Post-PCV7 Changes in Colonizing Pneumococcal Serotypes in 16 Massachusetts Communities, 2001 and 2004

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ABSTRACT. *Objective.* The introduction of heptavalent conjugate pneumococcal vaccine (PCV7) has raised concerns for replacement with nonvaccine serotypes in both invasive disease and asymptomatic carriage. Analysis of colonizing serotypes among healthy children in the community provides critical data on such changes.

Methods. Nasopharyngeal specimens were obtained from children who were younger than 7 years during well-child or sick visits in primary care practices in 16 Massachusetts communities during 2001 and 2004. Susceptibility testing and serotyping were performed on isolated *Streptococcus pneumoniae* strains. Vaccination history with PCV7 was abstracted from the medical record.

Results. Among colonizing pneumococcal isolates, PCV7 serotypes decreased from 36% to 14%, and non-PCV7 serotypes increased from 34% to 55%. Overall carriage did not change (26% to 23%); neither did carriage of potentially cross-reactive serotypes (30% to 31%). The most common non-PCV7 serotypes were serotypes 11, 15, and 29. There was a substantial increase in penicillin nonsusceptibility from 8% to 25% in non-PCV7 serotypes; 35% were highly resistant to penicillin. Penicillin nonsusceptibility increased from 45% to 56% among PCV7 serotypes while remaining stable among PCV7 potentially cross-reactive strains (51% vs 54%).

Conclusions. Pneumococcal colonization has changed after the introduction of PCV7, both in serotype distribution and in patterns of antibiotic resistance. The frequency of nonvaccine strains has increased, and the proportion of nonvaccine isolates that are not susceptible to penicillin has tripled. This shift toward increased carriage of nonvaccine serotypes warrants vigilance for changes in the epidemiology of invasive pneumococcal disease. *Pediatrics* 2005;116:e408–e413. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2338; Streptococcus pneumoniae, *pneumococcal conjugate vaccine, antibiotic resistance, colonization.*

ABBREVIATIONS. PCV7, heptavalent pneumococcal conjugate vaccine; PNSP, penicillin nonsusceptible *Streptococcus pneumoniae*; MDR, multidrug resistance; AOM, acute otitis media.

Before the release of a conjugate vaccine for US children, *Streptococcus pneumoniae* caused invasive disease in 1 in 500 to 600 children who were younger than 2 years.[1] In addition, rising antibiotic resistance among pneumococcal strains was a major concern among public health officials.[2,3] By 1999, 38% of laboratory isolates in children who were younger than 2 years were nonsusceptible to penicillin,[4] with higher rates reported in local areas.[5–7]

In February 2000, heptavalent pneumococcal conjugate vaccine (PCV7) was released to provide immunity to the 7 serotypes responsible for 85% of pediatric invasive pneumococcal disease[8] and 78% of penicillin-nonsusceptible *S pneumoniae* (PNSP) isolates in children.[9] Prelicensure trials showed a 90% reduction in invasive disease[10] and a 23% reduction in all-cause pneumonia in the first 2 years of life.[11] Postlicensure studies have also shown declines in invasive pneumococcal disease from 188 per 100 000 to 59 cases per 100 000 in US children who are younger than 2 years.[4,12]

Despite the success of PCV7 in reducing invasive disease, critical questions remain about the changing pneumococcal reservoir. Some trials of immunization with PCV7 have shown a 50% to 65% decrease in carriage of vaccine serotypes[13–15] and have raised concerns about replacement of vaccine serotypes with nonvaccine serotypes that may ultimately result in invasive disease.[16,17] Although, currently, the majority of invasive disease is caused by vaccine-included serotypes, the relationship between carriage of and invasive disease is complex and varies by serotype.[18,19] Shifts in colonizing serotypes after PCV7 may serve as early indicators of changes in invasive disease.

We assessed secular trends in community-level *S pneumoniae* carriage and resistance after the licensure of PCV7. Community-level analyses assess the full impact of both direct and indirect (herd immunity) effects of vaccines. In 2001, we conducted surveillance for pneumococcal carriage among generally healthy children in 16 distinct Massachusetts communities.[20] At that time, just after introduction of PCV7, we found that 26% of children carried *S pneumoniae* overall and that PCV7 serotypes accounted for 36% of isolates.[20] Resistance to penicillin (and

other antimicrobials) was concentrated among PCV7 serotypes and potentially cross-reactive serotypes, with penicillin nonsusceptibility of 45% and 51%, respectively. By November 2003, all children through 3.5 years of age were born into the era of routine PCV7 immunization in infancy. In this context, we resampled the same 16 communities in the winter and spring of 2003–2004 to determine (1) changes in carriage of PCV serotypes, PCV7 cross-reactive serotypes, and non-PCV7 *S pneumoniae* serotypes; (2) changes in overall antimicrobial resistance; and (3) serotype-specific changes in antimicrobial resistance.

METHODS

Data Collection

Nasopharyngeal specimens were collected from young children in pediatric and family practice physician offices in 16 Massachusetts communities between November 17, 2003, and April 16, 2004. We had performed surveillance in the same 16 communities from March 13 to May 11, 2001, as part of the baseline microbiologic data collection for a randomized trial of community-level intervention to promote judicious antibiotic prescribing for children.[20] These 16 communities were selected on the basis of physical geographic separation, evidence that few children crossed community boundaries to seek pediatric care, and diversity of size and demographic characteristics using available US Census data. In 2001, 31 private practice offices participated, and in 2004, 23 offices participated, all of which had participated in 2001.

In 2001, children were eligible for inclusion if they were younger than 7 years, resided in a study community, and presented for either a routine well-child or "sick visit" at a participating practice.[20] Parental consent and nasopharyngeal swabs were obtained by either trained study personnel or trained office practice nurses. PCV7 vaccination history was recorded from the medical record. In 2004, to increase sample size, we modified criteria to include children who received care in the study practices and lived beyond the zip code boundaries of the community. Recruitment in 2004 was independent of participation in 2001. All study procedures were approved by the Harvard Pilgrim Health Care institutional review board.

Microbiologic Processing

Nasopharyngeal samples were processed for *S pneumoniae* growth, antibiotic susceptibility, and serotype as previously described.[20] Standard National Committee for Clinical Laboratory Standards susceptibility breakpoints were used to classify organisms as susceptible, intermediate, and resistant.[21] Two definitions of multidrug resistance (MDR) were used: resistance to the β-lactam class plus 1 other antibiotic class (MDR1) and resistance to at least 3 antibiotic classes (MDR2). Penicillins, cephalosporins, and carbapenems were considered a single class. Comparisons of third-generation cephalosporin resistance were performed using 2004 breakpoint criteria.[21,22] We had previously reported carriage data from 2001 using the breakpoint criteria at that time. These 2001 data were reanalyzed with 2004 criteria for this analysis.

Serotypes included in the PCV7 were considered vaccine serotypes, and serotypes from serogroups that were not in PCV7 were considered nonvaccine serotypes. Serotypes in the same serogroup as vaccine serotypes (eg, 6A and 6B both are serogroup 6 strains) but not specifically included in the vaccine were classified as potentially cross-reactive serotypes. The extent to which the vaccine provides protection in vivo varies by serotype, but there is likely to be clinically important cross-protection against some of these strains. For quality control, we reserotyped a 36% random sample (82 of 226) of pneumococcal isolates from 2004 in a blinded manner and calculated percentage concordance.

Data Analysis

Microbiologic data were analyzed using SAS software version 8.2 (SAS Institute, Cary, NC). Proportions of children who carried *S pneumoniae* and proportions of isolates that were nonsusceptible to antibiotics were calculated and compared between the 2004 and previously published 2001 sample[20] using Fisher exact tests. Carriage proportions were calculated by sampling period and by age group (<6 months, 6–<12 months, 12–<24 months, 24–<36 months, and ≥36 months). Resistance patterns were analyzed for the 2004 sample, by vaccine group (PCV7, PCV7 cross-reactive, and non-PCV7 serotypes) and by individual serotype and compared with the 2001 sample.

RESULTS

We collected 996 nasopharyngeal samples from children in 23 practices from November 17, 2003, through April 16, 2004 (Table 1), 2 of which were lost in transit. Of the 994 remaining samples, 73% (726) came from children who lived within the specified 16 Massachusetts communities described in Table 2; the remainder were patients of these practices who lived outside the designated community zip codes. Because pneumococcal carriage and descriptive characteristics of these children were similar to those who lived within the designated zip codes, data were combined for analysis. Fifteen percent (153) of participants were siblings of other participants, compared with 12% (87) in 2001.

Pneumococcal carriage was similar between 2001 and 2004 (Table 2). Age-specific pneumococcal carriage increased in children who were younger than 6 months (8% in 2001 vs 22% in 2004; P = .01) and decreased in those who were older than 36 months (30% in 2001 vs 19% in 2004; P = .002). Overall carriage of *Haemophilus influenzae* was 15% in 2004 compared with 17% in 2001 (P = .4), and overall carriage of *Moraxella catarrhalis* was 26% in 2004 compared with 16% in 2001 (P < .0001).

Of the 232 *S pneumoniae* isolates, 226 were serotyped (6 were unable to be grown after transfer). The proportion of PCV7 serotypes declined from 36% (51 of 143) in 2001 to 14% (32 of 226) in 2004 (P < .0001), whereas non-PCV7 serotypes increased from 34% (49 of 143) in 2001 to 55% (125 of 226) in 2004 (P < .0001; Fig 1). The proportion of PCV7 cross-reactive isolates remained stable. In all age groups, the proportion of PCV7 strains carried decreased, whereas the proportion of non-PCV7 serotypes either remained the same (<6-month-olds) or increased (all other age groups). There was no difference in the proportion of serotypes included in the 23-valent adult pneumococcal polysaccharide vaccine between 2001 (57%; 82

TABLE 1. Characteristics of Massachusetts Children Who Provided Nasopharyngeal Specimens in 2001 and 2004

|	2001, N (%)	2004, N (%)
Age	N = 742	N = 994
0–<6 mo	123 (17)	55 (6)*
6–<12 mo	112 (15)	120 (12)
12–<24 mo	144 (19)	229 (23)
24–<36 mo	104 (14)	143 (14)
>36 mo	259 (35)	447 (45)*
Gender	N = 741	N = 994
Female	340 (46)	524 (53)
Race	N = 707	N = 948
White	548 (78)	800 (84)
Black	50 (7)	35 (4)
Hispanic	53 (8)	51 (5)
Asian	20 (3)	21 (2)
Other	36 (5)	41 (4)

* Significant difference between 2001 and 2004, P < .0001.

TABLE 2. Characteristics* and Pneumococcal Carriage of Participating Massachusetts Communities

Community	Population Size (1000s)	Median Family Income ($1000s)	% Nonwhite	2001		2004	
				Total, N	Carriage, N (%)	Total, N	Carriage, N (%)
1	67	52	7	41	13 (32)	42	2 (5)
2	80	41	15	55	9 (16)	60	15 (25)
3	46	36	7	33	8 (24)	53	13 (24)
4	40	45	5	60	12 (20)	30	8 (27)
5	52	76	5	41	12 (29)	80	22 (28)
6	37	93	10	28	6 (21)	42	12 (29)
7	94	40	39	78	21 (27)	97	15 (15)
8	139	47	25	35	8 (23)	68	16 (24)
9	102	32	8	49	19 (39)	73	25 (34)
10	115	33	19	48	9 (19)	72	23 (32)
11	34	56	2	35	5 (14)	78	29 (37)
12	28	67	3	35	11 (31)	45	6 (13)
13	30	59	3	44	20 (46)	73	10 (14)
14	52	56	5	30	8 (27)	39	6 (15)
15	30	50	7	94	23 (24)	63	9 (14)
16	38	48	3	36	6 (17)	79	21 (27)
Total	983	52	10	742	190 (26)	994	232 (23)

* Based on US Census data for 2000.

Fig 1. Percentage of pneumococcal isolates within each vaccine group for 2001 and 2004. Percentage of PCV7 among all isolates was 36% in 2001 and 14% in 2004 ($P < .0001$). Percentage of potentially PCV7–cross-reactive isolates was unchanged (30% vs 31%), and percentage of non-PCV7 isolates increased from 34% to 55% ($P < .0001$). Proportional penicillin nonsusceptibility is shown in hatched bars and was significantly higher among non-PCV7 isolates in 2004 (25%) versus 2001 (8%; $P = .01$). All P values reflect 2-tailed Fisher exact tests.
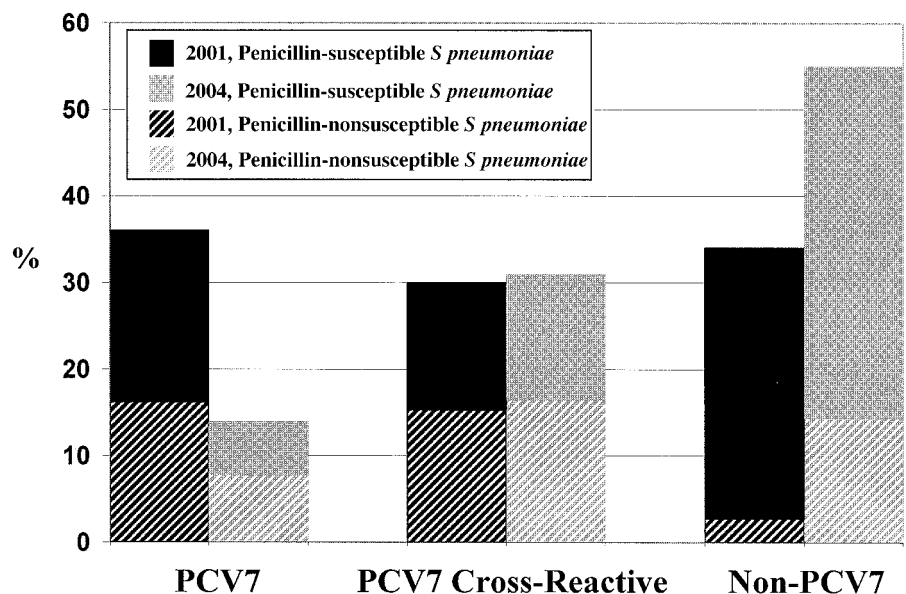
of 143) and 2004 (50%; 114 of 226). Serotype concordance during repeat serotyping was 96.3%. Previous studies that compared concordance of pneumococcal serotyping between laboratories showed a similar serotype discordance level.[23]

Every PCV7-included serotype decreased as a proportion of isolates, except for 9V, which had no representation in 2001 and 1 isolate in 2004 (Fig 2). Serotype 19F showed minimal decline and thus increased proportionally among PCV7 serotypes from 31% (16 of 51) in 2001 to 63% (20 of 32; $P = .007$) in 2004. Among PCV7 cross-reactive serotypes, there was a significant decrease in the proportion of serotype 6A (53% [23 of 43] to 32% [22 of 69]; $P = .03$) but significant increases in 19A (14% [6 of 43] to 38% [26 of 69]; $P = .009$) and 23A (2% [1 of 43] to 20% [14 to 69]; $P = .008$).

The most common non-PCV7 serotypes ($N = 125$) in 2004 were 15 ($N = 34$), 29 ($N = 19$), 11A ($N = 18$), 22F ($N = 9$), 10A ($N = 7$), and 35F ($N = 7$). Between

2001 and 2004, there was a significant increase in serotype 29 (2% in 2001 vs 8% in 2004; $P = .04$) and a trend toward an increase in serotype 15 (8% in 2001 vs 15% in 2004; $P = .07$). There were insufficient numbers to detect a significant change in the remaining serotypes.

Vaccine penetration (receipt of at least 1 PCV7 dose) increased from 60% in 2001 to 96% in 2004 among children who were younger than 12 months and from 38% to 79% among children who were at least 12 months of age. Among children who were at least 12 months of age and received 1 or more doses of PCV7, non-PCV7 strains increased from 8% (16 of 191) in 2001 to 14% (87 of 623) in 2004 ($P = .05$). Children who were at least 12 months of age and had not received any doses of PCV7 (primarily older children who were born before the introduction of PCV7) had similar percentages of non-PCV7 carriage in 2001 (7%; 20 of 306) as compared with 2004 (10%; 16 of 164; $P = .27$). In 2001, overall carriage of PCV7
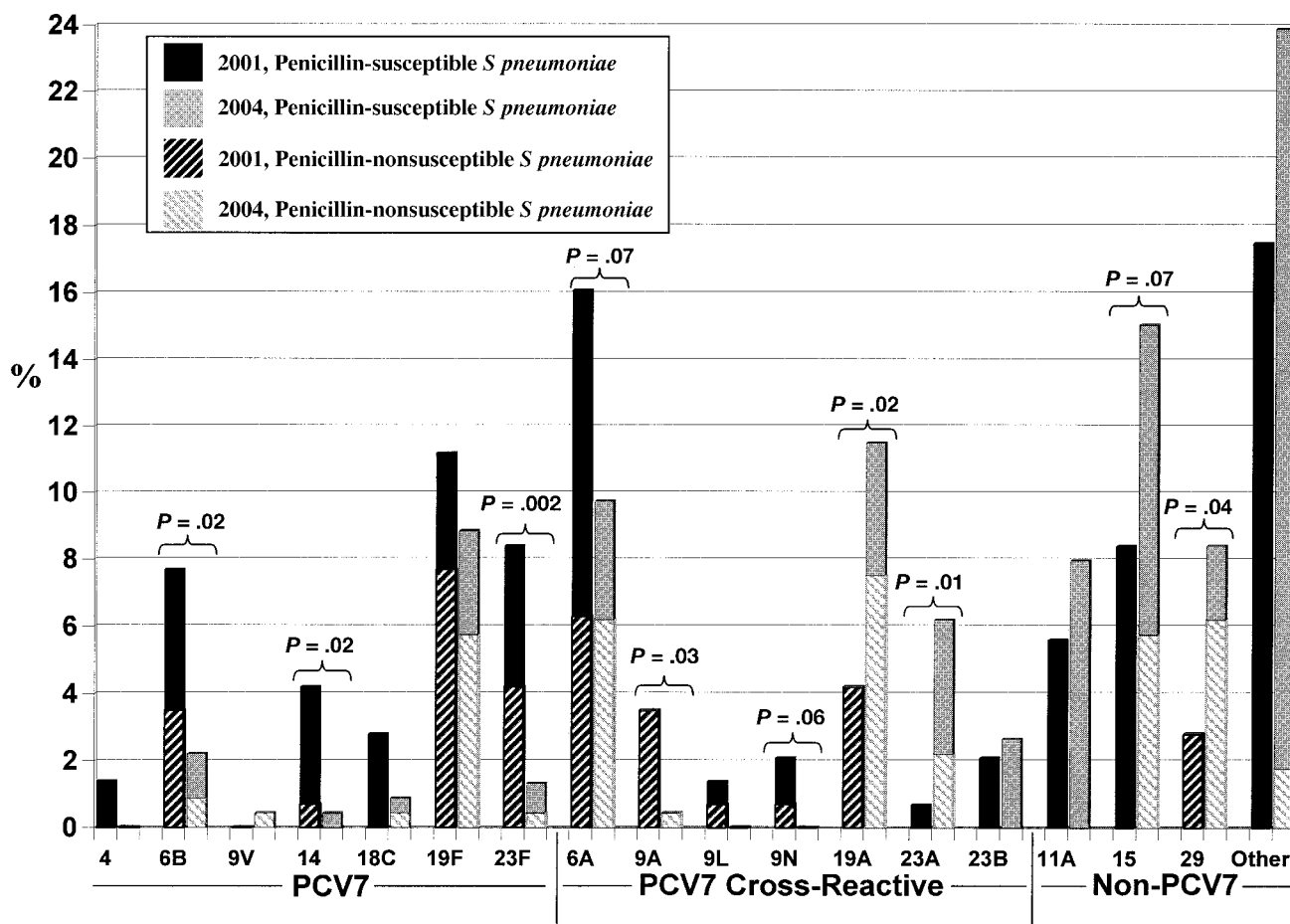
Fig 2. Distribution of pneumococcal serotypes as a percentage of total serotypes in 2001 shown in comparison with that in 2004. *P* values for Fisher exact tests demonstrating trends and significant changes between serotype-specific proportional carriage in 2001 and 2004 are shown. Hatched bars represent the proportion of isolates for a given serotype that are nonsusceptible to penicillin.

serotypes among those who were at least 12 months of age was low among both vaccine recipients (5%; 10 of 191) and nonrecipients (3%; 8 of 306). No reduction in overall carriage of vaccine serotypes was seen in 2004, although the proportion of PCV7 serotypes among carriers declined.

Overall carriage of a PNSP isolate was similar in 2001 (7%; 49 of 695) and 2004 (9%; 86 of 988). However, penicillin nonsusceptibility declined among PCV7 isolates and increased among non-PCV7 isolates (Fig 1). The former reflected a decrease in high-level penicillin-resistant isolates, whereas the latter

TABLE 3. Overall Pneumococcal Serotypes and Antibiotic Resistance by Surveillance Period*

Serotypes	Year	PCN-I, % (n)	PCN-R, % (n)	PNSP, % (n)	E-NS, % (n)	Clin-NS, % (n)	T/S-NS, % (n)	Ctx-NS, % (n)	MDR1, % (n)	MDR2, % (n)
PCV7	2001	12% (6)	33% (17)	45% (23)	35% (18)	12% (6)	41% (21)	27% (14)	43% (22)	31% (16)
	2004	19% (6)	38% (12)	56% (18)	34% (11)	13% (4)	47% (15)	6% (2) P = .02	44% (14)	38% (12)
PCV7–cross-reactive	2001	28% (12)	23% (10)	51% (22)	19% (8)	0% (0)	51% (22)	16% (7)	40% (17)	9% (4)
	2004	43% (30)	10% (7) P = .06	54% (37)	32% (22)	4% (3)	26% (18) P = .009	4% (3) P = .04	35% (24)	20% (14)
Non-PCV7	2001	2% (1)	6% (3)	8% (4)	6% (3)	0% (0)	8% (4)	6% (3)	2% (1)	2% (1)
	2004	16% (20) P = .009	9% (11)	25% (31) P = .01	14% (18)	11% (14) P = .01	14% (18)	0% (0) P = .02	14% (18) P = .02	10% (13)
Total†	2001	13% (19)	21% (30)	34% (49)	20% (29)	4% (6)	33% (47)	17% (24)	28% (40)	15% (21)
	2004	25% (56) P = .008	13% (30) P = .06	38% (86)	23% (51)	9% (21)	23% (51) P = .04	2% (5) P < .0001	25% (56)	17% (39)

PCN indicates penicillin; E, erythromycin; Clin, clindamycin; T/S, trimethoprim-sulfamethoxazole; Ctx, ceftriaxone; I, intermediate-level resistance; R, high-level resistance; NS, nonsusceptible.
* Two-tailed Fisher exact tests are provided comparing changes in proportional antimicrobial susceptibility within vaccine groups between 2001 and 2004 isolates.
† Based on isolates with both antibiotic susceptibility and serotype data. In 2001, 23 isolates were lost after antibiotic susceptibility tests but before serotyping.

reflected an increase in intermediate resistance to penicillin (Table 3).

Penicillin nonsusceptibility varied among commonly carried serotypes. In 2004, the proportion of PNSP was 64% in 6A, 0% in 11A, 38% in 15, 65% in 19A, 65% in 19F, 36% in 23A, and 74% in 29 (see Fig 2).

Changes in susceptibility to additional antibiotics is shown in Table 3. Ceftriaxone nonsusceptibility declined significantly between 2001 and 2004 isolates, largely as a result of declines in intermediate resistance (14% in 2001 vs 0.4% in 2004; $P < .0001$). This decline was seen across PCV7, PCV7 cross-reactive, and non-PCV7 serogroups, even when accounting for the fact that National Committee for Clinical Laboratory Standards breakpoints had changed between 2001 and 2004.[22] Trimethoprim-sulfamethoxazole nonsusceptibility also declined significantly. On the contrary, clindamycin nonsusceptibility increased, particularly among non-PCV7 serotypes. Clindamycin nonsusceptibility was highly correlated with macrolide nonsusceptibility (6 of 6 in 2001; 20 of 21 in 2004). Fluoroquinolone nonsusceptibility was minimal in both 2001 (3%; 4 of 143) and 2004 (0%; 0 of 226). Notably, among non-PCV7 serotypes, nonsusceptibility significantly increased for penicillin, clindamycin, and MDR (Table 3). The proportion of isolates that were resistant to 3 or more antibiotic classes increased from 9% (4 of 43) to 20% (14 of 69) among PCV7 cross-reactive serotypes and from 2% (1 of 49) to 10% (13 of 125) among non-PCV7 serotypes.

DISCUSSION

The licensure of PCV7 was accompanied by projections of decreased *S pneumoniae* carriage, invasive disease, and antibiotic resistance.[13,15,17] When evaluating young healthy children in the same 16 Massachusetts communities in 2001 and 2004, we found significantly increased carriage of nonvaccine strains and increased antibiotic resistance among nonvaccine serotypes.

Despite the significant decline in PCV7 serotypes, overall pneumococcal carriage did not change between 2001 and 2004 because of significant increases in the carriage of non-PCV7 serotypes. This serotype replacement was seen in all pediatric age groups studied and resulted in similar proportions of pneumococcal carriage in age groups between 6 and 36 months for both sampling periods. Among children who were ≥36 months of age, overall carriage declined between 2001 and 2004. This is not surprising given differential vaccination of children of this age in 2004 compared with 2001 (unlikely to be vaccinated unless at high risk). By contrast, we have no clear explanation for the observed increased rate of carriage among young infants (<6 months).

These changes suggest a rapid replacement of vaccine serotypes by nonvaccine serotypes, either by the unmasking of previous minority strains[24] or by replacement of previous PCV7 carriage by serotypes unaffected by vaccine immunity. Another possibility is serotype switch,[25] whereby pneumococcal strains express a new capsular serotype, possibly to evade host immunity. This phenomenon has been described between 15B and 15C,[26] 19F and 23F,[27] 9V and 11A,[28] and others.[25]

Although serotype replacement has been a concern after the release of the conjugate pneumococcal vaccine, experts hoped that antibiotic resistance would decrease because resistance had been highly concentrated in PCV7 and PCV7 cross-reactive serotypes.[1,20,29] As hoped, our serial community-based sampling showed that high-level penicillin resistance declined 38% and nonsusceptibility to third-generation cephalosporins decreased 88% across all isolates. However, this reduction in high-level penicillin resistance, produced by the reduction in carriage of certain PCV7 and PCV7 cross-reactive serotypes, was offset by increased carriage of nonvaccine serotypes, in which intermediate penicillin resistance has risen significantly. Antibiotic resistance among non-PCV7 pneumococcal serotypes (which had been negligible in 2001) increased to 25%, and resistance to 3 or more antibiotic classes increased to 10%.

In addition to increasing intermediate penicillin resistance, non-PCV7 strains showed an increase in clindamycin nonsusceptibility that was highly associated with macrolide resistance. Until now, most *S pneumoniae* isolates that are resistant to macrolides in the United States have displayed the M phenotype, related to a macrolide-specific efflux mechanism.[30] The mechanism of resistance associated with dual macrolide and clindamycin resistance is related to the MLS phenotype, which is a result of target modification at the 50S ribosomal subunit.[30] As the prevalence of non-PCV7 carriage increases, antibiotic exposure may be providing a selective pressure toward the emergence of additional resistance in these serotypes.

These data must be interpreted with the following caveats. First, we assume that carriage among children who seek care from primary care providers reflects carriage in their community. Although this assumption depends on the distribution of patients in a given practice, we believe it to be better than sampling schemes in child care settings that likely overrepresent shared colonizing strains. Second, the surveillance period occurred later in the season in 2001 compared with 2004 and may have affected carriage prevalence slightly, although we expect the proportion of serotypes among carriers to be unaffected. Third, because we sampled only twice, it is possible that we have observed natural fluctuations in the pneumococcal carriage state, rather than a trend related to the introduction of pneumococcal conjugate vaccine. We believe this unlikely given the magnitude and consistent direction of the shifts.

These data provide insight into the impact of PCV7 on pneumococcal carriage in young children. All communities included both immunized and unimmunized children, but, by 2004, all children who were younger than 42 months were born after routine PCV7 immunization began. As reflected in our study subjects, Massachusetts has one of the highest documented immunization rates in the United States.[31] In this sample, we find evidence for in-

creased carriage of non-PCV7 serotypes among vaccinated children who were older than 12 months.

It remains to be seen whether invasive infections caused by non-PCV serotypes will become more common. Recent data[32] suggest that nonvaccine serotypes, including novel ones,[33,34] may become important pathogens and that increased antibiotic resistance among these strains[33,34] may have adverse consequences for children over time. Continued evaluation of the pneumococcal reservoir may presage changes in strains that are responsible for localized and invasive disease as a result of the widespread use of PCV7. Such information may inform clinicians' expectations of antibiotic resistance in pneumococcal infections as well as development of the next generation of conjugate pneumococcal vaccines.

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Huang et al. Post-PCV7 Changes in Colonizing Pneumococcal Serotypes in 16 Massachusetts Communities, 2001 and 2004. PEDIATRICS 2005;116:e408–e413.

An error appeared in the article by Huang et al, titled "Post-PCV7 Changes in Colonizing Pneumococcal Serotypes in 16 Massachusetts Communities, 2001 and 2004," that was published in the September 2005 issue of *Pediatrics* Electronic Pages (2005;116:e408–e413). The authors reported serotype and resistance data on pneumococcal isolates from young children in 16 Massachusetts communities sampled in 2001 and 2004. In doing additional genetic analysis of these isolates, they discovered a small number (4.6%) with a discrepancy between the serotyping result based on antibody reaction (historically, the gold-standard method) and the serotypes suggested by the genetic sequence types.[1]

The authors repeated antibody-based serotyping of discrepant strains and have found most mismatched serotypes to be those predicted by genetic analysis. The serotype reassignments have resulted in small (mostly single-integer) changes in the percentages of specific serotype groups reported in the article. The key findings of the paper remain unchanged, both in terms of clinical and statistical significance. Nasopharyngeal carriage of non-PCV7 strains has increased, antibiotic resistance within non-PCV7 strains has increased substantially, and the resistance rates among isolates included in the
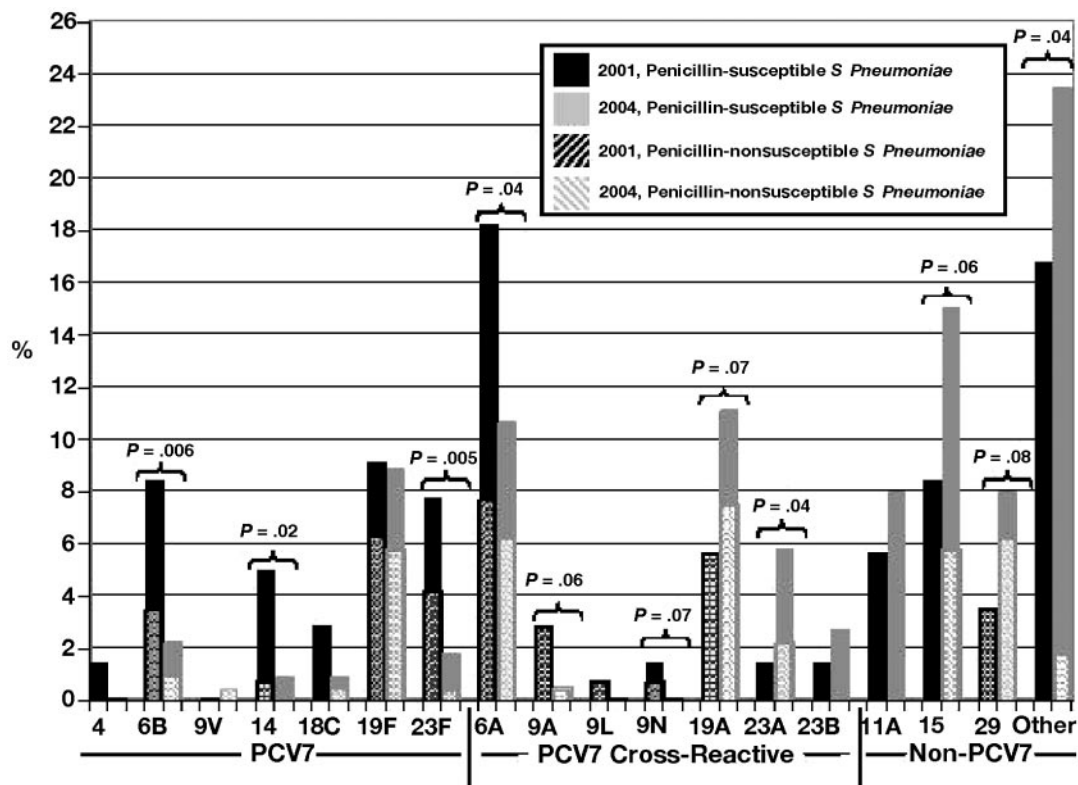

FIGURE 2

Distribution of pneumococcal serotypes as a percent of total serotypes in 2001 shown in comparison to that in 2004. *P* values for Fisher's exact tests demonstrating trends and significant changes between serotype-specific proportional carriage in 2001 and 2004 are shown. Hatched bars represent the proportion of isolates for a given serotype that are nonsusceptible to penicillin.

PCV7 vaccine, those potentially cross-reactive, and those not included in the vaccine remain as previously reported.

Nevertheless, it is worth noting changes in some of the reported numbers of individual serotypes and their resistance profiles. The authors provide a corrected Fig 2 to reflect changes in 17 of 369 reported isolates, resulting in small changes in any given serotype. Although statistical significance remains unchanged for most serotypes, the authors do report 2 serotype groups (6A, Other) that now show a statistically significant difference, and 4 serotype groups (9A, 19A, 23A, 29) that change from a statistically significant difference to a trend toward significance.

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Han et al. Unexpected Increased Mortality After Implementation of a Commercially Sold Computerized Physician Order Entry System. PEDIATRICS 2005;116:1506–1512.

Two errors appeared in the article by Han et al, titled "Unexpected Increased Mortality After Implementation of a Commercially Sold Computerized Physician Order Entry System," that was published in the December 2005 issue of *Pediatrics* (2005;116:1506–1512). In the Results section, on page 1509, second column, the authors wrote: "Furthermore, because pharmacy could not process medication orders until they had been activated, ICU nurses also spent significant amounts of time at a separate computer terminal and away from the bedside." The sentence should have read as follows: "Furthermore, ICU nurses spent signficant amounts of time at a separate computer terminal and away from the bedside to acknowledge new medication orders."

On page 1510, first column, the authors wrote: "After CPOE implementation, because order entry and activation occurred through a computer interface, often separated by several bed spaces or separate ICU pods, the opportunities for such face-to-face physician-nurse communication were diminished." The sentence should have read as follows: "After CPOE implementation, because order entry and acknowledgment occurred through a computer interface, often separated by several bed spaces or separate ICU pods, the opportunities for such face-to-face physician-nurse communication were diminished."