

The Impact of the Pneumococcal Conjugate Vaccine on Antimicrobial Resistance in the United States Since 1996: Evidence for a Significant Rebound by 2007 in Many Classes of Antibiotics

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Background: The impact of the introduction of the pneumococcal conjugate vaccine over antimicrobial resistance has not been well established. The present study models the changes in resistance over time for all major classes of antibiotics.

Methods: Susceptibility data on a total of 129,652 isolates from The Surveillance Network[®] surveillance database during the period 1996–2007 were available for analysis, as well as age, specimen source, inpatient or outpatient location, and census region. Cubic splines in a logistic regression mixed model were used to model changes of the resistance rates over time in the United States, taking into account risk factors, so that separate adjusted curves were modeled for each antibiotic.

Results: Yearly resistance prevalence to most antibiotics had been increasing in the period 1996–2001. Adjusted prevalence rates in a multivariate model declined in the period 2001–2004 for penicillin, erythromycin, amoxicillin/clavulanate, trimethoprim/sulfamethoxazole, tetracycline, ceftriaxone, and multidrug. These same antibiotics showed a significant rebound for the period 2004–2007, with the largest overall increase for erythromycin, followed by amoxicillin/clavulanate, tetracycline, multidrug, penicillin, trimethoprim/sulfamethoxazole, and ceftriaxone. Changes in both decline and rebound were more marked for children <5 years old and for otitis media isolates.

Conclusion: The indirect effect of the pneumococcal conjugate vaccine introduction on yearly resistance prevalence for several antibacterials as well as for multidrug resistance is one of blunting of a prior sustained increase, with a significant but short-lived decrease in resistance rates, and a significant rebound in adjusted rates for the period 2004–2007.

Introduction

S *TREPTOCOCCUS PNEUMONIAE* IS one of the most important bacterial causes of community-acquired pneumonia, otitis media, and meningitis, affecting children and adults worldwide.^{8,23} Since the introduction of the seven-valent pneumococcal conjugate vaccine in 2000, substantial decreases in the U.S. rates of invasive pneumococcal disease have been observed among children,²⁸ with a larger than expected herd or indirect effect among unvaccinated older children, adults, and the elderly.^{4,11}

Before the introduction of the conjugate vaccine, resistance to macrolides, penicillin, and trimethoprim/sulfamethoxazole (TMP/SMX) had been steadily increasing to alarming levels,¹⁹ especially among young children and acute otitis media

isolates.¹⁵ More troublesome was the emergence and dissemination of multidrug-resistant (MDR) strains throughout the United States, defined as resistance to three or more antibiotic classes, reaching levels of 21% by 1999.¹⁹ Since MDR phenotypes involve several drug classes, including macrolides, β -lactams, sulfonamides, and tetracyclines, few agents, mainly fluoroquinolones and third-generation cephalosporins, have maintained a high level of antipneumococcal activity.²⁷

Population-based surveillance studies carried out after the introduction of the conjugate vaccine in the United States have shown steep declines in the incidence of drug-resistant *S. pneumoniae* for several antimicrobial classes.¹⁴ Among children <2 years of age, disease caused by macrolide-resistant strains decreased fivefold from 1999 to 2002.²⁵

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Overall yearly period prevalence resistance rates for several antimicrobial classes in children <5 years of age and among those with invasive disease also have decreased accordingly.²⁰

In response to the selective pressure of the conjugate vaccine on vaccine serotypes, increased prevalence carriage of nonvaccine serotypes including strains harboring reduced antibiotic susceptibility has been observed.²⁰ Resistance has apparently increased due to the expansion of previously recognized clones of nonpneumococcal conjugate vaccine 7 isolates, particularly serotypes 19A, 15A, and 35B.^{7,12}

Demonstrating the effect of the vaccine on resistance rates over time necessitates the availability of certain amount of data before the introduction of the vaccine, and use of a statistical model that takes into account the fact that resistance rates are correlated over time and do not increase or decrease linearly, and that temporal changes may be location dependent (inpatient vs. outpatient). The source of the isolate, the age group, and the region in the country also need to be taken into account, since they have been shown to be independent risk factors that may have been impacted by the vaccine; for example, the effect is presumably more important among infants than adults.

The objective of the present study is to estimate and contrast the changes over time in *S. pneumoniae* antimicrobial resistance in the United States before and after the introduction of the seven-valent pneumococcal conjugate vaccine, through an appropriate nonlinear model after adjusting for other factors that may affect resistance.

Subjects and Methods

The Surveillance Network[®] (TSN; Eurofins Medinet, Washington, DC) was the data source used for this investigation and analysis. TSN is an electronic database of strain-specific, qualitative, and quantitative antimicrobial susceptibility test data reported by clinical laboratories in North America that has been used extensively in the past²⁶ to evaluate various trends regarding antimicrobial susceptibility. In addition to antimicrobial susceptibility profiles, other query parameters that were used individually or in any combination for analysis of antimicrobial susceptibility data included organism identification, the nine regions of the U.S. Census Bureau, age, location (inpatient or outpatient), and specimen source.

This study focused specifically on *S. pneumoniae* and used TSN data collected from 1996 to 2007. Multidrug resistance was defined as full resistance (*i.e.*, did not include isolates categorized as intermediate susceptibility) to three or more antibiotic classes: penicillins, cephalosporins, macrolides, quinolones, tetracyclines, and sulfas. Only strains tested simultaneously against three or more antimicrobial agents of different classes were included in the multidrug resistance analysis of prevalence and distribution of resistance. The overall prevalence of *S. pneumoniae* isolated from inpatient and outpatient specimens was calculated by using all organism groups and species isolated from each patient group as the denominator. The outpatient designation indicates that the specimen submitted for culture was obtained from subjects seen in an outpatient setting.

Age was categorized into four groups: <5 years old, 5–18 years old, 19–65 years old, and older than 65. Four categories of clinical specimen source were analyzed and included blood/cerebrospinal fluid [CSF] (invasive), sputum, acute

otitis media, and nasopharyngeal isolates. Antimicrobials considered for the analysis were penicillin ($\geq 2 \mu\text{g/ml}$), erythromycin (≥ 1), tetracycline (≥ 8), ceftriaxone (≥ 4), TMP/SMX (≥ 4), clindamycin (≥ 0.5), levofloxacin (> 8), and amoxicillin/clavulanate (≥ 8 , amox/clav). The same Clinical and Laboratory Standards Institute breakpoints⁵ were used for the categorization of resistance for all years.

The levels and trends in antimicrobial resistance are presented as yearly prevalence $\pm 95\%$ confidence interval (95% CI). To evaluate these trends, cubic and linear splines were used to model the changes over time. Each antimicrobial has its own intercept and curve shape, given by a four-knot cubic spline or a linear spline that hypothesizes an initial rise, a decline, and subsequent rise in the rate of resistance. The cubic spline is used to get the best shape for the curves and the linear splines for the significance or lack thereof of specific changes over time.

The cubic or linear splines were included in a logistic regression model to examine the association between time and various risk factors such as age group, source of the isolate, location (inpatient or outpatient), and census region. Since the data from year to year are not independent, mixed models were used to take into account the dependence of resistance prevalence from the current year to the past. STATA 10[®] (StataCorp, College Station, TX) was used to estimate adjusted resistance rates and 95% CIs.

Results

The study consisted of 129,652 unique *S. pneumoniae* isolates, with an average of 10,804 per year (range

TABLE 1. CHARACTERISTICS OF THE ISOLATES: AGE GROUP, SOURCE, LOCATION, AND U.S. CENSUS REGION

Variable	Number of isolates	Percentage
Age groups		
<5	34,620	26.7
6–18	8,984	6.9
19–65	51,247	39.5
65+	34,801	26.8
Source		
Blood/CSF	38,291	29.5
Sputum	40,799	31.5
Nasopharynx	25,733	19.8
Ear	6,619	5.1
Other	18,210	14.0
Location		
Inpatient	69,972	54.0
Outpatient	59,680	46.0
Region		
East North Central	15,295	11.8
East South Central	8,472	6.5
Mid Atlantic	10,983	8.5
Mountain	12,969	10
New England	3,712	2.9
Pacific	20,578	15.9
South Atlantic	25,732	19.6
West North Central	11,490	8.9
West South Central	20,421	15.8

CSF, cerebrospinal fluid.

TABLE 2. OVERALL, UNADJUSTED (CRUDE) RESISTANCE RATES BY YEAR AND ANTIBIOTIC

Year	Penicillin	Erythromycin	Ceftriaxone	Tetracycline	TMP/ SMX	Amox/ clav	Levofloxacin	Clindamycin	Multidrug resistance
1996	15.6	18.3	6.3	20.5	34.8	15.5	a	a	14.6
1997	18.9	24.8	6.6	19.2	34.8	18.1	0.6	a	16.5
1998	16.5	27.0	5.0	18.0	34.8	18.6	0.5	a	16.8
1999	21.3	31.5	5.6	19.9	38.2	18.2	1.0	a	20.2
2000	23.2	33.6	5.2	20.0	36.7	9.0	1.2	a	20.8
2001	22.8	34.3	4.4	19.3	36.1	4.2	1.3	a	21.0
2002	17.7	30.7	1.4	17.2	29.0	2.5	1.0	9.7	16.4
2003	15.4	31.4	1.4	16.8	27.2	2.7	1.1	11.6	16.2
2004	15.6	31.5	1.6	15.8	26.1	4.6	1.2	13.2	16.6
2005	15.3	35.6	1.3	19.6	25.8	6.3	0.7	16.2	19.0
2006	15.2	36.1	1.3	20.4	26.1	8.4	0.8	18.0	19.3
2007	17.8	37.1	1.7	22.0	27.2	11.6	0.8	22.9	19.3

^aNo available isolates for these years.
 TMP/SMX, trimethoprim/sulfamethoxazole; amox/clav, amoxicillin/clavulanate.

3,141–14,138). The lowest number was for 1996. There were >10,000 isolates for each year starting in 1999. Average age of the subjects was 41.14 ± 31.49 standard deviation. Other characteristics of the isolates can be seen in Table 1.

The unadjusted, crude yearly resistance rates for most antimicrobials studied showed a constant increase since 1996, with a peak between 1998 (amox/clav) and 2001 (erythromycin), a decline that reaches a nadir between 2003 (penicillin) and 2004 (tetracycline), and a rebound that reaches its maximum in 2007. Exceptions to this rule are ceftriaxone, which had been declining slowly since 1996, faster after 2002 and showed a very limited rebound in 2007, and clindamycin, which had been increasing steadily since 2002 (no data are available before 2002). Levofloxacin resistance has had little modification over the years, with a peak of 1.3% in 2001, and very little change afterward, 1.2% in 2004 and 0.8% in 2007. Multidrug resistance follows a similar pattern as of penicillin and erythromycin as is depicted in Table 2.

The changes of crude resistance rates in children <5 years old can be seen in Table 3. The rebound in the period 2004–2007 is close to the prior nadir in erythromycin, amox/clav, and tetracycline. Note the sharp and significant increase in clindamycin resistance.

These crude estimates need to be adjusted for slight changes in age distribution, source, and location that tend to occur over time and place. A multivariate model that contains all risk factors with a four-knot cubic spline can be seen in Fig. 1 for three antibiotics to demonstrate how the model applies to trends of different shapes. The nonlinear model adequately showed the initial rise in erythromycin and penicillin and the slight decline in ceftriaxone, and the subsequent fall and rise in the adjusted rate of resistance. The model fits the data well as evidenced by the 95% CIs. Moreover, every curve has its own distinct shape according to the changes over time of each particular antibiotic and the adjustment provided by other risk factors.

The multivariate model can be used to test for each rise and decline taking advantage of adjusted rates for all time and the fact that the rates themselves are correlated. This particular statistical query utilizes all the data and not specific points in time and tests the shifts in the nonlinear movement of the curves. These differences and their respective 95% CIs for overall estimates are shown in Fig. 2.

The difference in the coefficient for change can be considered statistically significant when the CI for the percent difference in the graph does not contain zero. Before 2001 the largest significant rise in resistance was among the

TABLE 3. OVERALL, UNADJUSTED (CRUDE) RESISTANCE RATES BY YEAR AND ANTIBIOTIC IN CHILDREN <5 YEARS OF AGE

Year	Penicillin	Erythromycin	Ceftriaxone	Tetracycline	TMP/ SMX	Amox/ clav	Levofloxacin	Clindamycin	Multidrug resistance
1996	19.8%	20.3%	8.3%	21.6%	46.5%	14.6%	a	a	18.2%
1997	22.0%	29.3%	8.2%	16.3%	47.8%	24.6%	a	a	19.8%
1998	20.7%	35.3%	7.5%	21.0%	49.4%	27.7%	a	a	23.1%
1999	32.0%	44.7%	8.9%	21.8%	56.3%	25.6%	0.6%	a	29.8%
2000	32.7%	46.6%	8.0%	24.7%	53.7%	18.5%	0.2%	a	28.7%
2001	32.0%	44.9%	7.0%	24.9%	48.8%	4.6%	0.3%	a	29.5%
2002	24.8%	40.2%	2.3%	21.3%	41.0%	4.1%	0.2%	12.2%	23.5%
2003	20.7%	37.5%	2.6%	19.5%	34.7%	5.5%	0.7%	14.0%	21.2%
2004	21.1%	38.1%	2.6%	19.0%	35.3%	8.3%	0.4%	18.2%	22.1%
2005	20.6%	40.9%	2.1%	22.4%	33.8%	10.1%	0.1%	23.7%	24.0%
2006	21.3%	44.8%	2.0%	25.9%	38.5%	17.4%	0.5%	26.7%	26.1%
2007	27.6%	45.7%	3.1%	30.4%	41.1%	21.4%	0.6%	34.2%	27.9%

^aNo available isolates for these years.

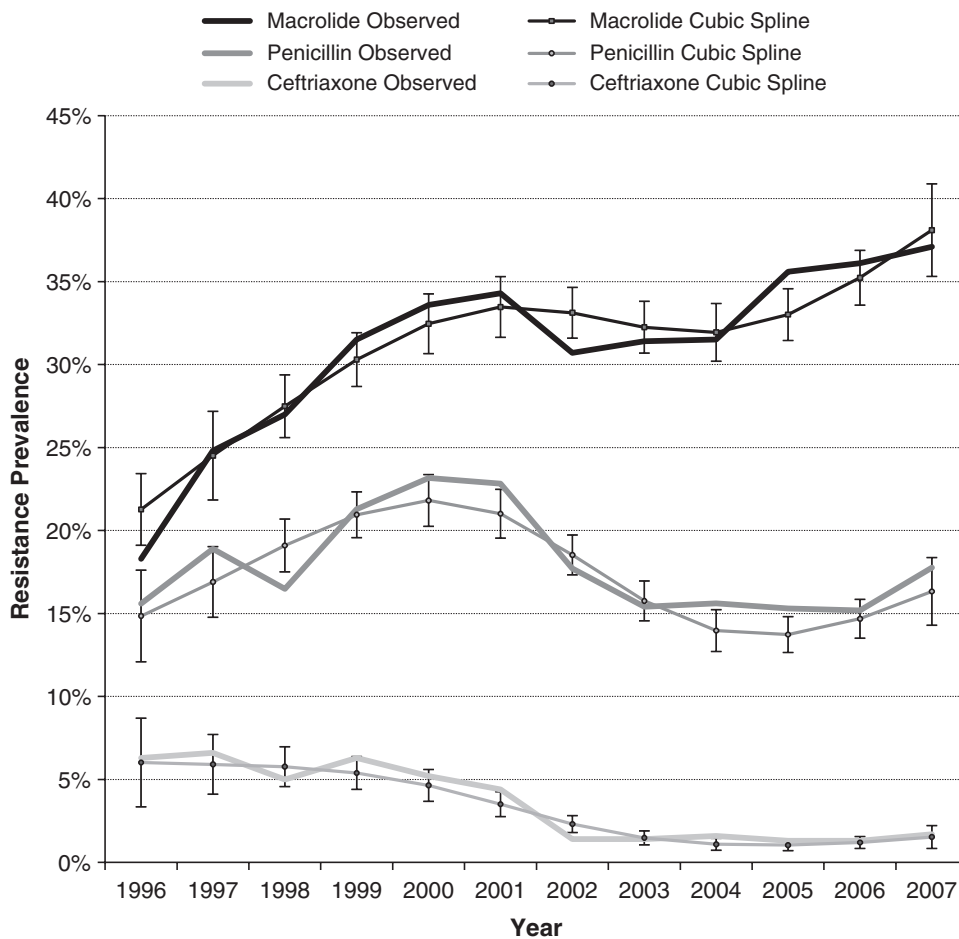


FIG. 1. Crude and adjusted resistance prevalence by year.

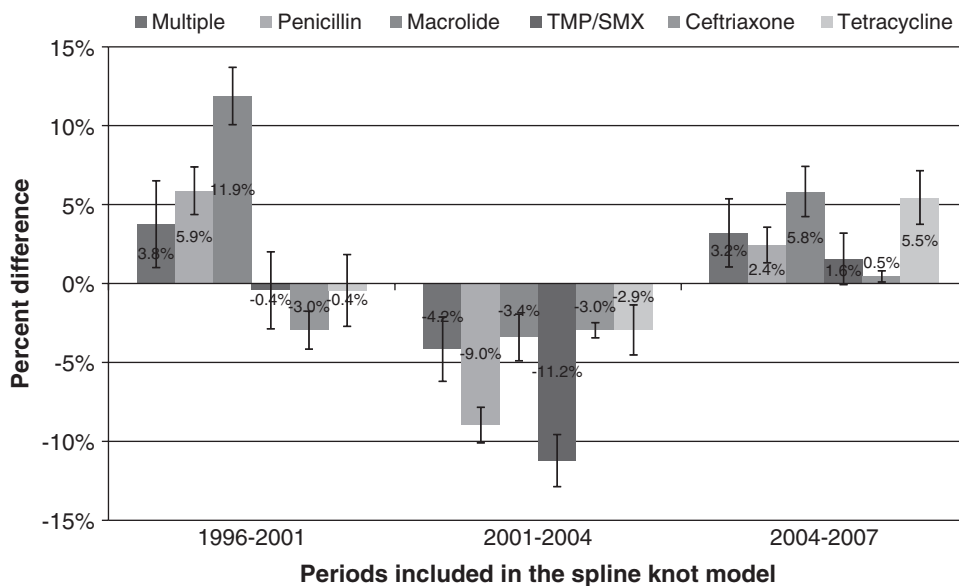


FIG. 2. Differences between adjusted estimates for resistance rates over time for acute otitis medium isolates.

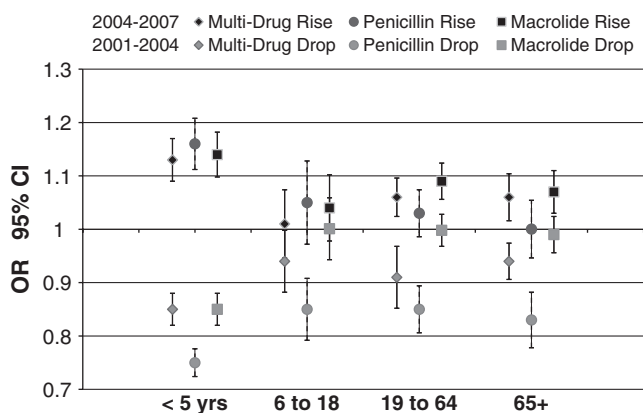


FIG. 3. Odds of increasing or decreasing resistance in a multivariate model in two periods of time.

macrolides, while there was no change in TMP/SMX and tetracycline. In the period immediately after the introduction of the conjugate vaccine, the graph shows the greatest declines for penicillin and TMP/SMX, while the smallest (although still statistically significant) correspond to macrolides and tetracycline. In the period after 2004, there are statistically significant rebounds for penicillin, macrolide, and tetracycline as depicted in Fig. 2.

Not included in the analysis shown in Fig. 2 is amox/clav because of a vastly different curve, with a small rise between 1996 and 1999, a sixfold drop to 2002 and a fourfold rise to 2007. Levofloxacin has also a different curve, increasing slowly until 2001 (1.1%, 95% CI 0.8–1.3%) with a small but borderline decline in a multivariate model by 2007 (0.6%, 95% CI 0.5–0.8%). Clindamycin is a special case since it shows a strong linear trend. A linear multivariate model without splines for clindamycin shows a significant twofold increase between 2002 and 2007 (odds ratio [OR] 2.1, 95% CI 2.0–2.2).

The changes over time are more marked for children <5 years old when compared to older children and adults. This is the case for the odds of decreasing resistance rates during the period 2001–2004, as well as for the odds of increasing resistance rates during the period 2004–2007. Figure 3 shows the odds of a rise in resistance as values >1 and the odds of a decline in resistance as values <1 for penicillin, macrolide (erythromycin), and multidrug. The largest effects are seen in children <5 years old, with smaller effects among

those 6–18 years old (most CIs include 1), and significant rebounds among macrolide and MDR isolates in adults and the elderly.

The effect of age group membership over the observed temporal changes is one of intensity. In a multivariate model, after adjusting for other risk factors, temporal changes are more marked in children <5 years old than other age groups but still follow the same trends. There are other significant risk factors, such as location (outpatient or inpatient), source of the isolate, and census region. These risk factors change the size of the resistance rates, but have no impact on the relative temporal changes and age effect (the curves are parallel). As an example, the size of the impact of location and source for selected antibiotics and multidrug resistance can be seen in Table 4 with source having larger ORs.

The pattern over time of invasive isolates (blood/CSF) is similar in shape as overall rates, but with significantly lower resistance rates, with the most notable difference being smaller changes in amox/clav but with a sharply rising increase in clindamycin resistance. This effect is more clearly seen in crude rates as shown in Fig. 4. Using meningeal breakpoints ($\geq 0.12 \mu\text{g/ml}$) for penicillin CSF isolates does not change the shape of the curve, only the relative size of the numbers, with 2004 values of 35.2% (38/108) and 38.1% for 2007 (40/105).

Census region follows the same pattern in a multivariate model of no effect modification for the relative changes produced by time and age group membership. By 2007, those isolates that came from the South Atlantic East South Central regions were 2.4 times more likely (95% CI 1.98–2.89) to be penicillin resistant than those from the Mountain-Pacific regions. The OR for erythromycin was 2.8 (95% CI 2.4–3.3) for the same comparison. Ceftriaxone and multiple resistance followed the same pattern, but there were no significant differences among regions for TMP/SMX and tetracycline.

Discussion

This study has taken advantage of a very large database of U.S. isolates, an appropriate statistical model that takes into account the correlation of resistance rates over time and place, and the availability of important population-based risk factors to generate adjusted period prevalence rates of antimicrobial resistance in *S. pneumoniae*.

The indirect impact of the introduction of the pneumococcal conjugate vaccine on penicillin, erythromycin,

TABLE 4. INDEPENDENT EFFECT OF LOCATION AND SOURCE OF THE ISOLATE AMONG SELECTED ANTIBIOTICS

	Penicillin	Erythromycin	Ceftriaxone	Multidrug resistance
Location				
Inpatient	Referent	Referent	Referent	Referent
Outpatient	0.95 (0.91–0.98)	0.96 (0.93–0.99)	0.88 (0.81–0.98)	1.01 (0.98–1.05)
Source				
Invasive (blood/CSF)	Referent	Referent	Referent	Referent
Sputum	1.68 (1.60–1.77)	1.64 (1.57–1.71)	1.43 (1.25–1.64)	1.87 (1.78–1.95)
Nasopharynx	1.55 (1.47–1.65)	1.69 (1.61–1.78)	1.71 (1.46–1.99)	1.83 (1.74–1.93)
Ear	3.17 (2.95–3.42)	2.93 (2.72–3.14)	2.93 (2.42–3.52)	3.04 (2.84–3.26)

OR \pm 95% CI in a multivariate model containing age, source, location, census region, and cubic splines. OR, odds ratio; CI, confidence interval.

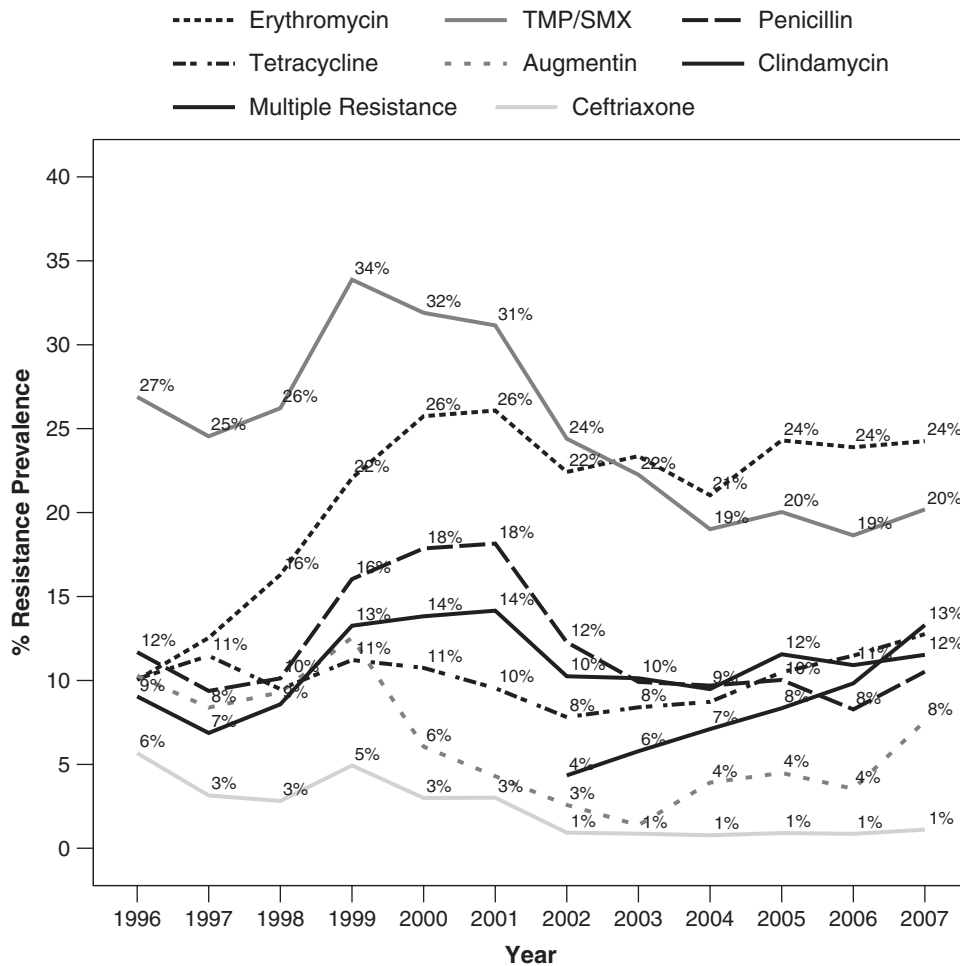


FIG. 4. Unadjusted resistance rates for invasive (blood/cerebrospinal fluid) isolates over time.

TMP/SMX, amox/clav, tetracycline, and multidrug resistance appears to be one of blunting of what was perceived as an inexorable increase until 1999, with a significant but short-lived decrease in resistance that has ostensibly run its course. Penicillin, erythromycin, and tetracycline showed a significant rebound while TMP/SMX and ceftriaxone were flat as evidenced by the changes observed for the period 2004–2007. The notable exception is levofloxacin, which did not demonstrate significant change over the 10-year period studied.

The emergence of resistance in *S. pneumoniae* is believed to be caused by a direct effect of cumulative antimicrobial consumption.²¹ Most of the resistance in the prevaccine period was found in strains carried in the nasopharynges of children, where there was an association with vaccine serotypes 6A, 6B, 9V, 19F, and 23F and high-level penicillin as well as multidrug resistance.¹⁰ Moreover, pneumococcal infections of the upper respiratory tract were more often due to the colonizing serotypes and were more likely to be antibiotic resistant.¹

It is a well-known fact that young children play an important role in the transmission of pneumococcal infections within the community³ as evidenced by increased carriage rates in adults with constant contact with children,¹³ and the key role of day care centers as sources of many reported outbreaks of drug-resistant disease in the United States.^{2,9}

Not long after the introduction of the vaccine in 2000, reports started to emerge of a decrease in drug-resistant invasive disease, mostly among isolates with a penicillin minimum inhibitory concentration ≥ 2.0 mg/dl.¹⁶ A Centers for Disease Control and Prevention study showed a 83% decrease (95% CI 82–85%) among invasive disease strains resistant to both penicillin and erythromycin among children younger than 2 years, consistent with a similar drop in susceptible strains.¹⁷

To demonstrate a change in resistance prevalence in a surveillance study that is not population based, one needs to do more than the naive comparison of 1 year (*e.g.*, 1996) with another year (*e.g.*, 2001). Such comparison would ignore the fact that cyclical changes other than seasonal changes may exist. Additionally, there may be long-term trends operating in the population that would be ignored by a pair-wise comparison. A more complex issue is the natural correlation that exists in a given locale in time that makes the next year's resistance prevalence close to the previous year, which invalidates the independence assumption of simple statistical tests.

Using a multivariate model and establishing fixed periods of time only for comparison purposes (each antibiotic has a slightly different peak), the antibiotics penicillin, erythromycin, and amox/clav switched from a significant increase

in resistance prevalence before the introduction to the vaccine to a significant decrease for the period 2001–2004. TMP/SMX and tetracycline were roughly stable prior the introduction of the vaccine, but showed a significant decrease for the period 2001–2004. The only antibiotic studied that was decreasing in resistance prevalence before the introduction of the vaccine was ceftriaxone, and resistance to this agent continued to decline in the period 2001–2004.

The size of the decline in penicillin resistance prevalence for the period 2001–2004 is more marked in children younger than 5 years ($-10.3\% \pm 0.8\%$), than in adults older than 65 ($-7.9\% \pm 0.6\%$), and among otitis media isolates ($-12.7\% \pm 1.1\%$) when compared to invasive (blood/CSF) isolates ($-7.1\% \pm 0.5\%$). This trend was consistent across antibiotics and among MDR isolates.

Among children younger than 5 years, the largest declines in the period 2001–2004 are for TMP/SMX ($-12.5\% \pm 1.1\%$), followed by penicillin, multiple resistance, erythromycin, and tetracycline. Acute otitis media isolates have slightly larger declines with the same trend across antibiotics. The explanation of these trends stems from the larger prevalence of resistant isolates among vaccine serotypes in younger children and those with otitis media,²⁵ or with the smaller impact of a herd effect for older children, adults, and the elderly.

Mathematical models of serotype replacement had predicted a rebound in resistance prevalence given continued antimicrobial consumption pressure.^{12,18} Evidence of serotype replacement was seen early in vaccine trials,⁶ and confirmed later by several epidemiological studies.^{23–25} The timing for the initiation of the rebound was a surprise, but at least one study²⁰ had shown some evidence that the replacement process of vaccine serotypes by nonvaccine serotypes had reached a complete switch in younger children by 2005.

The antibiotics studied with the exception of levofloxacin have shown significant temporal changes in resistance prevalence in multivariate models for the periods 2001–2004 and 2004–2007. The largest overall increase for the period 2004–2007 was seen in erythromycin ($5.8\% \pm 1.6\%$), followed by amox/clav, tetracycline, multidrug resistance, penicillin, TMP/SMX, and ceftriaxone. The rationale for the rebound is that given a constant antimicrobial consumption pressure, as the nonvaccine serotypes replaced vaccine serotypes, they acquired resistance roughly at a rate that was proportional to the replacement process.

The rebound in multidrug resistance (3.2 ± 1.1) was likely due to transmission advantage of the newly multiresistant nonvaccine serotypes. Hanage *et al.*¹² found no evidence that penicillin resistance in nonvaccine serotypes is due to either serotype switching or *de novo* acquisition, but that resistance increased through the expansion of nonvaccine serotype clones (19A, 15A, and 35B). Clonal spread of resistant serotype 19A has contributed particularly to multidrug resistance.¹⁸ The introduction of a vaccine with extended coverage could presumably stop this trend.

The lack of rebound in levofloxacin could stem from the fact that it is not licensed for use in children, so there is little consumption pressure, and no transmission advantage among the few quinolone-resistant isolates found in children. In 2007, only 2% (33/12654) of all isolates that were multiple resistant were also levofloxacin resistant.

A limitation of this study is that isolates come from passive surveillance that is not population based. The isolates from different census regions may not be completely representative as they are subject to selection bias. Most isolates represent subjects with a variety of infections. Vaccine status of the subject or other characteristics like prior therapy were not known.

This large surveillance study has attempted to demonstrate the effect of the pneumococcal conjugate vaccine over antimicrobial resistance in the United States after taking into account other risk factors in a nonlinear multivariate model. The study shows the significant indirect effect of the vaccine over resistance rates immediately after the introduction of the vaccine in 2000, and a consistent and significant rebound in resistance prevalence among most of the antibiotics studied. As the impact of the vaccine wanes, the expectation is that resistance rates will continue to increase at a rate that is proportional to the cumulative consumption of antibiotics.

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Disclosure Statement

No competing financial interests exist.

References

1. Bedos, J.P., S. Chevret, C. Chastang, P. Geslin, and B. Regnier. 1996. Epidemiological features and risk factors for infection by *Streptococcus pneumoniae* strains with diminished susceptibility to penicillin. *Clin. Infect. Dis.* **22**: 63–72.
2. Breiman, R.F., J.C. Butler, F.C. Tenover, J.A. Elliot, and R.R. Facklam. 1994. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* **271**:1831–1835.
3. Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases, 10th edition. Available at www.cdc.gov/vaccines/pubs/pinkbook, accessed April 13, 2009. Washington, DC: Public Health Foundation, 2002, pp. 257–289. (Online.)
4. Centers for Disease Control and Prevention. 2005. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998–2003. *MMWR Morb. Mortal Wkly. Rep.* **54**:893–897.
5. Clinical and Laboratory Standards Institute. 2008. Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement. CLSI document M100-S18. Wayne, PA: Clinical and Laboratory Standards Institute.
6. Dagan, R., N. Givon-Lavi, O. Zamir, M. Sikuler-Cohen, L. Guy, J. Janco, P. Yagupski, and D. Fraser. 2002. Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. *J. Infect. Dis.* **185**:927–936.
7. Farrell, D.J., K.P. Klugman, and M. Pichichero. 2007. Increased antimicrobial resistance among nonvaccine serotypes of *Streptococcus pneumoniae* in the pediatric population after the introduction of 7-valent pneumococcal vaccine in the United States. *Pediatr. Infect. Dis. J.* **26**:123–128.
8. Fedson, D.S., J.A. Scott, and G. Scott. 1999. The burden of pneumococcal disease among adults in developed and

- developing countries: what is and is not known. *Vaccine* 17:S11–S18.
9. Frazão, N., A. Brito-Avô, C. Simas, J. Saldanha, R. Mato, S. Nunes, N.G. Sousa, J.A. Carriço, J.S. Almeida, I. Santos-Sanches, and H. de Lencastre. 2005. Effect of the seven-valent conjugate pneumococcal vaccine on carriage and drug resistance of *Streptococcus pneumoniae* in healthy children attending day-care centers in Lisbon. *Pediatr. Infect. Dis. J.* 24:243–252.
 10. Givon-Lavi, N., R. Dagan, D. Fraser, P. Yagupsky, and N. Porat. 1999. Marked differences in pneumococcal carriage and resistance patterns between day care centers located in a small area. *Clin. Infect. Dis.* 29:1274–1280.
 11. Hammit, L.L., D.L. Bruden, J.C. Butler, H.C. Baggett, D.A. Hurlburt, A. Reasonover, and T.W. Hennessy. 2006. Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease. *J. Infect. Dis.* 193:1487–1494.
 12. Hanage, W.P., S.S. Huang, M. Lipsitch, C.J. Bishop, D. Godoy, S.I. Pelton, R. Goldstein, H. Huot, and J.A. Finkelstein. 2007. Diversity and antibiotic resistance among non-vaccine serotypes of *Streptococcus pneumoniae* carriage isolates in the post-heptavalent conjugate vaccine era. *J. Infect. Dis.* 195:347–352.
 13. Hendley, J.O., M.A. Sande, P.M. Stewart, and J.M. Gwaltney. 1975. Spread of *Streptococcus pneumoniae* in families. I. Carriage rates and distribution of types. *J. Infect. Dis.* 132:55–61.
 14. Hennessy, T.W., R.J. Singleton, L.R. Bulkow, D.L. Bruden, D.A. Hurlburt, D. Parks, M. Moore, A.J. Parkinson, A. Schuchat, and J.C. Butler. 2005. Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in Alaska Natives: progress towards elimination of a health disparity. *Vaccine* 23:5464–5473.
 15. Jacobs, M.R. 1996. Increasing importance of antibiotic-resistant *Streptococcus pneumoniae* in acute otitis media. *Pediatr. Infect. Dis. J.* 15:940–943.
 16. Kaplan, S.L., E.O. Mason, E.R. Wald, G.E. Shutze, J.S. Bradley, T.Q. Tan, J.A. Hoffman, L.G. Givner, R. Yogev, and W.J. Barson. 2004. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics* 113:443–449.
 17. Kyaw, M.H., R. Lynfield, W. Schaffner, A.S. Craig, J. Hadler, A. Reingold, A.R. Thomas, L.H. Harrison, N.M. Bennett, M.M. Farley, R.R. Facklam, J.H. Jorgensen, J. Besser, E.R. Zell, A. Schuchat, and C.G. Whitney. 2006. Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N. Engl. J. Med.* 354:1455–1463.
 18. Mera, R. 2005. Predicting the future *Streptococcus pneumoniae* resistance landscape. *Curr. Opin. Pharmacol.* 5:459–464.
 19. Mera, R.M., L.A. Miller, J.J. Daniels, J.G. Weil, and A.R. White. 2005. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States over a 10-year period: Alexander Project. *Diagn. Microbiol. Infect. Dis.* 51: 195–200.
 20. Mera, R., L.A. Miller, T.R. Fritsche, and R.N. Jones. 2008. Serotype replacement and multiple resistance in *Streptococcus pneumoniae* after the introduction of the conjugate pneumococcal vaccine. *Microb. Drug Resist.* 14:101–107.
 21. Mera, R.M., L.A. Miller, and A. White. 2006. Antibacterial use and *Streptococcus pneumoniae* penicillin resistance: a temporal relationship model. *Microb. Drug Resist.* 12:158–163.
 22. Munoz-Almagro, C., I. Jordan, A. Gene, C. Latorre, J.J. Garcia-Garcia, and R. Pallares. 2008. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of 7-valent conjugate vaccine. *Clin. Infect. Dis.* 46: 174–182.
 23. Robinson, K.A., W. Baughman, G. Rothrock, N.L. Barrett, M. Pass, C. Lexau, B. Damaske, K. Stefonek, B. Barnes, J. Patterson, E.R. Zell, A. Schuchat, and C.G. Whitney. 2001. Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States, 1995–1998. Opportunities for prevention in the conjugate vaccine era. *JAMA* 285:1729–1735.
 24. Sá-Leão, R., S. Nunes, A. Brito-Avô, N. Frazão, A.S. Simões, M.I. Crisóstomo, A.C.S. Paulo, J. Saldanha, I. Santos-Sanches, and H. de Lencastre. 2009. Changes in pneumococcal serotypes and antibiograms carried by vaccinated and unvaccinated day-care centre attendees in Portugal, a country with widespread use of the seven-valent pneumococcal conjugate vaccine. *Clin. Microbiol. Infect.* Apr 23. [Epub ahead of print].
 25. Stephens, D.S., S.M. Zughair, C.G. Whitney, W.S. Baughman, L. Barker, K. Gay, D. Jackson, W.A. Orenstein, K. Arnold, A. Schuchat, and M.M. Farley. 2005. Incidence of macrolide resistance in *Streptococcus pneumoniae* after introduction of pneumococcal conjugate vaccine: population-based assessment. *Lancet* 365:855–863.
 26. Styers, D., D.J. Sheehan, P. Hogan, and D.F. Sahn. 2006. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among *Staphylococcus aureus*: 2005 status in the United States. *Ann. Clin. Microbiol. Antimicrob.* 5:2.
 27. Whitney, C.G., M.M. Farley, J. Hadler, L.H. Harrison, C. Lexau, A. Reingold, L. Lefkowitz, P.R. Cieslak, M. Cetron, E.R. Zell, J.H. Jorgensen, A. Schuchat, R.R. Facklam, and N.M. Bennett. 2000. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N. Engl. J. Med.* 343:1917–1924.
 28. Whitney, C.G., M.M. Farley, J. Hadler, L.H. Harrison, N.M. Bennett, R. Lynfield, A. Reingold, P.R. Cieslak, T. Plishvili, D. Jackson, R.R. Facklam, J.H. Jorgensen, and A. Schuchat. 2003. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N. Engl. J. Med.* 348:1737–1746.

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