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Immunization, Antibiotic Use, and Pneumococcal Colonization Over a 15-Year Period

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BACKGROUND: Rates of invasive pneumococcal disease have declined since widespread introduction of pneumococcal conjugate vaccines (PCVs) in the United States. We evaluated the impact of immunization status and recent antibiotic use on an individual child's risk of colonization.
METHODS: This study extends previously reported data from children <7 years of age seen for well child or acute care visits in Massachusetts communities. Nasopharyngeal swabs were collected during 6 surveillance seasons from 2000 to 2014. Parent surveys and medical record reviews confirmed immunization status and recent antibiotic use. We estimated the proportions of children colonized with PCV7-included, additional PCV13-included, and non-PCV13 serotypes. Risk factors for colonization with additional PCV13-included and non-PCV13 serotypes were assessed by using generalized linear mixed models adjusted for clustering by community.
RESULTS: Among 6537 children, 19A emerged as the predominant serotype in 2004, with substantial reductions in 2014. Among non-PCV serotypes, 15B/C, 35B, 23B, 11A, and 23A were most common in 2014. We observed greater odds for both additional PCV13 and non-PCV13 colonization in younger children, those with more child care exposure, and those with a concomitant respiratory tract infection. Adjusted odds for additional PCV13 colonization was lower (odds ratio 0.48 [95% confidence interval 0.31–0.75]) among children up-to-date for PCV13 vaccines. Recent antibiotic use was associated with higher odds of additional PCV13 colonization but substantially lower odds of non-PCV13 colonization.
CONCLUSIONS: Despite the success of pneumococcal vaccines in reducing colonization and disease due to targeted serotypes, ongoing community-based surveillance will be critical to evaluate the impact of interventions on pneumococcal colonization and disease.

Over the past decade and a half, we have witnessed dramatic declines in the United States in invasive pneumococcal disease in young children, [1 – 4] reductions in pneumonia hospitalizations, [5 – 8] and herd protection against vaccine type disease in older adults [9, 10] as a consequence of widespread use of pneumococcal conjugate vaccine (PCV) 7 beginning in 2000. Although replacement with nonvaccine serotypes, particularly 19A, emerged as a concern, invasive disease rates never reached the same level in the United States as those seen during the pre-PCV7 era.[11, 12] PCV13, which became available in 2010, had the added benefit of targeting serotype 19A that was then responsible for the vast majority of invasive disease in the United States. Further reductions in overall rates

of invasive disease and colonization were anticipated.[13–15] We and others reported reductions in rates of vaccine-type colonization and disease shortly after PCV13 was introduced in 2011, with concomitant increases in nonvaccine-type pneumococcal colonization.[16, 17]

We have previously reported analyses of pneumococcal surveillance in Massachusetts communities between 2000 and 2011. With this study, we extend the data to include isolates collected from 2013 to 2014 and analyze the entire collection from 2000 to 2014 to assess impact of serial introduction of pneumococcal vaccines. In addition, as patterns of antibiotic resistance have changed in the pneumococcal population, often associated with particular serotypes, we are able to assess the impact of previous recent antibiotic use on pneumococcal colonization by serotype in young children.

Methods

Study Design and Population

Our study population included children <7 years of age seen for well child or acute care visits in Massachusetts communities during 6 surveillance seasons over a 15-year period. Eight communities were sampled in each of the 6 respiratory illness seasons during 2000 to 2001, 2003 to 2004, 2006 to 2007, 2008 to 2009, 2010 to 2011, and 2013 to 2014, hereafter referred to as 2001, 2004, 2007, 2009, 2011, and 2014. An additional 8 communities were also sampled in the first 2 surveillance seasons, and 1 urban community was sampled in the third, fifth, and sixth surveillance seasons. Methods for sample collection and processing have been previously described in detail.[17–19] Briefly, we obtained nasopharyngeal swabs from children presenting to their primary care physician's office for well-child care or an illness-related visit. During these visits, we asked parents to respond to a survey to identify potential risk factors for pneumococcal colonization. We also conducted medical record reviews to confirm immunization status and prescribing of antimicrobial agents in the previous 6 months. Children were considered up-to-date (UTD) on either the PCV7 series or PCV13 series by the following criteria: if they had received ≥1 dose if <6 months of age; ≥2 doses if 6–11 months; ≥3 doses if 12–15 months; or ≥4 doses if 16 months or older. Because PCV13 was not available in Massachusetts until April 2010, we considered children to be UTD with PCV13 in the 2011 season if they had received the following: ≥1 dose of PCV13 if <6 months; ≥2 doses of PCV13 if 6–11 months; ≥3 doses of any pneumococcal vaccine with at least 1 dose of PCV13 if 12–15 months; or ≥4 doses of any pneumococcal vaccine with at least 1 dose of PCV13 if 16 months or older. This study was approved by the Harvard Pilgrim Health Care Institutional Review Board.

Laboratory Methods

Nasopharyngeal swabs were plated within 24 hours of collection on selective media with gentamicin for identification of *Streptococcus pneumoniae*. Serotype was determined by using the Quellung reaction to antisera to specific capsular antigens (Serum Statens Institute, Copenhagen, Denmark). Pneumococcal isolates were identified as PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), additional PCV13-included serotypes (1, 3,

5, 6A, 7F, 19A), and non-PCV13 serotypes. Antibiotic susceptibility testing was performed by using E-tests for penicillin, ceftriaxone, erythromycin, clindamycin, trimethoprim-sulfamethoxazole, and vancomycin. Pneumococci were classified as susceptible, intermediate, or resistant based on current Clinical and Laboratory Standards Institute breakpoints for nonmeningeal isolates. *S pneumoniae* isolates were considered nonsusceptible to penicillin if they showed intermediate (4.0 mg/L) or resistant (≥8.0 mg/L) isolate susceptibility.20 Nonsusceptibility was also defined as any intermediate or resistant isolate at the following thresholds: ceftriaxone (2.0 mg/L, ≥4.0 mg/L), erythromycin (0.5 mg/L, ≥1.0 mg/L), and clindamycin (1.0–2.0 mg/L, ≥4.0 mg/L).

Data Analysis

We calculated the proportion of children colonized with PCV7 serotypes, additional PCV13 serotypes, and non-PCV13 serotypes in each year of surveillance. To better visualize temporal trends, we constructed heat maps of the proportion of children colonized with individual PCV7, additional PCV13, and non-PCV13 serotypes over time. We also calculated the proportion of antibiotic-resistant isolates among all pneumococci isolated, along with serotypes responsible for antibiotic resistance. Individual risk factors Associated with carriage of additional PCV13 serotypes (with serotypes not covered by PCV7) and non-PCV13 serotypes were assessed by using generalized linear mixed models utilizing logistic regression to adjust for clustering (nonindependence) of subjects within communities. All analyses were performed by using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

Study Population

We obtained nasopharyngeal samples for surveillance for pneumococcal colonization in Massachusetts' communities in children <7 years of age in 2001 (N = 678), 2004 (N = 987), 2007 (N = 1540), 2009 (N = 1011), 2011 (N = 1164), and 2014 (N = 1157). Over the study period, a greater proportion of children in samples from these Massachusetts communities spent time in daycare, fewer children had smokers in the household, and more children were breastfed for longer periods of time (Table 1).

Temporal Trends in Pneumococcal Colonization

Overall, the rate of pneumococcal colonization ranged from 23% to 32% (Fig 1). Declines in overall pneumococcal colonization rates appeared to follow in the first several years after the introduction of PCV7 (ie, 2004 lower compared with 2001, P = .039) and PCV13 (ie, 2014 lower compared with 2011, P = .09). The decline after PCV7 introduction was transient, and it appeared to be because of declines in colonization with vaccine serotypes, before replacement with and expansion of nonvaccine serotypes. We do not have data after 2014 to understand whether declines after PCV13 will be similarly transient. We then considered rates of colonization by individual serotype and over time among children during each surveillance

TABLE 1 Characteristics of Study Population for Pneumococcal Surveillance in Massachusetts, 2001–2014

	2001	2004	2007	2009	2011	2014
	N = 678 (%)	*N* = 987 (%)	*N* = 1540 (%)	*N* = 1011 (%)	*N* = 1164 (%)	*N* = 1157 (%)
Communities						
A	5	8	8	12	11	11
B	10	10	8	12	11	11
C	5	8	10	13	12	11
D	7	6	9	12	11	11
E	5	8	5	11	12	11
F	6	7	7	15	11	11
G	5	7	8	14	11	11
H	5	5	8	12	11	11
Other communities	52	41	37	0	9	11
Age group (mo)						
<6	9	5	9	8	7	7
6–<12	17	12	17	17	18	14
12–<24	21	23	26	23	23	27
24–<59	36	42	35	38	35	36
60–<84	17	18	13	14	16	16
Female	46	53	48	48	46	47
Young siblings						
0	53	50	58	54	53	50
1	37	39	34	37	37	41
≥2	10	11	8	9	10	9
Child care (h)						
0–<4	56	49	50	43	46	44
4–10	15	12	8	12	12	12
11–20	6	14	8	12	11	10
>20	24	26	33	33	33	34
Smoker in household	30	21	20	26	22	20
Breastfeeding						
No	39	35	27	29	24	23
Yes, for <3 mo	18	17	19	20	20	21
Yes, for 3–6 mo	24	21	24	22	26	25
Yes, for >6 mo	19	27	30	28	30	31
Presence of respiratory tract infection at time of swab (chart only)	29	27	46	39	33	33
Race						
White, non-Hispanic	78	84	53	82	69	68
Black, non-Hispanic	7	4	28	5	12	13
Hispanic	8	6	12	7	11	13
Asian/Pacific Islander	3	2	2	4	5	5
Other	5	5	4	1	3	1

season (Fig 2). Serotypes are grouped on the heat map as PCV7 serotypes in decreasing prevalence order (19F, 23F, 6B, 14, 18C, 9V, 4), additional PCV13 serotypes (19A, 3, 7F, 6A), and frequent non-PCV13 serotypes (15B/C, 35B, 23B, 11A, 23A, 15A, 35F, 33F, 21, 10A, 22F, 16F, 7C, 6C). We did not observe any children colonized with serotypes 1 or 5 throughout the 15-year study period. As anticipated, PCV7 serotypes were most common in 2001 and began to wane in 2004 before disappearing in 2007 (Fig 2A), although serotype 19F persisted longer compared with other PCV7 serotypes. Among the PCV13 serotypes, 19A emerged as the predominant serotype in 2004 and remained so until substantial reductions were noted in 2014. Interestingly, serotype 6A (which is a PCV13 serotype) gradually declined after the introduction of PCV7. Among non-PCV serotypes, several emerged as common colonizers in

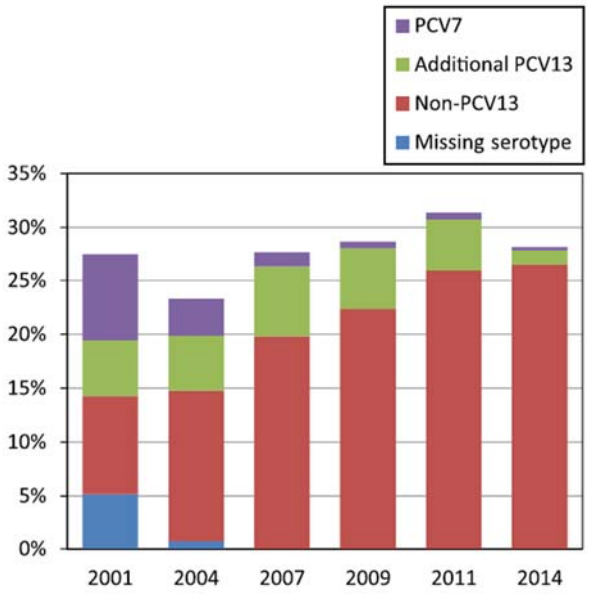

FIGURE 1
Pneumococcal colonization by vaccine serotype in selected Massachusetts communities from 2001 to 2014. PCV7 was recommended for use in 2000 and PCV13 was recommended to replace PCV7 in 2010.

11A, and 23A (Fig 2B). 15B/C and 11A were already the most prevalent of the non-PCV serotypes in 2001, and 35B and 23A emerged as more common serotypes in 2004. These serotypes continued to expand in subsequent years as might have been anticipated. In contrast, 15A, 35F, 10A, and 22F occurred more commonly relative to other non-PCV serotypes in 2001 or 2004, yet they did not succeed as predominant colonizers in 2014. More recently, serotype 23B emerged in 2009, and it appears to have rapidly expanded to become the third most common serotype in 2014. Finally, serotype 6C has an unusual pattern in that the prevalence initially rose from 2001 to 2009 followed by a decline after widespread use of PCV13 vaccines, which might have been anticipated because of cross reactivity with 6A.[21, 22]

Pneumococcal Colonization by Antibiotic Susceptibility

Between 2001 and 2011, penicillin nonsusceptibility declined substantially and remained low, cephalosporin nonsusceptibility declined initially followed by a rebound, and macrolide nonsusceptibility appeared to rise (Fig 3, Supplemental Fig 4). In the 2014 season, erythromycin nonsusceptibility was most common (34.7%), followed by ceftriaxone (12.3%), clindamycin (9.2%), and penicillin (5.8%) nonsusceptibility. We did not observe any isolates with vancomycin resistance. Among nonsusceptible isolates in 2014, serotype 19A was responsible for 15.4% of penicillin-intermediate isolates, 66.7% of penicillinresistant isolates, 15% of ceftriaxone nonsusceptible isolates, 4.4% of erythromycin nonsusceptible isolates, and 13.3% of clindamycin nonsusceptible isolates. Although serotype 19A declined in prevalence between 2009 and 2014, we did not note any overall decline in the proportion of nonsusceptible isolates. Rather, rates of resistance continue to rise for each drug class, with serotype 35B accounting for 82.5% of ceftriaxone nonsusceptible isolates and various nonPCV13 serotypes accounting for 94.7% of erythromycin nonsusceptible isolates.

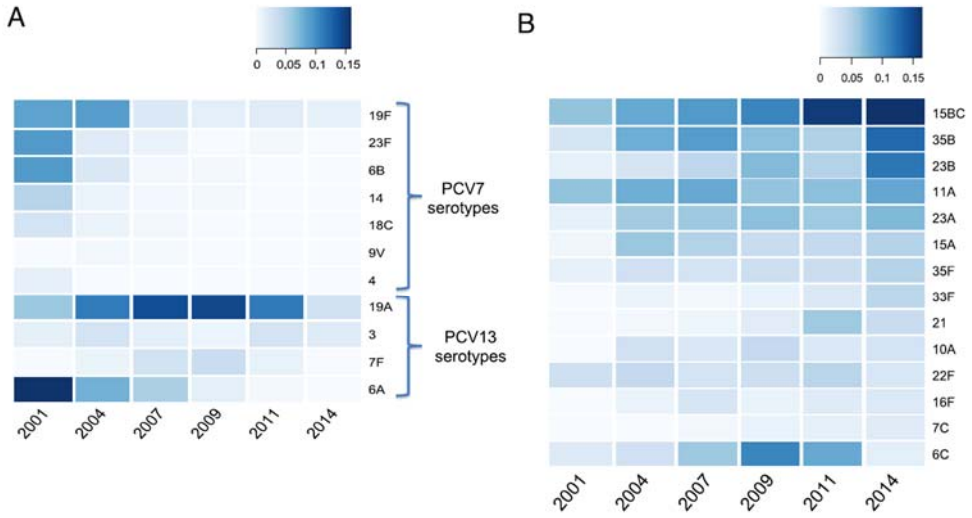

FIGURE 2
Pneumococcal colonization by serotype from 2001 to 2014 for (A) PCV7 and additional PCV13 serotypes, and (B) non-PCV13 serotypes. The scale represents the proportion of children swabbed that were colonized with each serotype.

Risk Factors Associated With Colonization

We examined risk factors for additional PCV13 colonization and non-PCV13 colonization over the entire study period in Massachusetts. We observed a greater risk for additional PCV13 colonization and for non-PCV13 colonization among younger children, those who had more hours of child care exposure, and those with a respiratory tract infection on the day of sampling (Table 2). When our data were pooled across all study years, the presence of a smoker in the household was significantly associated with additional PCV13 colonization in adjusted models (odds ratio [OR] 1.46 [95% confidence interval (CI) 1.10–1.94]), although it was not associated with non-PCV13

colonization (OR 0.86 [95% CI 0.73–1.02]). The adjusted odds for additional PCV13 colonization was lower (OR 0.48 [95% (CI) 0.31–0.75]) among children who were UTD for PCV13 vaccines. In contrast, vaccination with either PCV7 or PCV13 was associated with a higher risk of non-PCV13 colonization across all study years (OR 1.29 [95% CI 1.06–1.58] for PCV7; OR 1.66 [95% CI 1.34–2.06] for PCV13). Finally, recent antibiotic use was generally associated with higher risk of additional PCV13 colonization, predominantly 19A, perhaps reflecting selection of resistant 19A carriage by antibiotic use. In contrast, substantially lower rates of non-PCV13 colonization were noted among children with recent antibiotic use.

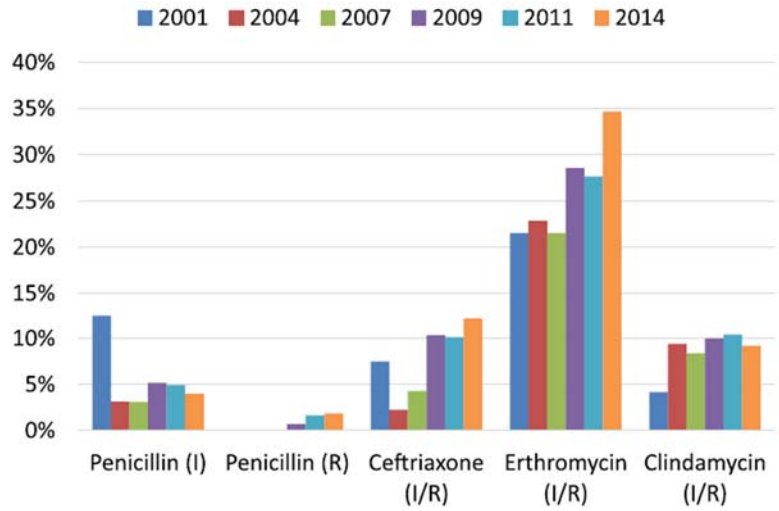

FIGURE 3
Antibiotic nonsusceptibility of pneumococcal isolates from 2001 to 2014. I, indicates intermediate susceptibility; R, indicates isolates are resistant.

Discussion

We have had the unique opportunity to monitor the impact of PCV7 and PCV13 vaccinations among young children in Massachusetts' communities over a 15-year period between 2000 and 2014. Our long-standing partnerships with pediatric practices in Massachusetts and the patients they serve have been critical for our success in documenting the near elimination of colonization with PCV7 serotypes and substantial ongoing declines in additional PCV13 serotype colonization.[17 – 19, 23– 25] Benefits of these vaccines have also been seen in reductions in the incidence of pneumococcal pneumonia and invasive pneumococcal disease in the United States, because of targeted serotypes for both children who have been directly protected through vaccination and for older adults through herd immunity.[10, 26, 27] However, replacement with nonincluded serotypes remains a risk with vaccines that do not cover the full range of serotype diversity. As new selective pressures are applied, such as the introduction of a vaccine into a community, the void may be filled by nontargeted serotypes, as was observed after PCV7.

Several key findings deserve further consideration. First, we note that PCV7 serotypes, with the exception of 19F, nearly disappeared from these communities by 2004, ~3 years after the introduction and rapid adoption of PCV7 in Massachusetts.
In a previous trial of PCV7 vaccines, the presence of serotype-specific serum immunoglobulin G was not associated with a reduction in acquisition of serotype 19F, which may explain our findings of lower effectiveness in this population.[28, 29] Next we observed rapid reductions in certain additional PCV13 serotypes ~3 years after introduction of PCV13, although, notably, serotypes 19A and 3 continued to be present at low rates in 2014. Possible reasons for the persistence of 19A and 3 include genetic diversity leading to less effective immune responses [22, 30, 31] or selection pressure from recent antibiotic use.[32 – 34] Of note, first-line penicillins continue to be the most frequently prescribed antibiotic across all age groups among young children in Massachusetts, which may result in the continued success of 19A associated with penicillin resistance.[35] Third, the prevalence of serotype 6A declined with PCV7 vaccination, and serotype 6C declined with additional PCV13 vaccination, which may have been due to cross-protective effects of the capsular serotypes that were included in each vaccine.[21, 22] Finally, despite our best efforts to understand factors associated with success of certain serotypes under selective pressure, the complex interplay of a multitude of host and organism factors challenges our ability to predict serotypes-specific success. In particular, it is impossible between individual antimicrobial use, use of

TABLE 2 Factors Associated With (A) Additional PCV13 Serotype Colonization and (B) Non-PCV13 Serotype Colonization in Our Study Population From 2001 to 2014

	Additional PCV13 Serotype Colonization		Non-PCV13 Serotype Colonization	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age group (mo)		.0006		<.0001
<6	2.43 (1.26–4.68)		1.73 (0.99–2.17)	
6–<12	2.74 (1.64–4.59)		2.46 (1.45–2.70)	
12–<24	2.30 (1.41–3.73)		2.26 (1.43–2.55)	
24–<60	1.49 (0.95–2.34)		1.70 (1.15–1.90)	
60–<84	1.0		1.0	
Female	0.95 (0.73–1.23)	.71	0.97 (0.85–1.11)	.65
Child care (h)		<.002		<.0001
0–<4	0.55 (0.40–0.75)		0.46 (0.39–0.54)	
4–10	0.67 (0.43–1.06)		0.75 (0.60–0.94)	
11–20	0.71 (0.44–1.14)		0.90 (0.72–1.13)	
>20	1.0		1.0	
Smoker in household	1.46 (1.10–1.94)	.0096	0.86 (0.73–1.02)	.08
Presence of respiratory tract infection at time of swab[a]	1.37 (1.05–1.79)	.019	1.47 (1.28–1.70)	<.0001
Vaccination UTD status		<.0001		<.0001
UTD for PCV7	1.16 (0.82–1.64)		1.29 (1.06–1.58)	
UTD for PCV13	0.48 (0.31–0.75)		1.66 (1.34–2.06)	
Not UTD for either	1.0		1.0	
Recent antibiotic use in past 6 mo		.034		<.0001
<2 wk ago	1.11 (0.69–1.78)		0.28 (0.19–0.42)	
2–<4 wk ago	1.63 (1.06–2.52)		0.40 (0.28–0.56)	
4–<8 wk ago	1.01 (0.62–1.66)		0.66 (0.50–0.87)	
8 wk–≤6 mo ago	1.58 (1.13–2.21)		0.46 (0.23–0.93)	
None	1.0		1.0	

[a] Respiratory tract infection is defined on the basis of symptoms or clinician diagnosis, including upper respiratory tract symptoms (rhinorrhea, congestion, sore throat), acute otitis media, otitis media with effusion, bronchiolitis, pharyngitis, upper respiratory tract infection, viral syndrome, and croup.

antimicrobial agents in the community between individual antimicrobial use, use of antimicrobial agents in the community, and serotype-specific characteristics and determine the impact those relationships have on the success of particular strains that continue to circulate in the community. Nonetheless, we have gained enormous knowledge about genetic mechanisms that may drive colonization patterns within our

communities.[36]

Both younger age and child care attendance appear to be fairly consistent risk factors for pneumococcal colonization. In addition, the presence of a respiratory tract infection increased the risk of detecting pneumococcal colonization, regardless of serotype. Viral infections may result in disruption of the epithelial barrier and entry of pathogens such as *S pneumoniae* via exposure of the basement membrane and exposure of fibronectin.[37, 38] Viral infections may also lead to upregulation of adhesion proteins, such as intracellular adhesion molecule 1 or platelet activating factor receptor that enable enhanced adherence of *S pneumonia* to the respiratory epithelium; alternatively, local cytokine production after viral infections may impair bacterial clearance leading to increased colonization density in the respiratory tract.[37, 39] The presence of smokers in the household was associated with higher rates of PCV13 colonization. Smoking may impair ciliary clearance and cause damage to respiratory epithelium, and it is known to be associated with invasive pneumococcal disease, although it remains unclear why this association did not hold for children colonized with non-PCV13 serotypes.[40, 41] Nonetheless, pneumococcal vaccination of adults who smoke may reduce the risk for pneumococcal colonization and invasive disease in young children residing in the same household. We also identified higher rates of non-PCV13 colonization (or non-PCV7 colonization in earlier years) in children UTD on pneumococcal vaccines, reinforcing the theory that replacement occurs when an open niche appears.[1, 42] Future vaccines that offer broad, serotype-independent coverage, such as protein-based vaccines, are in development and may offer a more permanent solution to reducing the burden of pneumococcal disease in the United States and worldwide.

Although our study is one of the largest to examine the impact of pneumococcal vaccines on trends in colonization in young, healthy US children, we note both strengths and limitations. First, our serial cross-sectional design allows us to assess colonization patterns in young children across different years. As a consequence, we do not have information on the duration of colonization within the nasopharynx in this population, which may be an important factor associated with the risk of disease and/or immunity. We also may not detect certain serotypes that only transiently colonize the nasopharynx before causing invasive disease, which may be why we did not observe colonization with serotypes 1 or 5. Nor did we detect cocolonization with multiple pneumococcal serotypes with our approach to processing of nasopharyngeal specimens. Another important limitation is that we did not consistently isolate other potential pathogenic and nonpathogenic organisms in the nasopharynx, which limits our ability to understand how the milieu of the nasopharynx affects pneumococcal colonization or clonal success. Further investigation using cultureindependent techniques may identify additional explanatory factors for the evolution and success of particular serotypes over time.

Conclusions

We describe our 15-year experience evaluating the impact of PVCs on colonization patterns in healthy, young children in Massachusetts' communities. Despite the success of these vaccines in reducing colonization and disease caused by these serotypes, replacement with nonvaccine serotypes remains an ongoing challenge. As newer

pneumococcal vaccines are developed, there will continue to be a need for monitoring both the intended and unintended consequences of altering the nasopharyngeal niche through immunization.

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instruments, coordinated and supervised data collection, and reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ms Huang conducts clinical studies in which participating hospitals and nursing homes receive contributed products from Sage Products, Molnlycke, 3M, Clorox, and Xttrium.

Dr Kleinman conducts trials in which participating hospitals and nursing homes receive contributed products from Sage Products and Clorox.

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