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Modeling pneumococcal nasopharyngeal acquisition as a function of anticapsular serum antibody concentrations after pneumococcal conjugate vaccine administration

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ABSTRACT

Background: A prior 7- and 13-valent pneumococcal conjugate vaccine (PCV7 and PCV13) study provided sufficient data ($N = 1754$; Jewish, $n = 1154$; Bedouin, $n = 595$; other, $n = 5$) to investigate the association between nasopharyngeal (NP) acquisition of common PCV7 serotypes and cross-reacting 6A (PCV7 + 6A) and IgG concentrations.
Methods: Using a logistic regression model, serotype specific association between postinfant series IgG concentration (age 7 months) and new NP acquisition between ages 7 and 24 months was assessed and adjusted for ethnicity. From a subset of subjects with new NP acquisition ($n = 9$–152 across serotypes studied), new acquisition percentiles and associated IgG concentrations were calculated.
Results: For the serotypes studied, new NP acquisition rates decreased as IgG concentrations increased. Ethnicity did not influence these associations despite differences in carriage rates. From the subset with new acquisitions, 50% of the events occurred at IgG concentrations >0.61–5.58 μg/mL; and 10% of the acquisitions occurred at IgG concentrations >2.48–17.69 μg/mL.
Conclusion: Remarkably high IgG concentrations are required to reduce NP acquisition. These IgG concentrations differ between serotypes. Ethnicity did not influence the association between high IgG concentrations and prevention of carriage despite differences in carriage rates. Since carriage determines transmission, these results may have important implications for herd protection.
Trial registration: ClinicalTrials.gov number, NCT00508742; http://clinicaltrials.gov/ct2/show/NCT00508742

1. Introduction

Streptococcus pneumoniae is an important cause of severe bacterial infections in children during their first years of life [1]. Nasopharyngeal (NP) colonization is a prerequisite for the development of pneumococcal disease and is responsible for transmission of pneumococci to other individuals. Importantly, NP colonization of pneumococci of serotypes included in the pneumococcal conjugate vaccines (PCVs) is reduced after vaccination with PCVs by preventing NP acquisition [2–5]. Studies suggested that there is an association between increasing serum antipolysaccharide immunoglobulin G (IgG) concentrations after PCV vaccination and decreasing probability of acquisition for some vaccine serotypes [4,6]. Serum IgG concentrations higher than that defined by the World Health Organization (WHO) as being sufficient to prevent invasive pneumococcal disease (IPD; ie, 0.35 μg/mL [7,8]) may be required to reduce NP colonization [9]. In addition, differences in IgG concentrations needed to prevent IPD [10] and NP colonization may also exist between serotypes [9]. A large 7- and 13-valent PCV (PCV7, PCV13) study [2] conducted in Israel in 2 ethnic populations (Bedouin and Jewish) provided sufficient NP acquisition and immunogenicity data to further investigate

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the association between NP acquisition and serum IgG concentration, as well as the influence of ethnicity on these associations.

2. Methods

2.1. Study design

This post hoc analysis examined data from a double-blind study comparing immunogenicity after the infant series (age 7 months) and toddler dose (age 13 months), new NP acquisitions between ages 7 and 24 months, and prevalence at predefined time points (ages 7, 12, 13, 18, and 24 months) in children immunized with PCV7 and PCV13; details of the study design were described previously [2]. Healthy Israeli infants were randomly assigned to receive PCV13 or PCV7 at ages 2, 4, 6, and 12 months. Blood samples were obtained at ages 7 months (1 month after the infant series) and 13 months (1 month after the toddler dose). Serum concentrations of anticapsular-binding IgG antibodies for each pneumococcal serotype included in PCV13 were determined using standardized enzyme-linked immunosorbent assays (ELISA). Eight NP swabs for pneumococcal cultures were collected at ages 2, 4, and 6 months for baseline and at ages 7, 12, 13, 18, and 24 months. All cultured swab samples that tested positive for *S. pneumoniae* were serotyped by the Quellung reaction [2].

Two ethnic populations were included in the study: Jewish and Bedouin. Although the Jewish and Bedouin children in southern Israel live in a single geographic area, they have limited social interactions and differ with regard to socioeconomic conditions and lifestyles. The Jewish population is largely urban. In contrast, the Bedouin population, formerly composed of desert nomads, is comparable to a developing population, with lower socioeconomic status, a higher number of children per household, and crowded living conditions. For these reasons, they are generally more exposed to pneumococcal carriage and disease [11].

The study was conducted by a single coordinating center overseeing activities at 11 clinical sites in southern Israel. The study was approved by the Institutional Ethics Committee of the Soroka University Medical Center and the National Ethics Committee. Written informed consent was obtained from the parent(s)/legal guardian(s) of each subject before enrollment in the study and before performance of any study-related procedures.

2.2. Statistical analysis

To achieve an appropriate sample size, data for the 7 common serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) and cross-reacting serotype 6A were combined from the PCV13 and PCV7 arms of the study. The association between new NP acquisition collected between ages 7 and 24 months and pneumococcal IgG concentration 1 month after the infant series (age 7 months) for each serotype studied was assessed from a logistic regression model using new NP acquisition rate reduction (dependent variable) as a function of the logarithm of IgG concentrations (independent variable); this was also adjusted by ethnicity. A new acquisition was defined as detection of a given serotype that was not previously identified at baseline (ages 2, 4, and 6 months), or at any other time point before the detection. Therefore, only 1 new acquisition was counted for each serotype per participant over the observation period between ages 7 and 24 months [2]. The NP acquisition rate describes the number of acquisitions collected during the observation period between ages 7 and 24 months relative to the total number of subjects. The predicted new NP acquisition rate reduction corresponding to the antibody concentration threshold of 0.35 μg/mL and to selected percentiles of IgG concentration were calculated for the total population and for each ethnic subpopulation.

In addition, a subset of all subjects with NP acquisition of the serotypes studied were selected from the total population, and the percentage with IgG concentrations $\geqslant$0.35 μg/mL was calculated for each serotype studied. From this subset, the 50th, 75th, and 90th percentiles of IgG concentrations were selected and corresponding distribution-free confidence intervals (CIs) constructed around the points calculated. This was also calculated for each ethnic subpopulation.

3. Results

3.1. Participants and demographic characteristics

A total of 1866 healthy infants received either PCV13 or PCV7 at 2, 4, 6, and 12 months of age. The per-protocol population included 1754 subjects (Jewish, n = 1154; Bedouin, n = 595; other, n = 5) of whom 50.7% were female. The mean (standard deviation; SD) age was 2.2 (0.3) months at the first dose, 3.9 (0.4) months at the second dose, 5.7 (0.5) months at the third dose, and 12.5 (0.6) months at the toddler dose [2]. Significantly higher numbers of children per household were observed in the Bedouin versus Jewish population (mean [SD], 3.6 [1.6] vs 2.3 [0.9], respectively; $P < 0.001$). Statistically significant differences ($P < 0.001$) in living conditions were observed between the Bedouin population and the Jewish population (Table 1).

For the current analysis, subjects with data for IgG concentrations one month after the infant series (age 7 months) and at least

Table 1
Living conditions of Jewish and Bedouin subjects – per protocol population.

	Bedouin n = 595	Jewish n = 1154
Housing type[a], *n (%)*		
House	527 (88.6)	1152 (99.8)
Corrugated iron hut	67 (11.3)	2 (0.2)
Tent	1 (0.2)	0
Number of bedrooms[a]		
Mean (SD)	2.8 (0.7)	3.1 (0.9)
Median	3.0	3.0
Min, max	1, 7	1, 8
Number of children per household[a]		
Mean (SD)	3.6 (1.6)	2.3 (0.9)
Min, max	0, 8	0, 7
Number of individuals sleeping in child's room[a]		
Mean (SD)	3.4 (0.7)	2.9 (0.6)
Median	3.0	3.0
Min, max	1, 7	1, 5
Number of children in home attending school[a]		
Mean (SD)	1.2 (1.9)	0.6 (1.0)
Median	0	0
Min, max	0, 8	0, 7
Number of children in home not attending school[a]		
Mean (SD)	2.4 (1.2)	1.7 (0.8)
Median	2.0	2.0
Min, max	0, 6	0, 5
Immediately older sibling's childcare[a], *n (%)*		
Alone at child-minder's home	5 (0.8)	6 (0.5)
At home	339 (57.0)	66 (5.7)
Child-minder	10 (1.7)	16 (1.4)
Day care center	75 (12.6)	486 (42.1)
School	15 (2.5)	161 (14.0)
Not applicable	151 (25.4)	418 (36.2)

SD = standard deviation.

[a] A chi-square test was used to compare the living conditions between the two ethnic populations for categorical outcomes while a two-sample t-test was used to compare the ethnic populations for continuous outcomes. For each item listed a statistically significant difference between ethnic groups was determined (P-value < 0.0001).