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Research Article

Impact of PCV13 Vaccination on Pneumococcal Colonization in Mother-Infant Pairs

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Abstract

Background

Infants receive 13-valent pneumococcal conjugate vaccine (PCV13) as routine standard of care, at 2, 4, 6, and 12 months of age. Concerns remain regarding nasopharyngeal colonization with non-vaccine serotypes (NVSTs) post-PCV13 vaccination in infants.

Methods

Nasopharyngeal swabs from seventy-one mother-infant (M-I) pairs in a socioeconomically disadvantaged population were examined pre-and post-PCV13 vaccination for twenty-four serotypes of *Streptococcus pneumoniae* (SPN).

Results

Nine serotypes were detected, of which five were vaccine types and four were NVST. Eighty-seven percent of the serotypes belonged to NVST 11A. A significantly high proportion of the infants were found to be colonized with 11A at pre-vaccination (p=0.005) and post-vaccination dose one (0.001) levels, respectively, when compared to their mothers. Twenty- four percent of the infants developed otitis media before their twelfth birthday. No significant correlation was noted between the prevalence of VST or NVST colonization and the prevalence of otitis media in these infants. However, infants who breastfed (twenty percent) were significantly (p= 0.04) less likely to develop otitis media before their twelfth birthday compared to those who did not breastfeed (fifty-three percent).

Conclusions

Our study found a high proportion of infants colonized with NVST serotype 11A compared to their mothers. Although subsequent doses of PCV13 vaccination of infants did not lead to significant eradication of nasopharyngeal colonization of 11A in mothers or their infants, a considerable (p=0.08) reduction in the colonization status was noted from the pre-vaccination to post-vaccination dose three level. While the incidence of otitis media in these infants not impacted by their colonization with 11A, their breastfeeding status certainly was.

Keywords: Colonization; Nasopharyngeal; PCV13; Pneumococcal; Serotype

Introduction

Pneumococcal disease remains a major pathogen, causing invasive and non-invasive infections in young infants and children. In the United States, the PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) vaccine is administered to infants and children at 2, 4, 6, and 12 months of age as routine standard of care. The introduction of PCV13 in 2010 led to a tremendous decrease in the incidence of invasive pneumococcal disease (IPD) in young children [1,2]. The vast majority of these IPDs are caused by vaccine serotype (VT) pneumococci , and most of the remaining cases are now due to non–13-valent PCV (PCV13) types (NVSTs) [3-9]. Colonizing bacteria can be a precursor for an invasive disease in young children and individuals with weak immune systems [10- 12]. Thus, concerns remain regarding increasing rates of nasopharyngeal colonization (NP) with replacement non-vaccine serotypes (NVSTs) and the potential for IPD or non-IPD diseases, including otitis media and conjunctivitis.

Indeed, the pneumococcal disease spectrum can encompass several clinical presentations of IPD: bacteremic pneumonia; bacteremia without an identified source; meningitis; and, less frequently, osteoarthritis, peritonitis, or cellulitis. Although few serotypes (1, 3, 5, 7F, 14, 19A) were known to cause bacteremic pneumonia cases worldwide, prior to PCV implementation , a large number of serotypes were identified causing pneumococcal meningitis, both before and after PCV implementation [13]. Profound changes in the distribution of serotypes causing meningitis were observed following introduction of PCV13. After PCV13 implementation, 87.9% of meningitis cases were found to be caused by non-PCV13 serotypes [14]. Some serotypes have also been described as having higher disease potential than others in the literature [15-17]. Little is known about colonization with vaccines or NVST in vaccinated children and their adult household members following the PCV13 vaccination of children. The impact of colonization on the prevalence of otitis media in these children following PCV13 vaccination is also not well known. The primary objective of this study was to determine the frequency of specific serotypes of pneumococci colonizing nasopharynges in infants and children and their adults before and after PCV13 vaccination. The secondary objective was to determine if any correlation or association

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existed between colonization status and incidence/prevalence of otitis media in these children.

Methods

Study population

The protocol was reviewed and approved by the Institutional Review Board at Meharry Medical College (MMC), and informed written consents were obtained from each legal guardian. The study was conducted between May 2014 and June 2016. None of the mothers in the study had previously been vaccinated with pneumococcal polysaccharide (PPV23) or pneumococcal conjugate vaccines (PCV7 or PCV13).

Seventy-one mother-infant pairs were enrolled into the study in the pediatric outpatient clinic at MMC in Nashville, Tennessee. Of these, thirty-eight pairs were enrolled at the pre- vaccination level at a mean age of one month. Thirty-three additional pairs were enrolled following PCV13 vaccinations at 2, 4, 6, or 12 months (designated as dose 1, 2, 3, or 4) and subsequent visit at fifteen months of age (Table 1). A cohort of only seventeen mother-infant pairs were available to be followed from a pre-vaccination to a post-vaccination dose one level. The infant groups thus included pre-vaccination and post-vaccination groups at dose 1, dose 2, dose 3, and dose 4. Nasopharyngeal swabs were collected from both mothers and infants (116 pairs) at each pre-vaccination and post-vaccination level.

Sample size calculation

Sample size calculation was based on the number of test blinded pneumococcal serotype isolates (200) available to the collaborator (Dr. Martinez). Two-hundred NP swab isolates were used to validate the multiplexed pneumococcal serotyping assay for these (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F) serotypes and cell wall polysaccharides (CWPS). The goal of this sample size was to obtain pilot data for future studies. The sample size was increased to 120 paired samples (infant and mothers) to account for a 20% loss on follow-up.

Samples collection/ storage

Swabs were stored in special transport media (provided by fx Immune lab) at -20 degrees centigrade. Samples were transferred in appropriate freezing conditions by associates from fx Immune laboratories. Relevant clinical data was collected from patients' medical records and verbal reports from the mother or the father. This included data such as socioeconomic status, breastfeeding history, parental smoking history, and number of otitis media up to twelve months of age.

Laboratory assessment

Nasopharyngeal swabs were tested by Multiplex Flow Cytometry for 24 ST of Streptococcus pneumoniae (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F [PCV13] and 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F [all contained in PPV23] at fx Immune Diagnostics Inc., Candler, North Carolina 28715 [18].

Statistical analysis

The prevalence of pneumococcal serotype-specific colonization between pre-vaccination and each post-vaccination level was evaluatedin mothers and infants by two-tailed Fisher's exact test. The effect of confounding variables (socioeconomic status, age of infant, smoking, breastfeeding) on colonization status and otitis media in infants was evaluated using ANOVA with Bonferroni correction, yielding a significance level of 0.01 or multiple logistic regression. Intercooled stata version 8.0 was used for statistical analyses.

Results

Seventy-one mother-infant pairs were enrolled in the study. Of these seventy-one pairs, thirty-eight were Hispanic by ethnicity, and thirty-three were non-Hispanic. There was a total of 232 samples tested. Sixty-eight percent (158 of 232) of the total samples, tested positive for either the vaccine or NVST (Table 1).

		Mother	Infant
Total Number of Samples		116	116
Number Samples Pre-Vaccination		38	38
Number Samples Post-Vaccination Dose 1		37	37
Number Samples Post-Vaccination Dose 2		15	15
Number Samples Post-Vaccination Dose 3		20	20
Number Samples Post-Vaccination Dose 4		6	6
Serotypes Detected	VT	4	4
	NVST (11A + others)	2	4
Total Number - Serotypes Detected	VT	4	7
	NVST (11A + others)	**47+ 2**	**90+ 8**

Table 1: Samples Distribution.

Nine serotypes were detected, of which five were vaccine type (VT) and four were NVST. The total numbers of VT (4, 14, 19A, 19F, and 23F) accounted for seven percent (11 of 158) of the isolated serotypes, while the NVSTs (11A, 12F, 15B, and 22F) accounted for ninety-three percent of the isolated serotypes (147 of 158); of the NVSTs detected, ninety-three percent belonged to serotype 11A.

Thirty-six percent of the mother-infant sample pairs (42 of 116) were found to have identical NVST 11A. Infants were more likely to have significantly (p=0.000) higher proportion with NVST (84%) than no serotype (23%) compared to their mothers who possessed NVST and no serotype in comparable proportions (Table 2).

Infants were significantly (p=0000; 0.009 and 0.009) more likely to have NVST 11A colonization than their mothers at pre-vaccination, and post-vaccination doses one and two, respectively. This difference was also noted when results were analyzed for the seventeen cohort of mothers and infants at pre-vaccination (p=0.005) and post-vaccination dose one (p=0.001) (Table 3).

When infants were evaluated for colonization status by number of vaccine doses, eighty-seven percent of infants were found to be colonized at pre-vaccination level, which was reduced to sixty-five percent at post-vaccination dose three (p=0.08) (Table 4).

This difference became significant (p=0.009) when sample size was projected to be doubled and keeping proportion the same (Table 5). Seventeen of 71 (24%) of the infants had developed an otitis media infection before their twelfth birthday. No significant difference in these infants was noted when compared between those who were colonized and not colonized.

Samples (n)	Number (%)	Number (%)	Number (%)	Number (%)	
	Identical serotypes (11A)	NVST	Vaccine ST	No	serotype detected
Mother (116)	42/ 116 (36)	49/ 116 (42)	4/ 116 (3)	67/ 116 (58)	
Infant (116)	42/ 116 (36)	98/ 116 (84)	7/ 116 (6)	27/ 116 (23)	
*p	ns	ns	ns	ns	

Table 2: Serotype Distribution in Mother-Infant Pairs (*Two-tailed Fisher's Exact Test).

	Pre-vaccine n (%)	Dose One- n (%)	*p
Mother	5/ 17 (29)	2/ 17 (12)	0.39
Infant	14/ 17 (82)	12/ 17 (71)	0.68
p	0.005	0.001	

Table 3: Mother-Infant Cohort - Prevalence of 11A (*Two-Tailed Fisher's Exact Test).

Prevalence	Pre-vaccine	Dose One	Dose Two	Dose Three	Dose Four
11A	n (%)	n (%)	n (%)	n (%)	n (%)
Mother	17/ 38 (45)	16/37 (43)	4/ 15 (27)	9/ 20 (45)	2/ 6 (33)
Infant	33/ 38 (87)	28/37 (76)	12/15 (80)	13/ 20 (65)	4/ 6 (67)
*p	0.000	0.009	0.009	0.34	0.56

Table 4: 11A Nasopharyngeal Colonization with Number of PCV13 Dosing(*Two-tailed Fisher's Exact Test).

Sample size (n)	Pre-vaccine- n (%)	Dose Three- n (%)	*p
Actual (71)	33/ 38 (87)	13/ 20 (65)	0.08
Doubled (142)	66/ 76 (87)	26/ 40 (65)	0.009

Table 5: Predicted NP Colonization in Infants Pre-Vaccination to Post-Vaccination Dose 3: If Sample Size were Doubled (*Two-Tailed Fisher's Exact Test).

However, of the infants who had developed an otitis media infection before twelve months of age, were significantly (p=0.04) less likely (53%) to have breast fed than those who breast fed (20%).

Discussion

Our study has demonstrated that introduction of the PCV13 vaccine has significantly reduced the pneumococcal colonization of serotypes targeted by the vaccine, but serotypes not covered by the vaccine have picked up the slack. The clinical significance of the enormous occupancy by NVST 11A as the replacement serotype is not yet well understood. An extremely high prevalence of 11A colonization with no evidence of invasive disease in this population may suggest that this serotype is poorly immunogenic and has the least invasive potential, as is also documented in the literature [19]. Our study shows a significantly higher proportion of infants are colonized with 11A compared to their mothers. This may suggest naïve immune responses in early phases of the infants' lives, under the condition of minimal or no exposure to the vaccine serotypes.

The difference in colonization status between infants and their mothers narrow with advancing vaccination doses (doses 3 and 4), further reinforce efficacy of the 13-valent conjugate pneumococcal vaccine. Thus, the potential of this vaccine to eradicate NVST 11A pneumococci from nasopharynges of these infants is demonstrated. A trend (p=0.08) is observed for NVST 11A colonization prevalence in infants from pre-vaccination to post-vaccination dose three, which is predicted to produce significant difference if sample size were doubled and keeping proportion the same. This finding further suggests the importance of administering optimal number of vaccination doses (complete series) in order to make a difference in achieving vaccine efficacy and preventing not only invasive pneumococcal disease with vaccine serotypes, but also eradicating colonizing serotypes from the nasopharynges. It is therefore, strongly recommended that the full vaccination series of four doses be completed by the twelfth birthday. Although non-vaccine serotype colonization in infants may play a role in the development of otitis media before their twelfth birthday, our study has failed to demonstrate this effect, most likely due to a small sample size. However, breastfeeding is an independent factor known to prevent otitis media in infants, and this effect is demonstrated in our study.

According to literature, serotypes with high disease potential are identified as 8, 12F, 24F, and 33F (15- 17). Our study has found 6 samples demonstrating colonization with NVST 12F at a mean of 6 months of age. This may be concerning because this may suggest that this serotype was more difficult to eradicate from the nasopharynges of our vaccinated infants even after 2 doses of the vaccine were administered. The high prevalence of serotype NVST 11A may be concerning. Although, no IPD has yet been documented in the United States with this serotype, studies in Korea have found this serotype was associated with high grade of multidrug antimicrobial resistance[20].

Conclusion

Pneumococcal conjugate vaccine (PCV13) is a very immunogenic vaccine with the potential to eradicate not only vaccine serotypes, but also clinically important non-vaccine serotypes from the nasopharynges of our study infants. Despite a high prevalence of nasopharyngeal colonization with serotype 11A, there is no evidence of a concurrent emergence of invasive pneumococcal disease or even otitis media in our study population. This is again explained by the serotype's low invasive potential. The reduced colonization frequency with vaccine or non-vaccine serotypes in mothers of our study infants may suggest an indirect effect of infant vaccination, or most likely through development of herd immunity in these mothers due to the infants' vaccination.

Ongoing monitoring of nasopharyngeal colonization in vaccinated children worldwide may be important for predicting invasive pneumococcal disease in infants and children. Our study findings indeed have implications for invasive pneumococcal disease surveillance as well as studies investigating vaccine impact. It may also be useful for

guiding antimicrobial susceptibility patterns and be clinically relevant in the management of infants and children with invasive pneumococcal disease, and more frequently evaluating cases of persistent or recurrent otitis media in specific population groups. We recommend prospective studies with a larger sample size in order to observe significant differences in the colonization and eradication of vaccine and non-vaccine serotypes from the pre-vaccine stage to subsequent doses in infants and beyond infancy, and even within family members.

We further recommend prospective studies evaluating nasopharyngeal colonization, urinary antigen excretions, and simultaneous serologic antibody assessment in blood. We also recommend prospective studies examining colonization rates (nasopharyngeal and urine) and invasive pneumococcal disease rates in infants following maternal immunization with a broader spectrum 23-valent vaccine, a cost-effective strategy for reducing IPD and infant mortality rate in vulnerable populations, including immune compromised children and even children with normal immunity from low and middle income countries.

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