

Non-vaccine Pneumococcal Serotypes Among Children with Invasive Pneumococcal Disease

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Objective: To report the percentage of non-vaccine pneumococcal serotypes and their antibiotic susceptibility pattern in children with invasive pneumococcal disease. **Methods:** Invasive pneumococcal isolates of children <5 years during January 2007 to December 2016 were serotyped by a co-agglutination reaction and sequential multiplex polymerase chain reaction. **Results:** Among the total 170 *S. pneumoniae* invasive isolates, 54 (31.8%) and 44 (25.9 %) were the serotypes, which are not included in current 10-valent or 13-valent vaccines, respectively. Very low resistance was observed against penicillin (4.5%) and all isolates were susceptible to cefotaxime. **Conclusions:** One-fourth to one-third of the *S. pneumoniae* serotypes in under-five children with invasive pneumococcal disease are not covered by existing pneumococcal vaccines in India.

Keyword: Immunization schedule, *Streptococcus pneumoniae*, Vaccination.

Though more than 95 serotypes of *S. pneumoniae* are identified, less than 15 serotypes causes more than 80% of invasive pneumococcal disease [1]. The prevalent serotypes vary at different geographical areas, and serogroup/types profile changes over the time in response to counter pressure generated due to introduction of vaccines. Surveillance studies worldwide have indicated a shift in prevalent circulating serotypes after vaccine introduction, and this has resulted in the increased prevalence of non-vaccine serotype pneumococcal strains [2-4].

India is in the process of universalizing the coverage of pneumococcal conjugate vaccine (PCV) in its Universal Immunization Program (UIP). In this study, we report the cumulative percentage of non-vaccine pneumococcal serotypes from invasive disease and their antibiotic susceptibility pattern in children below the age of five years. This cumulative percentage of serogroup/types distribution may serve as the baseline data to estimate post-vaccination changes.

METHODS

This study was conducted after approval by the ethics committee and Institutional review board of Christian Medical College, Vellore, India. A retrospective analysis of laboratory records was performed for a 10-year period (January 2007 to December 2016). Blood, cerebrospinal fluid (CSF) or sterile body fluids in children below the age of 5 years were collected and processed for culture. *S.*

pneumoniae was identified by standard microbiological methods that were uniform throughout the study period. Molecular identification of *S. pneumoniae* was confirmed by targeting the *lytA* region, using primers as described previously [5]. Antimicrobial susceptibility testing was performed using agar dilution method for Minimum inhibitory concentration (MIC) determination and interpreted according to the 2017 Clinical Laboratory Standard Institute (CLSI) break points.

Serotyping was routinely performed in the laboratory for all the *S. pneumoniae* isolates by a co-agglutination reaction using antisera obtained from Statens Serum Institute (Copenhagen, Denmark) [6]. In addition, sequential multiplex polymerase chain reaction (PCR) was performed with a total of 40 serotypes and the internal positive control *cpsA* locus using a modified CDC protocol and controls strains [7]. Serotypes included in 10-valent (PCV 10) vaccine (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F) 13-valent (PCV 13) vaccine (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A) were defined as vaccine serotypes, and other serotypes as non-vaccine serotypes (NVS).

RESULTS

Between January 2007 to December 2016, a total of 170 *S. pneumoniae* invasive isolates were identified from different clinical samples collected from children presenting to Christian medical college and hospital, Vellore. Most of the cases (76.7%; 130/170) were among children below 2 years of age. Among the isolates tested, 40% and 25% were from patients suffering from pneumonia and meningitis,

WHAT THIS STUDY ADDS?

- One-fourth to One-third of the *S. pneumoniae* serotypes causing invasive pneumococcal disease are not covered by currently available pneumococcal conjugate vaccines.

respectively; and remaining were from patients with sepsis or peritonitis. Among these, 54 (31.8%) and 44 (25.9%) isolates were NVS, which are not included in PCV10 and PCV13 vaccine, respectively. Most of these non PCV13 serotypes (45.2%) were isolates from pneumonia cases, followed by meningitis (26.1%) and sepsis (21.4%). Serotypes 11A, 15B and 33F were equally distributed in pneumonia, meningitis and sepsis cases. The serogroups/types distribution is given in **Web Fig. 1**. Fatal infections (9.52%, $n=42$) were caused by non-vaccine serogroup/types 10F, 17F, 15C and 33C. Higher resistance among NVS was seen against co-trimoxazole (93.1%) followed by erythromycin (22.7%). Very low resistance was observed against penicillin (4.5%) and all isolates were susceptible to cefotaxime. Serotype 11A and 15B were the only penicillin-resistant *S. pneumoniae* strains.

DISCUSSION

In this surveillance data, we document that almost one-third to one-fourth invasive pneumococcal disease strains are NNS. This is slightly higher compared to other Indian reports in under-five children. The major NVS 15B and 11A in this study were multidrug resistant, which was similar to other reports. Majority of isolates were recovered from children aged below 2 years.

Study by Balsells, *et al.* 2017 [8] reported that in countries which have introduced PCV, NVS serotypes accounted for 42.2% of childhood IPD cases. This varied in different regions from 28.5% to 71.9%. A systematic review [9] from India reported that serotypes 10F ($n=22$), 9N ($n=20$), 11A ($n=20$), 20 ($n=17$), 15B ($n=16$), 22F ($n=11$), 33F ($n=9$), 10A ($n=9$), 38 ($n=8$), 13 ($n=8$), and 15A ($n=7$) were the top 11 predominant non-vaccine serotypes, which accounted for 12.1% (147, $n=1215$) of invasive pneumococcal disease cases in India, among 22% of the NVS isolates in under-five Indian children.

The occurrence of non-vaccine (25.9%) serotypes from this study is not much different from other Indian studies [10-12]. Many countries describe an increase in serotype 19A and decrease in serotype 6A with the increased vaccine coverage [13]. Similar trends have also been observed post-PCV 13 with 35B, 15B/C, 23B and 15A serotypes [14], particularly prevalent in pediatric IPD [15]. PCV13 introduction may further shift the *S. pneumoniae* serotypes in India, it is imperative to monitor the afore mentioned profile post-vaccination.

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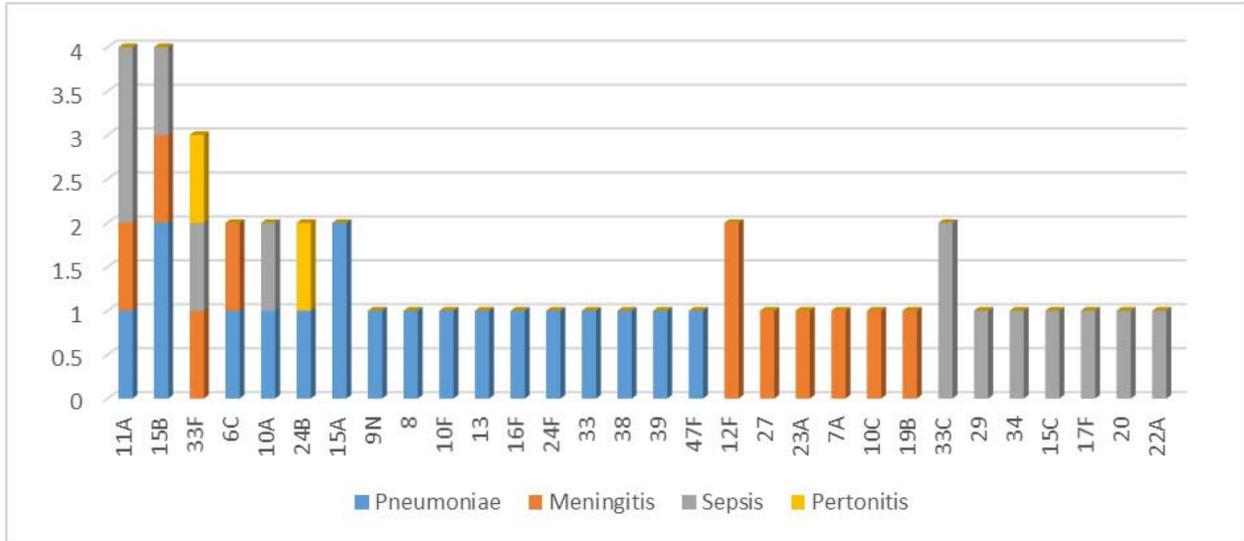
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WEB FIG. 1 Non vaccine serotype distribution among different clinical presentations.