VACCINE EFFECTIVENESS AND PNEUMOCOCCAL SEROTYPES IN PEDIATRIC OTITIS MEDIA IN THE ERA OF ROUTINE 13-VALENT PNEUMOCOCCAL VACCINATION IN THE UNITED STATES

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ABSTRACT

Background. Pneumococcal acute otitis media (AOM) in children due to vaccine related serotypes (St) declined after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13).
Methods. Patients <18 years with pneumococcal OM isolates from 2014-2019 from the U S Pediatric Multicenter Pneumococcal Surveillance Group were analyzed for demographics, immunization status, antimicrobial susceptibility and St distribution. p<0.05 was considered statistically significant. Vaccine effectiveness (VE) was calculated using a standard formula: 1-([PCV13St vaccinated (≥3 PCV13 doses) x Non-PCV13St unvaccinated (0-1 PCV13 doses)]/[PCV13St unvaccinated x Non-PCV13St vaccinated])
Results. 646 patients were identified. Patients with PCV13 St were older compared to patients with non-PCV13 serotypes (3.3 vs 1.5 median years, p<0.0001). Most isolates were from spontaneous drainage (71.4 %) and PE tube placements (26.9%). 36 different Sts were identified; 83.4% of isolates were non-PCV13 Sts; 35B represented 18.3% of all isolates. St 19A decreased over time (p=0.0003). 14% of isolates had penicillin MIC≥2 µg/ml and 2.1% had ceftriaxone MIC>1 µg/ml. (Figure) 634 patients had known vaccine status. VE was 86.4% (Table).
Conclusion. Non-PCV13 Sts caused most pneumococcal OM. St35B was the most common St. Sts 19A decreased as a cause of otitis. In this study the VE of≥3 PCV13 doses was 86% for pneumococcal OM.

OBJECTIVES

- To describe the current epidemiology of pneumococcal otitis media cases and isolates obtained from the U S Pediatric Multicenter Pneumococcal Surveillance Group (USPMPSG).
- To assess the vaccine effectiveness of PCV13 based on the USPMPSG study data over the years 2014 to 2019

INTRODUCTION

- Otitis media is most commonly seen in children less than 24 months of age with the most common bacterial organisms being *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* (NTHi), and *Moraxella catarrhalis*.
- Pneumococcal acute otitis media (AOM) in children due to vaccine related serotypes (ST) has declined after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13), although some serotypes, such has 3, 19A and 19F have persisted.
- Among non-vaccine serotypes, 35B has contributed substantially to both OM and invasive infections over the past few years. We have previously reported multidrug resistance among 35B isolates (*J Clin Microbiol* 2017;55:724-34).
- A 20-valent (**PCV20**) polysaccharide conjugate vaccine is currently under development, containing 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) to the serotypes currently found in PCV13.
- This study describes the current epidemiology of pneumococcal OM isolates obtained from the U S Pediatric Multicenter Surveillance study and explores the vaccine effectiveness of PCV13 over the past 6 years (2014-2019).

METHODS

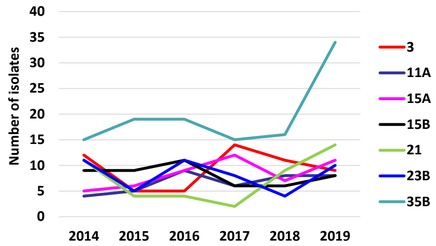
Patients and Isolates

- S. *pneumoniae* case reports and isolates from patients with ear infections were obtained from 5 hospitals participating in the U.S. pediatric pneumococcal multicenter surveillance study. The isolates were prospectively collected and stored in horse blood at -80°C in the Infectious Diseases laboratory, Texas Children's Hospital (TCH).
- Antimicrobial susceptibility (AS) data was obtained from each site as part of the data collection and interpreted according to Clinical Laboratory Standards Institute (CLSI) guidelines. The oral penicillin resistance (MIC≥2 µg/ml) and the ceftriaxone resistance (MIC≥4 µg/ml) breakpoints were used to determine resistance rates among the isolates. A penicillin MIC ≤ 0.06 µg/ml is considered susceptible and also can be used to predict susceptibility to amoxicillin and amoxicillin-clavulanate per CLSI guidelines.
- Isolates were serotyped using the Quellung reaction and specific antisera (Statens Serum Institut, Denmark; Cedarlane).
- Patient information included demographics, co-morbid conditions, site of infection, site of isolation and PCV13 administration status.

Statistical Analysis and Vaccine Effectiveness

- Mann-Whitney U, Chi-square, Fisher's exact test were computed using STATA 11 (College Station, Texas). Analyses were 2-tailed, and a p<0.05 was considered statistically significant.
- Vaccine effectiveness (VE) was calculated using a standard formula: 1-([PCV13St vaccinated (≥3 PCV13 doses) x Non-PCV13St unvaccinated (0-1 PCV13 doses)]/ [PCV13St unvaccinated x Non-PCV13St vaccinated])
- The study was approved by the Institutional Review Boards of each institution.

Figure 1. The Seven Most Common Serotypes causing pneumococcal otitis per year, 2014-2019



RESULTS

Patients, Immunization Status and Vaccine Effectiveness

- A total of 646 patients with isolates were identified within the time period from 5 children's hospitals. The majority of isolates were from spontaneous drainage (71.4 %) and PE tube placements (26.9%).
- Median age was 1.6 years (range 0-17.6), and 560 (86.7%) children were less than 5 years old.
- 393 (60.8%) were male
- 214 (33.2%) had an underlying condition.
- 633 (98%) patients had known vaccine status. Sixteen of 24 patients who did not receive any dose of either PCV7 or 13 vaccine, had a PCV13 serotype.
- VE was 86.4% (95%CI 77.2%-91.9%), using the data presented in Table 1.

Table 1. Vaccine effectiveness

Vaccine Effectiveness	0-1 Doses of PCV13	3 or More Doses of PCV13
PCV13 serotype	39	59
Non-PCV13 serotypes	41	456

Serotypes

- Thirty-six serotypes were identified (4 isolates were non-typeable) of which 6 serotypes [35B (18.3%), 3 (8.7%), 15A (7.7%), 15B (7.6%), 23B (7.6%) and 21 (6.8%)] caused more than half of the total OM infections (Figures 1 and 2).
- 107 (16.6%) isolates were of PCV13 serotypes.
- Patients with PCV13 serotypes were significantly older (median 3.3 vs. 1.5 years; p<0.0001).
- The 7 additional PCV20 serotypes caused 147 (22.8%) of the AOM infections, with 15B and 11A accounting for nearly 60% of these cases.
- Serotype 35B represented 18.3% of all isolates.
- Serotype 19A decreased significantly over time from 9% of 111 isolates in 2014 to 1.4% of 142 isolates in 2019. (p=0.0003)

Antimicrobial Susceptibility

- A total of 90 (14.4%) of 625 isolates with susceptibilities reported had a penicillin MIC ≥ 2 µg/ml. These were of serotypes 11A, 15A/C, 19A/F, 23B, 33A, 35B and two non-typeable isolates. 352 (56.1%) isolates had an MIC ≤ 0.06 µg/ml (susceptible).
- Greater than 90% of the observed penicillin resistance was associated with 3 serotypes, 19A, 35B and 15A: Resistance rates within each of these serotypes were 70.8% for 19A (17/24 isolates), 49.2% for 35B (58/118 isolates) and 14% of 15A (7/50 isolates).
- Only 2 (0.3%) of 595 isolates with reported ceftriaxone susceptibilities had a ceftriaxone MIC ≥ 4 µg/ml. Both isolates were of serotype 19A. An additional 8 isolates had an MIC of 2 µg/ml (intermediate) and were of serotypes 3, 15A, 19A/F, 33F and 35B.

Figure 3. Distribution of Penicillin and Ceftriaxone Minimal inhibitory concentrations (MICs) of otitis pneumococcal isolates

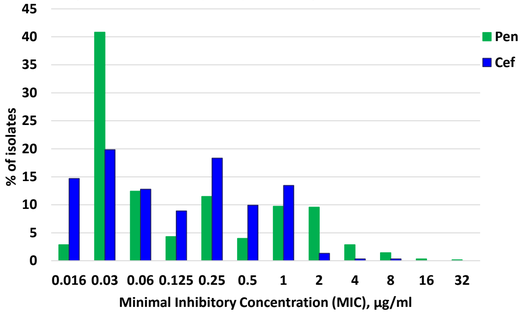
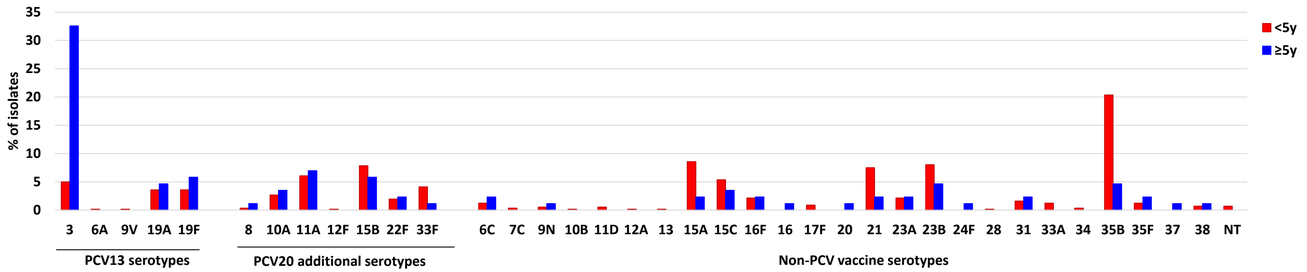


Figure 2. Serotypes Causing Pneumococcal Otitis Media among children 0-18 years old, 2014-2019



CONCLUSIONS

- Non-PCV13 serotypes caused 83% of the pneumococcal OM cases in this study.
- Serotype 35B was the most common serotype while serotype 19A decreased as a cause of otitis during the study period.
- For the study period of 2014-2019, the calculated VE for ≥3 PCV13 doses was 86% for pneumococcal OM.
- Penicillin resistance was most common among serotypes 19A, 35B and 15A.
- Recommendations regarding standard dose versus high-dose amoxicillin, with or without clavulanate, will require actual determination of amoxicillin MICs, considering the high proportion of AOM cases being caused by penicillin non-susceptible pneumococcal isolates in our study. However, the continuous changes in serotypes and the differences in antimicrobial susceptibility frequencies between serotypes emphasizes the need for continuous surveillance, especially with the potential introduction of new pneumococcal vaccines on the horizon.

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