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Anticipated Effects of Higher-valency Pneumococcal Conjugate Vaccines on Colonization and Acute Otitis Media

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Abstract

Background: Bacterial etiologies of acute otitis media (AOM) have shifted from the introduction of pneumococcal conjugate vaccines (PCVs), antibiotic selection and competition among species. We characterized *Streptococcus pneumoniae* (*Spn*), *Haemophilus influenzae* (*Hflu*) and *Moraxella catarrhalis* (*Mcat*) in the nasopharynx during well-child healthy visits and at the onset of AOM, and in middle ear fluid (MEF) of children with AOM to assess anticipated effects of higher-valency PCVs (PCV15 and PCV20).

Methods: From September 2021 to September 2023, we conducted a prospective longitudinal cohort study of PCV13 immunized children 6–36 months old. MEF was collected via tympanocentesis. Serotyping and antibiotic susceptibility testing were performed on *Spn*, *Hflu* and *Mcat* isolates.

Results: We obtained 825 nasopharyngeal and 216 MEF samples from 301 children. The order of frequency of nasopharyngeal colonization was *Mcat*, *Spn* and *Hflu*; *Hflu* was the predominant otopathogen in MEF. Among *Spn* isolates, non-PCV15, non-PCV20 serotypes predominated in the nasopharynx and in MEF; the most frequent serotype was 35B. Among MEF samples, 30% of *Spn* isolates were amoxicillin nonsusceptible; 23% of *Hflu* isolates and 100% of *Mcat* isolates were β-lactamase-producing.

Conclusion: The majority of *Spn* isolates among young children were non-PCV15, non-PCV20 serotypes, especially serotype 35B; therefore, the impact of higher-valency PCVs in reducing pneumococcal colonization or AOM is expected to be limited. *Hflu* continues to be the most frequent AOM pathogen. Antibiotic susceptibility data suggest a high dose of amoxicillin/

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clavulanate or alternative drugs that are effective against contemporary mix of otopathogens could be considered for optimal empiric selection to provide the best efficacy.

Keywords

S. pneumoniae ; *H. influenzae* ; *M. catarrhalis* ; acute otitis media; colonization

Asymptomatic nasopharyngeal colonization and acute otitis media (AOM) caused by *Streptococcus pneumoniae* (*Spn*), *Haemophilus influenzae* (*Hflu*) and *Moraxella catarrhalis* (*Mcat*) are common in young children. Nasopharyngeal colonization precedes disease and is the critical step in the pathogenesis of AOM.[1] Dynamic shifts in *Spn, Hflu and Mcat* causing AOM and their antibiotic susceptibility profiles and strain diversity have occurred due to multiple factors including the introduction of pneumococcal conjugate vaccines (PCVs),[2–4] antibiotic selection pressure,[5–7] and competition among species, with *Hflu* outcompeting *Spn* and *Mcat*, most of the time.[8]

PCVs have reduced invasive pneumococcal disease (IPD) and pneumococcal AOM caused by pneumococcal serotypes included in the vaccines.[9–12] The 7-valent PCV (PCV7) was introduced in 2000 in the United States and was proven to be efficacious in preventing AOM.[2] Following introduction, PCV7 replacement *Spn* serotypes emerged and antibiotic-nonsusceptible strains became predominant causes of AOM, especially resistant serotype 19A.[13,14] To address the phenomena of *Spn* serotype replacement occurring under vaccine pressure, 13-valent PCV (PCV13) was introduced in 2010. While the effectiveness of the 6 additional non-PCV7 serotypes against AOM was demonstrated,[4] licensure for an AOM indication was not granted by regulatory agencies in the United States.

Spn serotype replacement continued to occur under PCV13 pressure, and replacement serotypes increasingly caused AOM.[4,15,16] *Spn* serotype composition of higher-valency PCVs was based on the prevalence of those most frequently causing IPD beyond the PCV13 serotypes over a decade ago, resulting in the addition of serotypes 22F and 33F to produce PCV15 and 22F, 33F, 8, 10A, 11A, 12F, 15B to produce PCV20. However, differences in common serotypes causing IPD and more common mucosal infections, such as AOM, have been reported.[6,15,17,18]

While higher-valency pneumococcal vaccines should confer protection against a wider range of pneumococcal serotypes, increasing serotype coverage has been known to decrease the immunogenicity of certain shared serotypes.[19–21] Within serotypes contained in PCV13, lower vaccine effectiveness against IPD and AOM has been observed for *Spn* serotypes 3, 19A and 19F[22,23] even after receiving PCV13 vaccine. In the phase 3 clinical trial comparing 15-valent PCV (PCV15) and PCV13, numerically lower IgG antibody concentrations were reported for 12 of 13 shared serotypes (except serotype 3) among PCV15-immunized children.[24] Noninferiority criteria were met for all 13 shared serotypes except for one of the endpoints for serotype 6A after 3 primary doses. In the phase 3 clinical trial comparing PCV20 and PCV13, numerically lower IgG antibody concentrations were reported for all 13 shared serotypes among PCV20-immunized children. Noninferiority criteria were missed for 5 of 13 shared serotypes (1, 3, 4, 9V and 23F) for one of the endpoints, but were met for other endpoints.[25–27] Lower antibody concentrations are most

likely due to antigenic competition, although the clinical impact of the lower antibody levels from the new PCVs is currently unknown.

We collected data on nasopharyngeal colonization and AOM infection etiology during September 2021–September 2023, the immediate 2 years before new United States recommendations for use of PCV15 and PCV20 in young children, to inform estimates of the noninvasive pneumococcal serotype distribution among young children.[27–29] The objective of this report is to provide insight regarding the contemporary microbiology of nasopharyngeal colonization and AOM episodes in children and estimate the anticipated effects of PCV15 and PCV20 on these endpoints.

METHODS

Study Population

We enrolled children between ages 6 and 36 months in an ongoing prospective, longitudinal cohort study in greater Rochester, NY. Children were followed to a maximum of age 36 months. Eligibility for enrollment and continuation in the study included receipt of age-appropriate PCV13 immunization at 2, 4 and 6 months and a booster dose at 12–15 months. We collected nasopharyngeal samples at routine healthy, well-child visits when the children were 6, 9, 12, 15, 18, 24 and/or 30–36 months of age. Not all study participants completed all potential study visits and procedures because they entered the study at age >6 months, did not reach age 36 months during the 2 years of the study, or due to parent requests or logistical challenges. At the first and any subsequent episodes of AOM, nasopharyngeal samples and middle ear fluid (MEF) collected by tympanocentesis were obtained. We reviewed electronic medical records to obtain epidemiologic information about each child including the presence of a clinical viral upper respiratory infection (URI) and antibiotic prescription history. The study was approved by the Rochester General Hospital IRB and written informed consent was obtained from parents before entry into the study.

Tympanocentesis, Nasopharyngeal Sampling, Microbiology and Serotyping

Tympanocentesis, nasopharyngeal sampling, microbiology to detect *Spn*, *Hflu* and *Mcat* and serotyping of *Spn* and *Hflu* were performed as previously described.[15,16,30] PCR was performed on culture-negative MEF samples as described previously targeting 16S[31] and *lytA* gene for *Spn*.[32]

Antibiotic Susceptibility

Oxacillin sensitivity was determined for all *Spn* isolates by disc diffusion test. Antibiotic susceptibility of *Spn* isolates was determined in a subset with the VITEK 2 Gram Positive Susceptibility Card- AST-ST02. Seventeen isolates of *Spn* failed to give antibiotic susceptibility in the system. All *Hflu* and *Mcat* isolates were tested for β-lactamase production with the chromogenic cephalosporin disc method. Antibiotic susceptibility of *Hflu* isolates to 14 antibiotics was performed as described previously.[33] Isolates of *Hflu* were tested for capsular types a–f by PCR as previously described.[33]

Statistical Analysis

GraphPad Prism 8.2.1 (CA) was used for all statistical analyses. Differences were analyzed with the Fisher exact test and $P < 0.05$ (2-tailed) was considered statistically significant.

RESULTS

Study Population

The demographic characteristics and AOM risk factors of the 301 children enrolled during 2021–2023 are summarized in Table, Supplemental Digital Content 1, http://links.lww.com/INF/F573. None received any doses of PCV15 or PCV20.

Nasopharyngeal Isolates From Healthy and AOM Visits

Nasopharyngeal samples were obtained at 825 study visits: 652 samples from healthy visits and 173 from AOM episodes. *Mcat* was the most common pathogen identified at healthy (41%) visits and AOM (61%) episodes, followed by *Spn* (24% and 46%, respectively) and *Hflu* (10% and 42%, respectively) (Table 1). All 3 pathogens were identified more frequently ($P < 0.0001$ for all 3 bacteria) at AOM episodes versus healthy visits. During AOM episodes, 93% of children also had a clinically diagnosed viral URI. Detection of *Hflu* was 4 times more frequent at AOM episodes compared to healthy visits ($P < 0.0001$). *Spn* isolates identified at AOM episodes were more often oxacillin nonsusceptible compared to *Spn* isolates at healthy visits ($P = 0.05$). No difference in β-lactamase-producing strains in *Hflu* occurred between healthy and AOM episodes and all *Mcat* were β-lactamase positive. The proportion of different otopathogens identified at healthy visits during age 6–36 months did not vary by age (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/F573), with the percentage of visits with *Spn* detection ranging from 19% to 29%, *Hflu* from 3% to 19% and *Mcat* from 34% to 46%.

Middle Ear Fluid Isolates

There were 179 AOM episodes among 111 (37%) of 301 children enrolled. Tympanocentesis was performed in 139 (78%) of 179 episodes of AOM, yielding 216 MEF samples, due to bilateral tympanocentesis. *Hflu* (40%) was the most common bacterial isolate identified from MEF, followed by *Spn* (19%) and *Mcat* (17%) (Table 2). Among the *Spn* isolates, 46% were oxacillin nonsusceptible. Among the *Hflu* isolates, 27% were β-lactamase-producing strains. All *Mcat* isolates were β-lactamase-producing strains.

PCR was performed for *Spn*, *Hflu* and *Mcat* on 90 culture-negative MEF samples from 65 AOM episodes. *Spn*, *Hflu* and *Mcat* were detected in 11%, 43% and 29% of culture-negative episodes, respectively. Some of the children had multiple otopathogens detected by PCR in MEF. For 25 (38%) of these 65 culture-negative, PCR-positive AOM episodes, children received antibiotics shortly before sample collection. Overall, there were 19 (14%) of 139 AOM episodes where tympanocentesis was performed that were both culture- and PCR-negative that could not be explained by the child having recently received antibiotics.

Comparison of Otopathogens Detected in the Nasopharynx and MEF During AOM

During 139 AOM episodes when both nasopharyngeal and MEF samples were collected, multiple otopathogens were detected in the nasopharynx during 51% of AOM episodes compared with 13% in MEF (Table 3). The most common otopathogen combination in the nasopharynx was *Spn* + *Mcat* (22%) followed by *Hflu* + *Mcat* (14%). By pathogen, *Hflu* was present in the nasopharynx of 44% of AOM episodes and in MEF of 40% of AOM episodes. In contrast, *Spn* was present in 45% (nasopharynx) and 19% (MEF) of AOM episodes, and *Mcat* was present in 58% (nasopharynx) and 17% (MEF) of AOM episodes. Thus, *Hflu* was the most commonly detected otopathogen in the MEF although *Spn* and *Mcat* were more frequently detected in nasopharyngeal samples during AOM episodes.

S. pneumoniae Serotypes From Healthy and AOM Visits

Among PCV13 serotypes, 3 and 19F were found in the nasopharynx and MEF during AOM, whereas serotype 23F was found in the healthy nasopharynx (Table 4). Among PCV20, non-PCV15 serotypes, 15B and 11A were detected across all specimen sources. Serotype 35B was the most frequent non-PCV15, non-PCV20, serotype isolated across all specimen sources, and was detected more frequently in the nasopharynx at AOM episodes than at healthy visits ($P = 0.002$). Other frequently detected non-PCV20 *Spn* serotypes were 23A, 23B, 35D, 35F and 15C.

Projected Pneumococcal Serotype Coverage by PCV15 and PCV20 Vaccines

PCV13 serotypes were identified in 7%, 4% and 9% of specimens obtained from the healthy nasopharynx, AOM nasopharynx and MEF, respectively (Fig. 1A). Assuming 100% vaccine-type effectiveness, PCV15 will provide 2%, 1% and 0% additional coverage compared with PCV13 in the nasopharynx of healthy children, in the nasopharynx at the onset of AOM, and in the middle ear during the onset of AOM, respectively (Fig. 1B), whereas PCV20 will provide 13%, 10% and 21% additional coverage compared with PCV13, respectively.

Antibiotic Susceptibility of *S. pneumoniae* Isolates

We obtained antibiotic susceptibility testing results for 280/286 (98%) of *Spn* isolates (see Table, Supplemental Digital Content 3, http://links.lww.com/INF/F573). About 63% of specimens were obtained from the healthy nasopharynx, 28% from the nasopharynx at the onset of AOM and 9% from MEF. The proportion of nasopharyngeal isolates nonsusceptible to amoxicillin was lower during healthy visits (10%) compared to nasopharyngeal isolates and MEF isolates at the onset of AOM (21% and 30%, respectively), though differences were not statistically significant. Serotype 35B was the most common serotype associated with antibiotic-nonsusceptible *Spn*, in particular, β-lactam, erythromycin and trimethoprim/sulfamethoxazole nonsusceptibility (see Table, Supplemental Digital Content 4, http://links.lww.com/INF/F573).

Capsular Typing of *H. influenzae* Isolates

Capsular typing of *Hflu* by PCR was performed on 220 isolates. One healthy child nasopharyngeal isolate tested positive for capsular type a, and 7 isolates tested positive for capsular type f: 2 isolated from the healthy child nasopharynx, 3 isolated from

the nasopharynx at the onset of AOM and 2 isolated from MEF. The remaining 212 nasopharyngeal isolates tested negative for capsular types and were considered nontypeable (96% of isolates tested).

Antibiotic Susceptibility of *H. influenzae* Isolates

We obtained antibiotic susceptibility testing results from 98% (220/224) of *Hflu* isolates (see Table, Supplemental Digital Content 5, http://links.lww.com/INF/F573). Nasopharyngeal isolates at healthy visits exhibited lower nonsusceptibility to cefaclor and amoxicillin/clavulanate compared to nasopharyngeal isolates at the onset of AOM ($P = 0.02$ and $P = 0.01$, respectively) or to MEF isolates ($P = 0.01$ and $P = 0.04$, respectively).

DISCUSSION

We conducted a prospective, longitudinal cohort study in Rochester, NY to estimate the frequency of *Spn, Hflu* and *Mcat* colonization and etiologies of AOM among children before PCV15 and PCV20 introduction in the United States. This study adds to a body of work estimating dynamic changes involving these respiratory bacterial pathogens beginning before the introduction of PCV7,[34] after the introduction of PCV7[14,30,35,36] and after the introduction of PCV13 at several time points.[4,6,15–17,37,38] Our major findings are: (1) Among *Spn* isolates from the nasopharynx and MEF, non-PCV13, non-PCV15, non-PCV20 vaccine serotypes predominated, thus, additional serotype coverage conferred from PCV15 and PCV20 compared with PCV13 against *Spn* colonization or AOM is expected to be limited; (2) The most frequent *Spn* serotype across all specimen types was 35B, a serotype not included in either PCV15 or PCV20 and was the most common serotype associated with antibiotic-nonsusceptible *Spn*; (3) The order of frequency of nasopharyngeal colonization was *Mcat*, *Spn* and *Hflu* for both healthy and AOM visits, and it did not differ across the age span of 6–36 months of age; (4) *Spn*, *Hflu* and *Mcat* was detected significantly more frequently in the nasopharynx at onset of AOM, when virtually all children had a clinically diagnosed viral URI, compared with during healthy visits; (5) In contrast to nasopharyngeal colonization, *Hflu* was the predominant otopathogen in MEF during AOM episodes, suggesting that when present in the nasopharynx, *Hflu* progresses more frequently to cause AOM than *Spn* or *Mcat*; (6) 30% of *Spn* isolates in MEF were amoxicillin nonsusceptible, suggesting they would require high dose (80–100 mg/kg/day) for eradication; (7) 23% of *Hflu* isolates and 100% of *Mcat* isolates were β-lactamase-producing, suggesting that they would not be eradicated with amoxicillin.

Our results provide a needed baseline before implementation of PCV15 and PCV20 and allow estimation of the projected effects of these vaccines on nasopharyngeal colonization and AOM. Neither PCV15 nor PCV20 includes *Spn* serotype 35B, which was the most common pneumococcal isolate identified in our child cohort at times of health, onset of AOM and causing AOM, consistent with prior reports.[38] In a comparison of AOM and IPD cases during the years 2011–2019, in children after PCV13 vaccination that included study sites from our otitis media research center, the main serotypes causing AOM were 35B and 21, whereas serotypes 3, 19A, 22F, 33F, 10A and 12F caused IPD identified by the Active Bacterial Core surveillance system of the CDC.[39] In this study during the years

2021–2023, we did not identify any case of 19A causing AOM. The high proportion of *Spn* serotype 35B and other non-PCV15 or non-PCV20 serotypes will result in a relatively small incremental benefit over PCV13 in young children on colonization and AOM; similar limited incremental benefit will likely occur in Europe.[40] In all countries, AOM morbidity is high, causing occasional meningitis, bacteremia, suppurative complications and temporary hearing loss. The ecologic impact of AOM is substantial due to associated antibiotic treatment. AOM is the most common cause of pediatric outpatient visits and antibiotic prescriptions in the United States[41–43] that contributes to the selection of antibiotic-resistant microbes.[44] The economic burden of AOM is high, estimated at about $3 billion annually in the United States, when direct and indirect costs are calculated,[45,46] thereby making AOM a major factor in calculations of cost-effectiveness analyses of PCV immunizations in children.

While PCV15 and PCV20 include common serotypes associated with IPD, their effectiveness in preventing nasopharyngeal colonization, noninvasive mucosal infections such as AOM, acute sinusitis and nonbacteremic community-acquired pneumonia is currently unknown because these vaccines were licensed-based on safety and immunogenicity data.[29] The clinical relevance of numerically lower antibody levels induced by PCV15 or PCV20 compared with PCV13 for the shared serotypes that were reported in clinical trials remains unclear,[24,26] but is important to investigate in future studies of nasopharyngeal colonization and AOM. Prior studies have estimated that 2- and 4-times higher antibody levels are necessary to prevent AOM and nasopharyngeal colonization, respectively, than those needed to prevent IPD.[22] Alternatives to serotype-dependent pneumococcal vaccines, such as whole cell or protein-based vaccines, could be considered.[47]

We report here again, as previously,[34,48] that among the 3 bacterial otopathogens tested, *Hflu* is the most frequent cause of AOM. While the proportion of *Spn* in nasopharyngeal colonization and as a cause of AOM has shifted amid PCV introductions, *Hflu* has remained the most prevalent pathogen in MEF at the onset of AOM overall since the year 2002.[34,35] In addition, we observed here, as previously reported[33] that *Hflu* is an uncommon isolate from the nasopharynx when a child is healthy, but at an AOM episode, in the context of a viral URI, the organism finds the nasopharynx a more favorable niche and it predominates.

Here we also provide data on antibiotic susceptibility of *Spn and Hflu* isolated in the late post-PCV13 era from young children in a pediatric primary-care setting. Previously we have shown that new emerging strains have a different profile of antibiotic susceptibility compared to isolates in the pre-PCV13 era.[6] Penicillin nonsusceptibility among *Spn* and β-lactamase production by the *Hflu* and *Mcat*, influences antibiotic selection for treatment. For penicillin nonsusceptible *Spn* strains, higher dosages of amoxicillin can improve eradication, although, due to variable absorption of the drug, MEF levels can be low in some children.[49] Higher dosages of amoxicillin cannot overcome β-lactamase production by *Hflu* and *Mcat*. Based on the mix of otopathogens detected in MEF and the antibiotic susceptibility data of isolates tested in our cohort, high-dose amoxicillin/clavulanate or alternative drugs active against *Spn* and β-lactamase-producing *Hflu* and *Mcat* would be a better empiric choice for antibiotic treatment of AOM in preference to high-dose amoxicillin.[50,51] However,

efficacy is not assured because we observed that 6% of *Hflu* isolates were nonsusceptible to amoxicillin/clavulanate during AOM, most likely β-lactamase negative ampicillin-resistant strains.

Limitations of our study include that it occurred in 1 center in NY, although we have previously shown results of tympanocentesis at our center are similar to those in Virginia and Pennsylvania,[52] and our study population was comprised of children living in urban, suburban, and rural households of all economic levels. Because this study was conducted during a relatively short time frame (2021–2023), the number of subjects and samples was sometimes insufficient to identify statistically significant differences in some comparisons. Some children were lost to follow-up, and not every participant was sequentially sampled in the nasopharynx or consented to tympanocentesis. Some participants received antibiotics before MEF specimen collection. Another limitation of the study is that PCR serotyping (if applied) might have detected a few more MEF specimens with additional PCV15 or PCV20 serotypes.

We conclude that continued monitoring of the bacterial etiologies of AOM is vital to public health amid the introduction of PCV15 and PCV20 and continued high rates of antibiotic use for AOM treatment. Tympanocentesis-identified middle ear isolation of otopathogens is the gold standard for identifying etiologic agents causing AOM, and can be used to estimate vaccine impact on AOM caused by *Spn, Hflu* or *Mcat*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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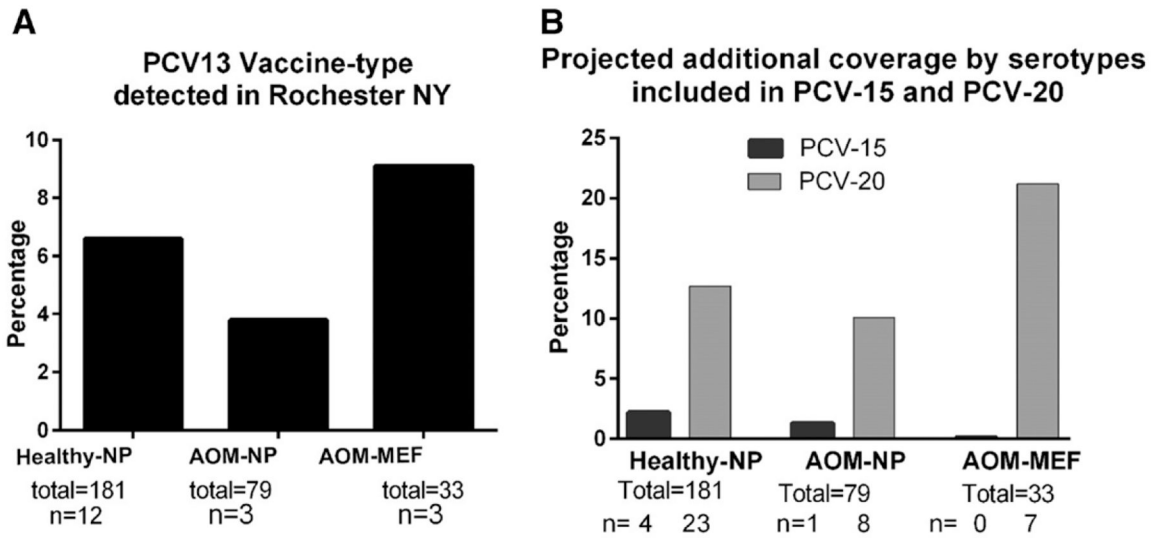

FIGURE 1.

A: Percentage of PCV13 vaccine serotypes identified in cultures from nasopharyngeal (NP) samples obtained at healthy well-child visits and at onset of AOM, and in middle ear fluid (MEF) obtained at onset of AOM. The most frequent PCV13 vaccine types were 3, 19F and 23F. B: Additional coverage beyond PCV13 by the additional serotypes in PCV15 and PCV20 based on 2021–2023 prevalence in the NP of children at healthy well-child visits and at the onset of AOM, and in MEF at the onset of AOM. The added serotypes in PCV15 are 22F and 33F, and in PCV20 are 8, 10, 11A, 12F, 15B, 22F and 33F.

TABLE 1.

Distribution of Otopathogens in Nasopharyngeal Samples at Healthy Visits and at Acute Otitis Media Episodes, 2021–2023

	Healthy	AOM	*P*-value Healthy Versus AOM	AOM Follow-up
	n = 652	n = 173*		n = 71
Spn	159 (24%)	79 (46%)	<0.0001	22 (31%)
Spn oxacillin nonsusceptible†	61 (38%)	41 (52%)	0.05	12 (55%)
Hflu	66 (10%)	73 (42%)	<0.0001	29 (41%)‡
Hflu β-lactamase-producing†	16 (24%)	17 (23%)	NS	9 (31%)
Mcat§	269 (41%)	105 (61%)	<0.0001	29 (41%)

*The percentage sum total in a column may be greater than 100% due to more than 1 type of otopathogen isolated from the same nasopharynx.

†The percentage of antibiotic susceptibility (oxacillin nonsusceptibility and β-lactamase production) is calculated from total *Spn* and *Hflu* isolates as the denominator, respectively.

‡*Hflu* was significant compared to Healthy ($P < 0.0001$) but not to AOM visits.

§All of the *Mcat* strains were β-lactamase (+).

NS indicates not significant.

TABLE 2.

Distribution of Otopathogens in Middle Ear Fluid Collected by Tympanocentesis at Acute Otitis Media Episodes, 2021–2023

Middle Ear Fluids	Total Taps	Total AOM Episodes With MEF Collection
	n = 216	n = 139
Spn	33 (15%)	26 (19%)
Spn oxacillin nonsusceptible *	14 (42%)	12 (46%)
Hflu	75 (35%)	56 (40%)
Hflu β-lactamase-producing *	16 (21%)	15 (27%)
Mcat †	29 (13%)	24 (17%)

Three episodes of AOM with tympanic membrane rupture and otorrhea were included; inclusion required that otorrhea cultures were obtained within 24 hours of rupture. No cases of group A streptococcus were observed in the cohort.

* The percentage of antibiotic susceptibility (oxacillin nonsusceptibility and β-lactamase production) is calculated from total *Spn* and *Hflu* isolates as the denominator, respectively.

† All of the *Mcat* strains were β-lactamase (+).

MEF indicates middle ear fluid.

TABLE 3.

Single and Combination of Multiple Otopathogens Colonizing the Nasopharynx and Middle Ear Fluid During an Acute Otitis Media Episode When Both Nasopharyngeal and Middle Ear Fluid Samples Were Collected

Total AOM Episodes (n = 139)	Nasopharynx (n = 139)	MEF (n = 139)
Spn only	11 (8%)	12 (9%)
Hflu only	21 (15%)	45 (32%)
Mcat only	20 (14%)	12 (9%)
Spn + *Hflu*	10 (7%)	6 (4%)
Spn + *Mcat*	31 (22%)	7 (5%)
Hflu + *Mcat*	19 (14%)	4 (3%)
Spn + *Hflu* + *Mcat*	11 (8%)	1 (1%)

These percentages are from AOM episodes for which both the nasopharyngeal and MEF samples were collected and excludes AOM episodes where either sample was not collected. Otopathogens were not detected in all AOM episodes. *Spn* + *Hflu* in the nasopharynx yielded both bacteria in the same MEF in all 6 cases. *Spn* + *Mcat* yielded both bacteria in the same MEF in 6 cases and 1 of each bacteria in separate MEF in 1 case. *Hflu* + *Mcat* yielded both bacteria in the same MEF in 4 cases. *Spn* + *Hflu* + *Mcat* yielded 3 bacteria in the same MEF.

TABLE 4.

Serotype Distribution of *Streptococcus pneumoniae* Isolated From Nasopharynx During Healthy and Acute Otitis Media Episodes, and From the Middle Ear Fluid, 2021–2023

	Healthy Nasopharynx	AOM Nasopharynx	AOM MEF	
	# of Isolates = 181	# of Isolates = 79	# of Isolates = 33	P-values Healthy Versus AOM-NP, Healthy Versus AOM MEF
PCV13 serotypes				
19F	6 (3%)	2 (3%)	2 (6%)	–
3	5 (3%)	1 (1%)	1 (3%)	–
23F	1 (1%)	0 (0%)	0 (0%)	–
Total PCV13 serotypes	12 (7%)	3 (4%)	3 (9%)	
PCV15, non-PCV13 serotypes				
22F	4 (2%)	1 (1%)	0 (0%)	–
PCV20, non-PCV15 serotypes				
15B	10 (6%)	5 (6%)	5 (16%)	ns, 0.06
11A	9 (5%)	2 (3%)	2(6%)	–
Total PCV20 serotypes	35 (20%)	11 (14%)	10 (31%)	
Non-PCV13, non-PCV15, non-PCV20 serotypes				
35B	29 (16%)	27 (34%)	7 (22%)	0.002, ns
23A	17 (9%)	6 (8%)	3 (9%)	ns, ns
23B	19 (11%)	5 (6%)	1 (3%)	ns, ns
35F	20 (11%)	3 (4%)	0 (0%)	0.06, 0.049
35D	4 (2%)	6 (8%)	5 (16%)	0.07, 0.005
21	8 (4%)	3 (4%)	2 (6%)	–
Nontypeable	9 (5%)	2 (3%)	1 (3%)	–
15C	3 (2%)	5 (6%)	3 (9%)	0.06, 0.048
16, 36 or 37	4 (2%)	4 (5%)	0 (0%)	–
7 (B or C)	5 (3%)	1 (1%)	0 (0%)	–
28	5 (3%)	1 (1%)	0 (0%)	–
6C	4 (2%)	1 (1%)	0 (0%)	–
15A	4 (2%)	1 (1%)	0 (0%)	–
10	4 (2%)	0 (0%)	0 (0%)	–

	Healthy Nasopharynx	AOM Nasopharynx	AOM MEF	
	# of Isolates = 181	# of Isolates = 79	# of Isolates = 33	P-values Healthy Versus AOM-NP, Healthy Versus AOM MEF
13	2 (1%)	1 (1%)	0 (0%)	–
24, 31 or 40	2 (1%)	0 (0%)	0 (0%)	–
27, 32 or 41	2 (1%)	0 (0%)	0 (0%)	–
7A	1 (1%)	1 (1%)	0 (0%)	–
33B	1 (1%)	0 (0%)	0 (0%)	–
35A	1 (1%)	0 (0%)	0 (0%)	–
25, 38, 43, 44, 45, 46 or 48	0 (0%)	1 (1%)	0 (0%)	–
Non-PCV20 serotypes	146 (80%)	68 (85%)	23 (68%)	
Not serotyped	2	0	1	–

Some strains were not fully typed (only pneumococcal-pooled sera serotyping identifications from Serum Institute was performed). Examples are group 10 and groups of serotypes such as 16, 36 or 37. Seven *Spn* were detected by PCR in culture-negative MEF samples that are not included in this table.