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Effect of Introduction of the Pneumococcal Conjugate Vaccine on Drug-Resistant *Streptococcus pneumoniae*

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ABSTRACT

BACKGROUND

Five of seven serotypes in the pneumococcal conjugate vaccine, introduced for infants in the United States in 2000, are responsible for most penicillin-resistant infections. We examined the effect of this vaccine on invasive disease caused by resistant strains.

METHODS

We used laboratory-based data from Active Bacterial Core surveillance to measure disease caused by antibiotic-nonsusceptible pneumococci from 1996 through 2004. Cases of invasive disease, defined as disease caused by pneumococci isolated from a normally sterile site, were identified in eight surveillance areas. Isolates underwent serotyping and susceptibility testing.

RESULTS

Rates of invasive disease caused by penicillin-nonsusceptible strains and strains not susceptible to multiple antibiotics peaked in 1999 and decreased by 2004, from 6.3 to 2.7 cases per 100,000 (a decline of 57 percent; 95 percent confidence interval, 55 to 58 percent) and from 4.1 to 1.7 cases per 100,000 (a decline of 59 percent; 95 percent confidence interval, 58 to 60 percent), respectively. Among children under two years of age, disease caused by penicillin-nonsusceptible strains decreased from 70.3 to 13.1 cases per 100,000 (a decline of 81 percent; 95 percent confidence interval, 80 to 82 percent). Among persons 65 years of age or older, disease caused by penicillin-nonsusceptible strains decreased from 16.4 to 8.4 cases per 100,000 (a decline of 49 percent). Rates of resistant disease caused by vaccine serotypes fell 87 percent. An increase was seen in disease caused by serotype 19A, a serotype not included in the vaccine (from 2.0 to 8.3 per 100,000 among children under two years of age).

CONCLUSIONS

The rate of antibiotic-resistant invasive pneumococcal infections decreased in young children and older persons after the introduction of the conjugate vaccine. There was an increase in infections caused by serotypes not included in the vaccine.

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ANTIBIOTIC-RESISTANT PNEUMOCOCCI complicate treatment decisions, cause treatment failures, and increase the costs of medical care. Worldwide, most antibiotic-resistant infections are caused by five of the seven serotypes in the 7-valent pneumococcal conjugate vaccine (6B, 9V, 14, 19F, and 23F).¹ In 1998, 24 percent of invasive pneumococcal isolates in the United States were nonsusceptible to penicillin, and these five serotypes comprised 78 percent of such strains.² Modeling predicted that in the absence of a pneumococcal conjugate vaccine, the proportion of pneumococcal strains that were nonsusceptible to both penicillin and erythromycin could reach 41 percent by 2004.³ Because of the association between serotype and resistance, the conjugate vaccine would be expected to reduce the incidence of disease caused by resistant strains, even though the vaccine is designed to induce antibodies against certain capsular types.

A pneumococcal conjugate vaccine was licensed for use in young children in the United States in 2000. The vaccine is recommended for all children under two years of age and for children two to four years of age who have certain chronic illnesses or other high-risk conditions.⁴ Data from 2001⁵ and from a single site in 2002⁶ indicated that there had been a large decrease in invasive disease, including infections caused by resistant strains. Whether vaccine use would induce the emergence of serotypes that were typically not resistant as clinically significant causes of resistant infections was unknown. In addition, the possibility that use of a vaccine that targets only 7 of 90 pneumococcal serotypes would lead to an increase in disease by nonvaccine types (so-called replacement disease) was a concern. We used population-based data from Active Bacterial Core surveillance, part of the Emerging Infections Program of the Centers for Disease Control and Prevention (CDC), to evaluate further the effect of the conjugate pneumococcal vaccine on invasive disease caused by antibiotic-resistant strains in the United States.

METHODS

Active Bacterial Core surveillance is an active, population-based system that has been described previously (www.cdc.gov/abcs).² We included cases of invasive pneumococcal disease identified from January 1, 1996, through December 31, 2004, in

eight surveillance areas: the Atlanta metropolitan area (eight counties); Portland, Oregon (three counties); San Francisco County, California; Minneapolis and St. Paul (seven counties); the Baltimore metropolitan area (six counties); the state of Connecticut; and parts of Tennessee (four counties). Seven counties comprising the Rochester, New York, metropolitan area were added in 1998. The surveillance methods for detecting cases of invasive pneumococcal disease did not change during the study period. The population under surveillance for this analysis ranged from 14.3 million to 16.9 million, including nearly 500,000 children under two years of age.

Active Bacterial Core surveillance methods defined a case of invasive disease as an illness in which pneumococcus was isolated from a normally sterile site, such as blood, cerebrospinal fluid, or pleural fluid. Isolates underwent susceptibility testing by broth microdilution at the CDC, the Minnesota Department of Health, or the University of Texas Health Science Center at San Antonio. Antibiotic susceptibility was defined according to break points for minimal inhibitory concentrations as determined in 2004 by the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards).⁷ Isolates with intermediate or high-level resistance were defined as nonsusceptible. Isolates were considered nonsusceptible to multiple antibiotics if they were nonsusceptible to at least three of the following: penicillin, erythromycin, trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol, clindamycin, rifampin, and levofloxacin.

Serotyping was performed at the CDC or the Minnesota Department of Health by the Quellung reaction. The 7-valent conjugate vaccine serotypes included types 4, 6B, 9V, 14, 18C, 19F, and 23F. Other serotypes in these serogroups, including 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B, were regarded as vaccine-related. All others were nonvaccine types.

Rates of invasive pneumococcal disease, expressed as the number of cases per 100,000 population, were calculated for the surveillance areas with the use of estimates from the U.S. Census Bureau for each respective year, followed by adjustment for race and age according to the U.S. population. Projected numbers of cases in the United States were determined by multiplying the adjusted rate by the U.S. population. Estimated

a decline of 51 percent [95 percent confidence interval, 50 to 53 percent]) and for disease caused by strains with reduced susceptibility to multiple antibiotics (from 4.1 to 1.7 per 100,000, a decline of 59 percent [95 percent confidence interval, 58 to 60 percent]). Rates of penicillin-nonsusceptible disease due to vaccine serotypes fell from 5.0 to 0.7 per 100,000 (a decline of 87 percent; 95 percent confidence interval, 86 to 88 percent) (Table 1). Rates of disease caused by vaccine-related strains increased by 54 percent (from 1.0 to 1.6 per 100,000); this change reflected a decrease (by 22 percent) in the rate of disease due to serotype 6A and a large increase (by 238 percent) in the rate of disease due to serotype 19A. The rate of penicillin-nonsusceptible disease due to nonvaccine serotypes increased from 0.2 per 100,000 in 1999 to 0.5 per 100,000 in 2004.

The decrease in the rate of penicillin-nonsusceptible disease was largest in Georgia (a decrease of 68 percent, from 11.1 per 100,000 in 1999 to 3.6 per 100,000 in 2004) and smallest in New York (a decrease of 11 percent, from 3.3 to 2.9 per 100,000). The rate of penicillin-nonsusceptible disease decreased by 65 percent (from 11.7 to 4.1 per 100,000) in Tennessee, by 60 percent (from 5.5 to 2.2 per 100,000) in Minnesota, by 57 percent (from 3.7 to 1.6 per 100,000) in Oregon, by 53 percent (from 3.8 to 1.8 per 100,000) in California, by 53 percent (from 5.8 to 2.7 per 100,000) in Maryland, and by 42 percent (from 4.9 to 2.9 per 100,000) in Connecticut. The change in rate was significant at all sites except New York.

The proportion of isolates that were penicillin-nonsusceptible increased from 21.6 percent in 1996 to 25.8 percent in 1999 and 25.9 percent in 2000 and fell to 21.6 percent in 2004 ($P < 0.001$ for the comparison between 1999 and 2004). The proportion of erythromycin-nonsusceptible isolates ranged from 10.7 percent in 1996 to 19.4 percent in 1999 and 20.6 percent in 2000; the proportion of isolates that were erythromycin-nonsusceptible did not change significantly after the introduction of the vaccine and was 18.1 percent in 2004 ($P = 0.23$ for the comparison with 1999 rates). When data from 1999 and 2004 were compared with respect to other drugs, significant decreases were seen in the proportion of isolates that were nonsusceptible to trimethoprim-sulfamethoxazole, cefuroxime, meropenem, or clindamycin or to three or more drug classes, but there

were no significant changes in the proportion of isolates that were nonsusceptible to cefotaxime, tetracycline, or levofloxacin. The proportion of isolates that were nonsusceptible to any tested antibiotic was 37.7 percent in 1999 and 33.6 percent in 2004 ($P = 0.002$). Most individual serotypes were not less resistant in 2004 than in 1999 (Table 2). Among the vaccine serotypes, only serotype 23F was significantly less often resistant in 2004 than in 1999; vaccine-related serotype 19A was resistant more often.

RATES OF DISEASE ACCORDING TO AGE

Children under Five Years of Age

The rates of penicillin-nonsusceptible invasive disease among children under five years of age ranged from 25.9 to 33.8 per 100,000 between 1996 and 1999, before the introduction of the conjugate vaccine, and fell to 7.5 per 100,000 in 2004. Rates of resistant infections were highest among children under two years of age, the target age for use of the conjugate vaccine. In this age group, the rate of invasive disease caused by penicillin-nonsusceptible pneumococci decreased by 81 percent (95 percent confidence interval, 80 to 82 percent), from a peak of 70.3 per 100,000 in 1999 to 13.1 per 100,000 in 2004 (Fig. 1). The rate of invasive disease due to erythromycin-nonsusceptible strains decreased by 80 percent (95 percent confidence interval, 78 to 81 percent), from 58.6 to 12.0 per 100,000, and the rate of disease due to strains with reduced susceptibility to both penicillin and erythromycin decreased by 83 percent (95 percent confidence interval, 82 to 85 percent), from 51.5 to 8.6 per 100,000. Among children two to four years of age, the rate of penicillin-nonsusceptible disease decreased by 60 percent (95 percent confidence interval, 56 to 65 percent), from 9.4 to 3.7 per 100,000 (Fig. 2). The rate of disease caused by strains nonsusceptible to multiple antibiotics decreased by 84 percent (95 percent confidence interval, 82 to 85 percent), from 53.8 to 8.8 per 100,000, among children under two years of age, and by 64 percent (95 percent confidence interval, 58 to 68 percent), from 6.2 to 2.3 per 100,000, among children two to four years of age.

Among children under two years of age, almost all infections caused by penicillin-nonsusceptible strains were due to vaccine and vaccine-related serotypes, both before and after introduction of the vaccine (Table 1). In this age group, a large reduction in disease caused by vaccine serotypes

was accompanied by an increase in non-vaccine-serotype disease. The rate of disease caused by nonsusceptible 19A, a vaccine-related serotype, increased markedly (from 2.0 to 8.3 per 100,000). Among children two to four years of age, the rate of penicillin-nonsusceptible disease caused by vaccine serotypes decreased by 98 percent (95 percent confidence interval, 96 to 99 percent), from 6.9 per 100,000 in 1999 to 0.2 per 100,000 in 2004.

Among children under two years of age, the proportion of cases due to nonsusceptible strains fell after vaccine licensure but then increased in 2004, such that no change overall was seen between 1999 and 2004 for most of the antibiotics tested (Fig. 3A). In this age group, the proportion of isolates with intermediate resistance to penicillin was 12.8 percent in 1999, 10.7 percent in 2000, 14.0 percent in 2001, 7.4 percent in 2002, 10.8 percent in 2003, and 18.4 percent in 2004; the prevalence of high-level resistance was 26.2 percent, 26.4 percent, 21.3 percent, 13.2 percent, 13.2 percent, and 19.1 percent, respectively. The proportion of isolates nonsusceptible to one or more antibiotics did not differ significantly between 1999 and 2004 either among children under two years of age (52.5 percent and 51.7 percent, respectively; P=0.87) or among children two to four years of age (43.5 percent and 40.0 percent, respectively; P=0.61). Individual serotypes were as likely to be resistant in 2004 as they were in 1999 (Table 2). In 2004, a single serotype, 19A, accounted for 35 percent (51 of 147) of all penicillin-nonsusceptible strains among children under two years of age, as compared with only 2 percent (13 of 711) in 1999.

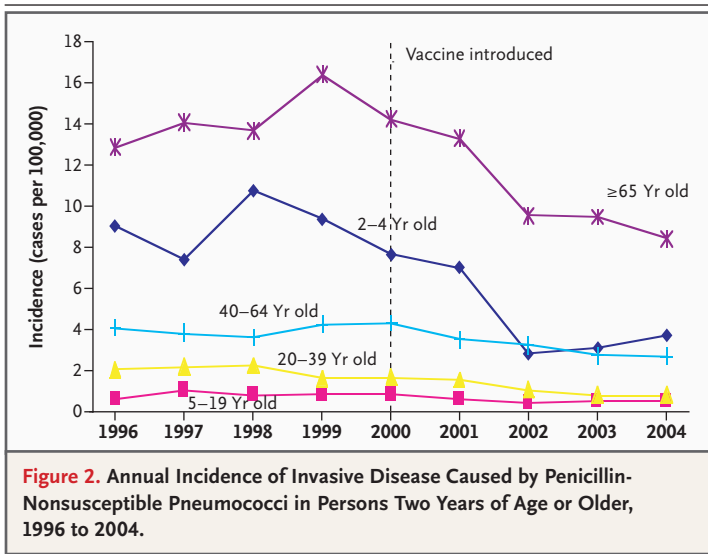
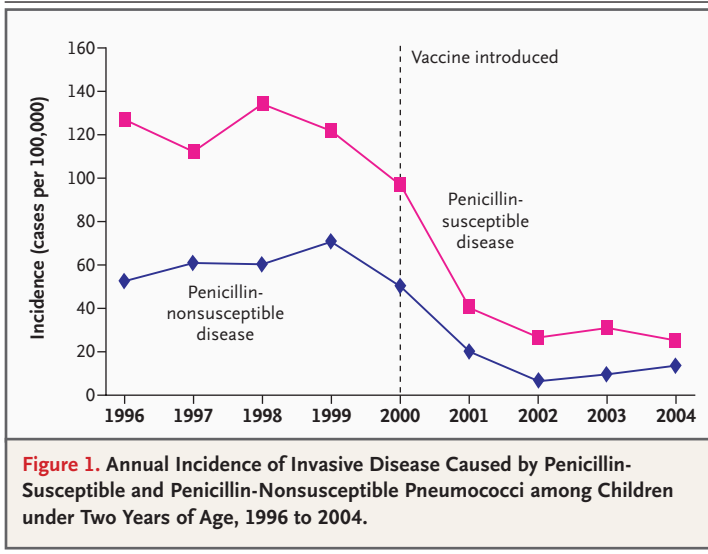
Persons Five Years of Age or Older

The rates of disease caused by penicillin-nonsusceptible strains also decreased among persons five years of age or older — a group that would not have received the conjugate vaccine (Fig. 2). The rates of penicillin-nonsusceptible disease were highest among adults 65 years of age or older; in this group, the rate of penicillin-nonsusceptible disease decreased from 16.4 per 100,000 in 1999 to 8.4 per 100,000 in 2004 — a reduction of 49 percent (95 percent confidence interval, 46 to 51 percent) (Table 1). The rate of penicillin-nonsusceptible disease decreased by 41 percent (95 percent confidence interval, 32 to 48 percent), from 0.9 to 0.5 per 100,000, among persons 5 to

Table 2. Total Number of Strains from Cases of Invasive Pneumococcal Disease and Percentage That Were Penicillin-Nonsusceptible (PNS) in 1999 and 2004, According to Serotype and Age.

Serotype	Persons of Any Age						Children <2 Yr of Age						Persons ≥65 Yr of Age					
	1999		2004		1999		2004		1999		2004		1999		2004			
	total no.	% PNS	total no.	% PNS	total no.	% PNS	total no.	% PNS	total no.	% PNS	total no.	% PNS	total no.	% PNS	total no.	% PNS		
All serotypes	3485	25.8	1930	21.6*	711	39.0	147	37.4	974	27.3	638	22.3*	551	36.1	139	30.9		
All vaccine serotypes	2228	32.6	417	24.3*	605	40.1	15	33.3	74	2.7	33	0.0	74	2.7	33	0.0		
4	375	1.1	130	0.0	50	0.0	2	0.0	74	36.9	11	63.6	65	36.9	11	63.6		
6B	230	36.1	42	45.2	86	39.5	3	33.3	65	—	21	61.9	74	62.2	21	61.9		
9V	270	56.7	58	62.1	40	60.0	0	—	74	100.0	25	56.0	170	44.7	25	56.0		
14	691	42.5	47	51.1	242	49.8	1	100.0	31	6.5	15	0.0	31	6.5	15	0.0		
18C	173	1.7	41	0.0	58	0.0	1	0.0	38	29.0	12	16.7	38	29.0	12	16.7		
19F	219	32.0	51	19.6	81	40.7	5	20.0	99	38.4	22	31.8	99	38.4	22	31.8		
23F	270	44.4	48	25.0*	48	64.6	3	66.7	146	38.9	160	42.1	146	38.9	160	42.1		
All vaccine-related serotypes	404	37.4	508	48.4*	64	50.8	63	67.7	77	36.0	53	39.6	77	36.0	53	39.6		
6A	187	38.4	132	39.4	29	55.2	10	60.0	34	61.8	68	55.2	34	61.8	68	55.2		
19A	99	51.0	281	63.6*	13	61.5	51	68.0	277	3.6	339	9.5*	277	3.6	339	9.5*		
All nonvaccine serotypes	853	2.6	1005	6.9*	42	7.1	69	11.6	277	11.6	339	9.5*	277	3.6	339	9.5*		

* P<0.05 for the change in the percentage of isolates that were not susceptible to penicillin from 1999 to 2004.



($P=0.63$), but there were no significant changes among those 20 to 39 years of age (proportion of erythromycin-resistant isolates, 11.9 percent in 1999 and 12.6 percent in 2004), among those 40 to 64 years of age (14.7 percent and 16.9 percent, respectively), or among those 65 years of age or older (18.6 percent and 18.5 percent, respectively).

The decrease in penicillin-nonsusceptible disease among older children and adults was due to a drop in disease caused by vaccine serotypes. Among adults 65 years of age or older, the rate of penicillin-nonsusceptible disease caused by vaccine serotypes decreased by 79 percent (Table 1). Conversely, a small but significant increase was seen in the rate of penicillin-nonsusceptible disease caused by nonvaccine serotypes and vaccine-related serotype 19A in this group.

FACTORS ASSOCIATED WITH RESISTANT INFECTIONS

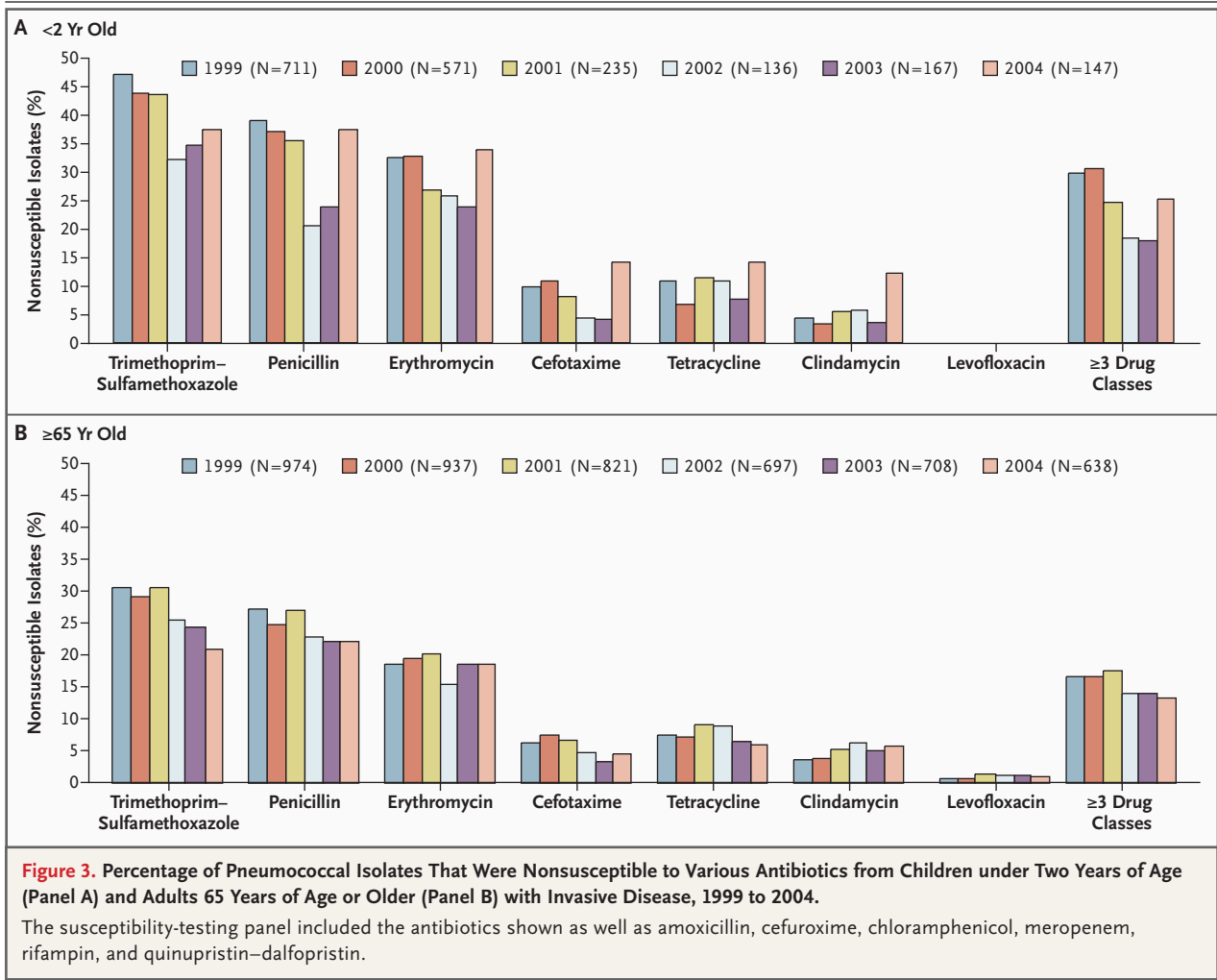
The proportion of cases of disease caused by penicillin-nonsusceptible strains differed somewhat among locations in 2004, ranging from 29.5 percent in Tennessee, 28.5 percent in Georgia, and 25.0 percent in New York to 15.5 percent in Oregon and 9.4 percent in California ($P<0.001$ for the comparison among the surveillance areas). After adjustment according to site, children under 5 years of age and adults 65 years of age or older were more likely to be infected with penicillin-nonsusceptible strains than were those 18 to 64 years of age (odds ratio, 2.5 [95 percent confidence interval, 1.8 to 3.6] and 1.2 [95 percent confidence interval, 1.0 to 1.6], respectively). No significant associations were seen between non-susceptibility to penicillin and race, hospitalization status, and diagnosis or outcome.

19 years of age; by 51 percent (95 percent confidence interval, 46 to 55 percent), from 1.6 to 0.8 per 100,000, among persons 20 to 39 years of age; and by 36 percent (95 percent confidence interval, 33 to 40 percent), from 4.3 to 2.7 per 100,000, among those 40 to 64 years of age.

The proportion of isolates that were nonsusceptible to penicillin fell among adults 65 years of age or older (Fig. 3B). A similar pattern of decrease in the proportion of penicillin resistance was seen in other age groups. For erythromycin, the proportion of isolates that were resistant decreased from 13.8 percent in 1999 to 11.4 percent in 2004 among persons 5 to 19 years of age

OVERALL CHANGES IN THE BURDEN OF DISEASE

The estimated annual number of cases of invasive pneumococcal disease in the United States decreased from 66,100 in 1999 to 36,600 in 2004. Cases due to strains that were nonsusceptible to at least one of the antibiotics tested decreased by 51 percent, from 25,000 in 1999 to 12,300 in 2004. The size of the decrease in resistant cases among children under five years of age (from an estimated 8800 cases in 1999 to 2000 cases in 2004) was similar to that among persons five years of age or older (from 16,300 to 10,300). The number of deaths due to invasive pneumococcal disease decreased from 7200 in 1999 to 4700 in 2004; deaths



caused by strains resistant to at least one antibiotic decreased from 2500 to 1600 annually.

DISCUSSION

The incidence of antibiotic-resistant invasive disease declined substantially after the introduction of the pneumococcal conjugate vaccine into the routine childhood immunization program. Among children under two years of age, the rate of penicillin-nonsusceptible invasive disease fell 81 percent; rates among children two to four years of age were 60 percent lower in 2004 than at baseline in 1999. These results complement earlier reports of a decline in resistant disease among children in other parts of the United States after the introduction of the conjugate vaccine.^{6,8,9} Because the vaccine was licensed in 2000, near-

ly all the children up through the age of four years in 2004 would have had the opportunity to receive the conjugate vaccine as an infant or toddler. According to estimates of U.S. vaccine coverage, only 73 percent of children 19 to 35 months old in 2004 had received at least three of the recommended four doses of conjugate pneumococcal vaccine.¹⁰ Therefore, the changes we report occurred in a setting in which many children were not fully vaccinated.

In addition to reductions in the rates among young children, reductions in the rates of invasive disease caused by resistant strains were documented among older children and adults, who would not have received the conjugate vaccine. With all age groups considered together, the estimated number of cases caused by strains with reduced susceptibility to penicillin or multiple

antibiotics fell by half after the introduction of the conjugate vaccine. Studies of adults have shown that exposure to children can increase the risk of colonization¹¹ and invasive disease.¹² Conjugate pneumococcal vaccines have been shown to reduce the risk of carriage and transmission of vaccine-type strains among vaccinees and their household members.¹³ The change that we observed in the rate of resistant disease among adults was due to a reduction in disease caused by vaccine serotypes — a finding suggesting that the vaccine interrupts the transmission of resistant pneumococci from children to adults. We found no reduction in the incidence of resistant disease caused by serotypes included in the 23-valent polysaccharide vaccine but not in the 7-valent conjugate vaccine (data not shown); therefore, it appears that the decline in invasive antibiotic-resistant disease among adults was not linked to an increase in the use of the polysaccharide vaccine. Polysaccharide-vaccine coverage among adults 65 years of age or older increased from 54 percent in 1999 to 64 percent in 2003.^{14,15}

We found an increase in resistant disease caused by nonvaccine types (so-called replacement disease), but the magnitude of this effect was relatively small. Most resistant infections from serotypes not in the vaccine were caused by serotypes 6A and 19A. A drop in the rate of disease caused by serotype 6A and a concurrent increase in the rate of disease due to serotype 19A suggest, as previously reported, that the 6B vaccine component provides cross-protection¹⁶⁻¹⁸ against serotype 6A disease but that the 19F component does not protect against 19A disease.^{16,19} The increase in resistant disease caused by serotype 19A is a concern. Serotype 19A is often resistant and is a common cause of respiratory tract infections.^{20,21} It is difficult to predict whether the increase in resistant serotype 19A or other serotypes not covered by the vaccine will continue. Nevertheless, this replacement disease has the potential to reduce the overall benefit of the vaccine against resistant infections.

Our analysis indicates that groups at particular risk for resistant infections have changed since the introduction of the conjugate vaccine. Before its introduction, young children had the highest risk of infections due to antibiotic-resis-

tant strains²; we noted similar rates of antibiotic-nonsusceptible disease among children under 2 years of age and adults 65 years of age or older. The multivariable model indicated that among those with infections, white children were no longer more likely than black children to have a resistant infection — a finding that represents a change from the results of analysis with a similar model based on 1998 data.² We continued to note geographic differences in the prevalence of resistance after the introduction of the vaccine, with resistance being most common among isolates from states in the southeastern United States.

Policymakers considering routine use of the pneumococcal conjugate vaccine in settings in which resistance is prevalent should recognize this reduction in resistant infections as an added benefit to vaccine use. Because many pneumococci remain resistant, the changes we report are not likely to change recommendations regarding the empirical treatment of pneumonia, otitis media, and meningitis; those recommendations are designed to cover the possibility of infection due to resistant pneumococci.²²⁻²⁵ Nonetheless, the drop in the rate of disease due to resistant strains may mean that fewer complications and treatment failures due to resistance will occur.

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CORRECTION

Effect of Introduction of the Pneumococcal Conjugate Vaccine on Drug-Resistant *Streptococcus pneumoniae*

Effect of Introduction of the Pneumococcal Conjugate Vaccine on Drug-Resistant *Streptococcus pneumoniae*. In Table 2 on page 1459, the total number of all nonvaccine serotypes in persons ≥ 65 years of age in 2004 should have been 339, not 33 as printed. Also, in Figure 3 on page 1461, the pink bars should represent values for 2004, not 2003, as printed. The article has been corrected on the *Journal's* Web site at www.nejm.org. We regret the error.