

Non-vaccine Serotypes of *Streptococcus Pneumoniae*: Readying India for Monitoring Pneumococcal Conjugate Vaccine Use

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The pneumococcal conjugate vaccine (PCV) was first used in 2000, beginning in the United States, and since then has become part of the routine vaccination schedule of 142 countries [1]. Although pneumococcal deaths have declined globally, in part as a result of vaccine use, an estimated 500,000 deaths due to pneumococcal disease among 1-59 months old children occurred worldwide in 2015 [2]. Approximately one-fifth of all childhood pneumococcal deaths occur in India [2]. Consequently, in 2017 India began the use of PCV in selected districts, proceeding in a phased manner toward national introduction. Establishing reliable information on pre-PCV disease epidemiology and serotype data is critical to monitor the impact of PCV.

In a recent study published in *Indian Pediatrics*, John and colleagues [3] report a 10-year retrospective analysis of laboratory records of children who presented with invasive pneumococcal disease (IPD) at a single center in Vellore, between 2007-2016. The report focuses on describing the prevalence and characteristics of serotypes causing IPD in under-five children that are not constituent serotypes in the currently licensed PCVs. This publication is one of several recent papers describing the pre-PCV epidemiology of IPD that will serve as a baseline against which future IPD surveillance efforts in the era of routine PCV will be described [4-6].

Among the approximately 96 pneumococcal serotypes that cause human disease, between 67% and 78% of serotypes that cause IPD in under-five children in India are present in licensed pneumococcal conjugate vaccines [7]. Across the world wherever evaluations have been undertaken, the PCV program has shown substantial impact on vaccine-type strains of pneumococcus. This paper concerns itself with characterizing non-vaccine serotypes because of the observation that while rates of vaccine-type pneumococcal disease inevitably fall with PCV use, the rates of non-vaccine-type disease are also affected [8]. In the era of 7-valent PCV use, most sites observed a

substantial reduction of IPD, driven by huge reductions in vaccine-type disease rates accompanied by substantially smaller rate increases in non-vaccine-type disease [8]. With the widespread use of higher-valent vaccines PCV10 and PCV13, which contain many of the serotypes that caused the majority of replacement disease in the PCV7 era, there have been even greater reductions of IPD among children and adults [9,10].

The emphasis placed by John and colleagues [3] on reporting non-vaccine serotypes obtained from Indian children with IPD is timely in light of the recent PCV rollout in India. PCV use in a region will, as expected, lead to substantial reduction in the burden of IPD and pneumonia deaths in children, and will have indirect benefits for older children and adults, particularly the elderly. It is prudent to monitor for changes in the spectrum of pneumococcal serotypes causing disease. It is noteworthy that India's indigenous 10-valent pneumococcal vaccine that is undergoing Phase III trials has a similar serotype spectrum compared to PCV10 and PCV13 [11], and is expected to have similar impact. Investigational next-generation PCVs consist of 15 to 24 serotypes, including the non-PCV13 serotypes 11A, 15B and 33F that have been identified in this article by John and colleagues [3].

It is important to be aware that challenges abound in monitoring PCV impact through IPD surveillance. These include accurate diagnoses of pneumococcal disease and identification of pneumococcal serotypes. Pneumococcus is a fastidious organism, requiring several conditions to be just right for its own identification. Laboratory pneumococcal yield is lowered by suboptimal sample collection and transport, lack of a carbophilic environment or sheep blood agar for its growth and the use of non-specific biochemical identification tests [12]. The expert team at Christian Medical College, Vellore, India, where this analysis was done, serves as a laboratory reference center for pneumococci in India and surrounding regions, and is well placed for the analysis presented in this article. By serotyping pneumococcal

isolates using a mixed approach of standard agglutination and PCR-based methods, they have shown that almost one-fourth of all IPD isolates in this pre-vaccine era were non-PCV13 serotypes. This is consistent with other reports from India and the world which show that serotypes resulting in disease are predominantly those that are vaccine-type, with 70-88% of these IPD-causing serotypes being present in the PCV10 and PCV13 products [7,13].

National surveillance of pneumococcal disease, along with national PCV policy and a strong antibiotic control program, have a major role in the control of antimicrobial resistance among *Streptococcus pneumoniae*. John and colleagues [3] report low penicillin resistance and significant macrolide resistance among their pneumococcal strains. It is unclear whether their observed prevalence of penicillin resistance considered both meningial and non-meningial susceptibility breakpoints. Following introduction of PCV, the prevalence of penicillin resistance among pneumococci tends to decrease, because the vaccine serotype strains are disproportionately more likely to be resistant than are the non-vaccine serotype strains. The serotypes reported to be associated with penicillin resistance in this paper – 11A and 15B – are worth monitoring once PCV is rolled out, especially because they are not in any of the currently licensed PCV products nor in the late-stage product under development in India. As non-vaccine serotype prevalence increases in the nasopharynx, the prevalence of resistance in these strains tends to rise slightly above the pre-PCV values, yet maintaining an overall reduction in pneumococcal resistance compared with the pre-PCV period [14]. The ANSORP study reported high macrolide resistance in Asia, which is also associated with fluoroquinolone and multidrug resistance [15]. A significant source of drug resistance is pneumococcal carriage in children, who are colonized in greater proportions and for longer periods, and are also exposed to antibiotics more often [16]. While the current report focuses on pneumococcal disease in children, surveillance of pneumococcal carriage in the community can yield valuable information on serotype replacement and its effect on transmission and drug resistance.

Finally, the ability of PCV to exert a herd protection effect has resulted in a significant reduction in vaccine serotype pneumococcal disease incidence and carriage in unvaccinated children and adults [8]. Observations reveal that the nasopharyngeal ecological niche is quickly replaced by non-vaccine serotypes, thereby eliminating vaccine-type carriage to various degrees, leading to reductions in vaccine-type transmission and disease in

vaccinated and unvaccinated populations [17]. Models predict that serotype competition may be reduced with the use of higher valent vaccines, underscoring the importance of monitoring non-vaccine type carriage and disease [18].

The promise of pneumococcal vaccines brings us ever closer to achieving our goals of reducing child mortality and morbidity. Paramount to ensuring optimal vaccine impact is achieving high vaccine coverage. Establishing a baseline for monitoring of vaccine serotype changes is the key to measuring the impact of PCVs on pneumococcal disease patterns and drug resistance in the region.

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