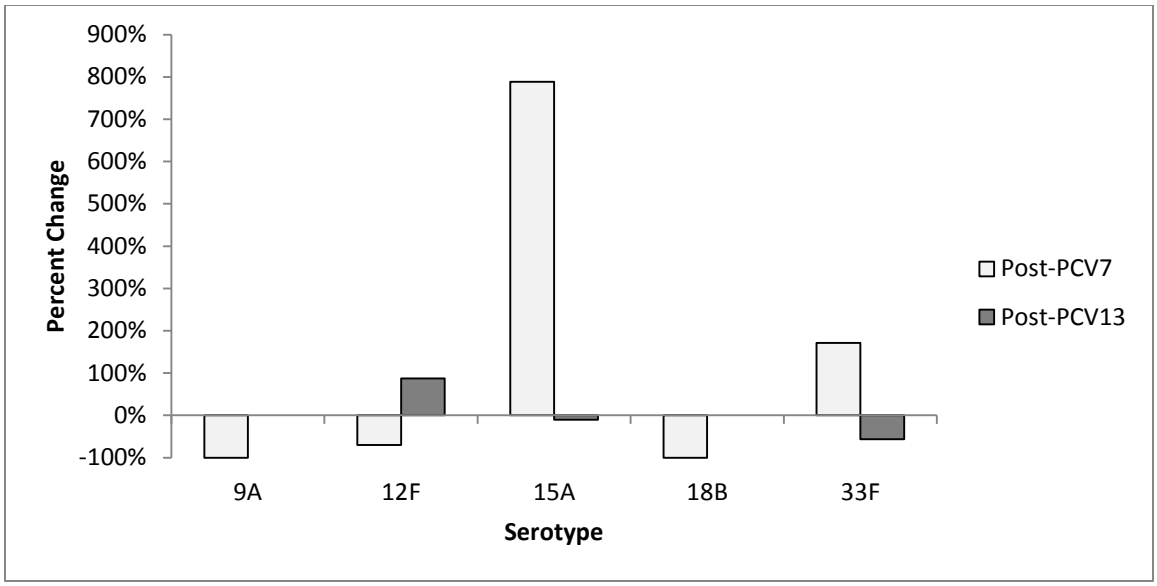

Figure 11. Percent Change in Invasive Pneumococcal Disease in the US, by Non-PCV13 Serotype, 1998-1999, 2009, and 2012.

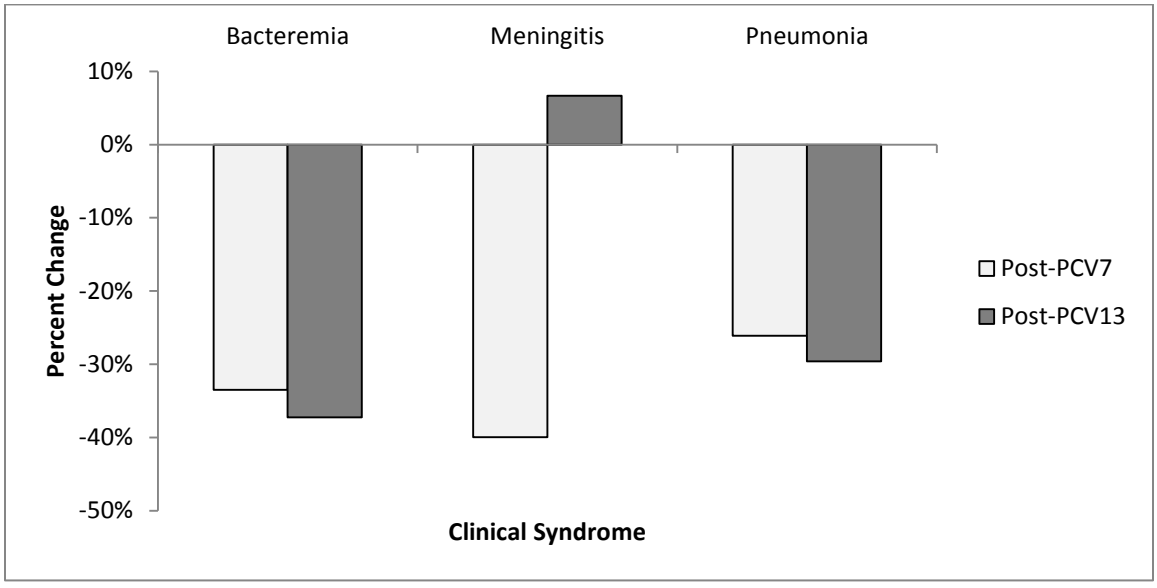

Figure 12. Percent Change in Invasive Pneumococcal Disease in the US, by Clinical Syndrome, 1998-1999, 2009, and 2012.

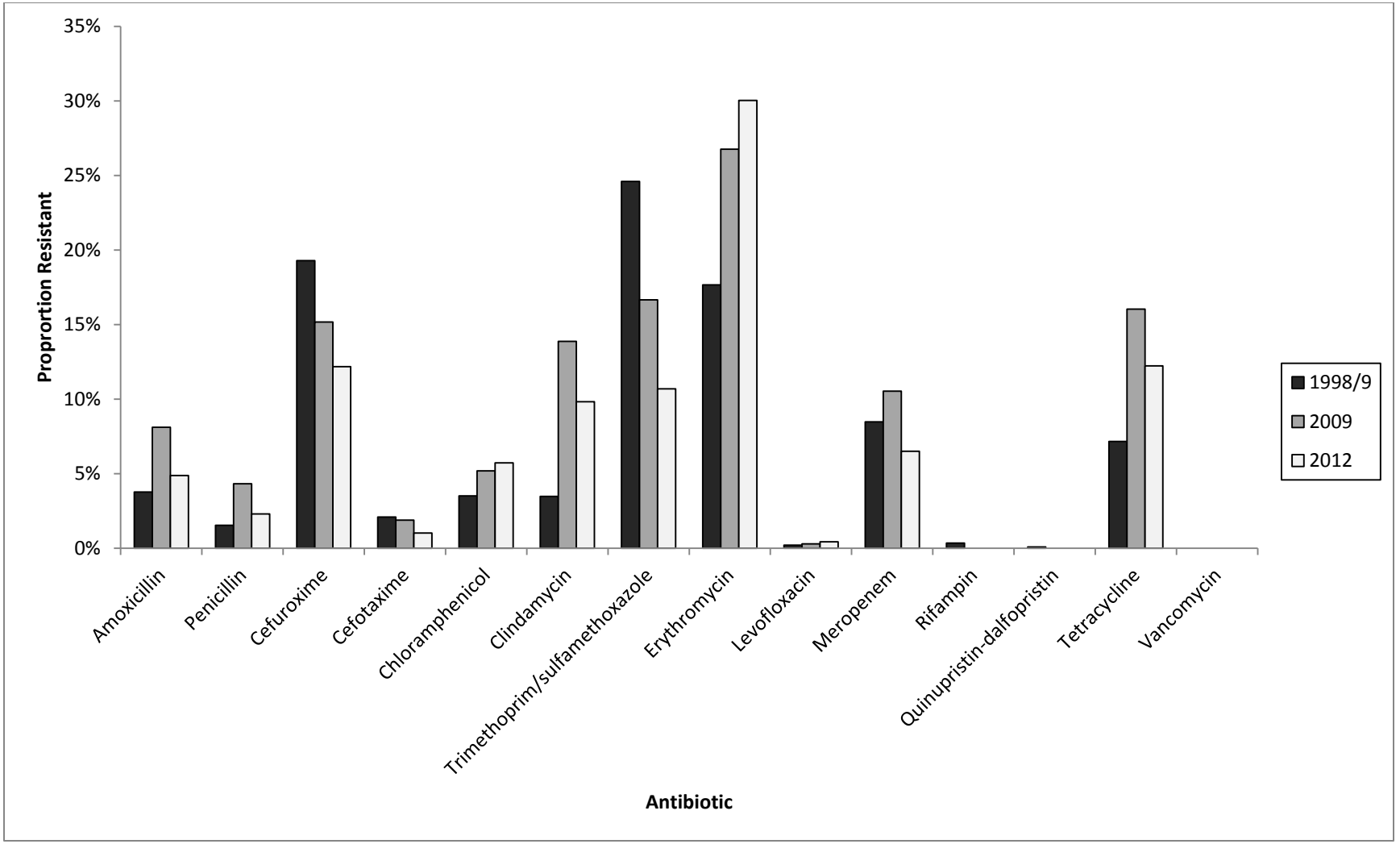

Figure 13. Proportion of Antimicrobial-Resistant *S. pneumoniae* Isolates in the US, 1998-1999, 2009, and 2012.

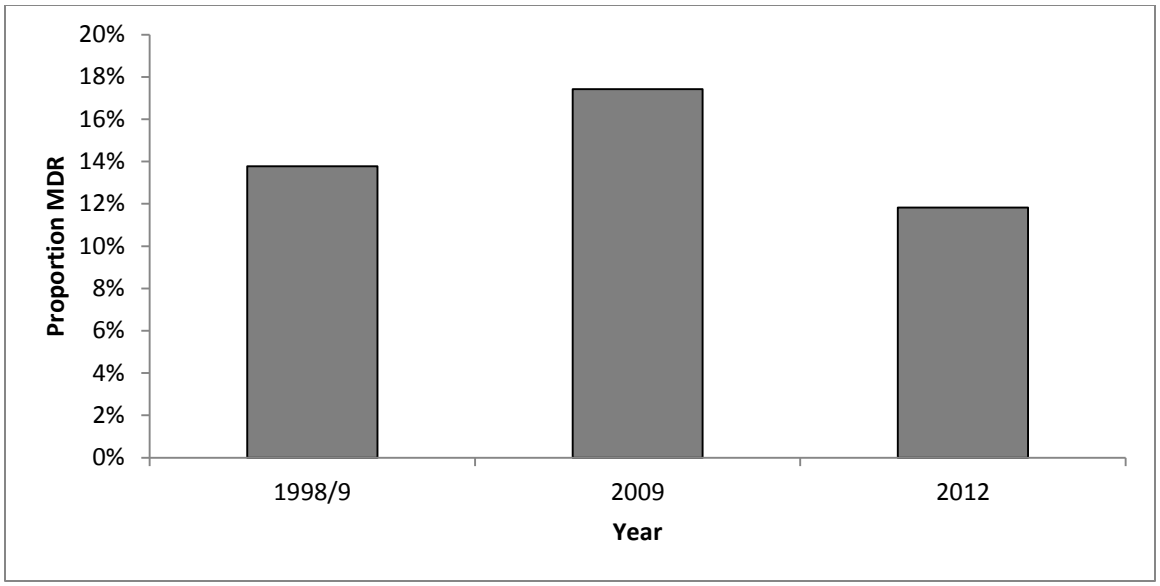

Figure 14. Proportion of Multidrug-Resistant *S. pneumoniae* Isolates in the US, 1998-1999, 2009, and 2012.

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