

Carrier-Induced Hyporesponsiveness to Pneumococcal Conjugate Vaccines: Unraveling the Influence of Serotypes, Timing, and Previous Vaccine Dose

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Background. Pneumococcal conjugate vaccines (PCVs) elicit lower immune response against serotypes carried before or at the time of vaccination (hyporesponsiveness) in infants. The limited studies conducted to date did not permit comprehensive insights regarding this phenomenon. This study, the largest ever conducted with both carriage and serologic endpoints, attempted to add insight on serotype-specific hyporesponsiveness in relation to the number of PCV doses administered before carriage acquisition.

Methods. In a double-blind randomized clinical trial (n = 1754 infants), 7-valent or 13-valent PCV was administered at ages 2, 4, 6, and 12 months. New acquisition was defined based on nasopharyngeal swabs at ages 2, 4, 6, 7, and 12 months. Serotype-specific immunoglobulin G levels were obtained 1 month after the infant series and 1 month after the toddler dose.

Results. A lower immune response after the infant series and the toddler dose was consistently observed for carriers of serotypes 6A, 6B, 18C, and 19F at predefined time points, with a similar trend observed in carriers of serotype 23F. In contrast, carriage of serotypes 9V, 14, and 19A did not generally affect immune responses. For some but not all serotypes, hyporesponsiveness was decreased with an increased number of vaccine doses received before acquisition. A complex interrelationship between carriage and immune response was observed between cross-reacting serotypes.

Conclusions. Carrier-induced hyporesponsiveness to PCVs is common, differs among serotypes, and depends on timing of carriage acquisition and prior number of administered PCV doses.

Clinical Trials Registration. NCT00508742.

Keywords. *Streptococcus pneumoniae*; pneumococcal conjugate vaccine; NP acquisition; hyporesponsiveness.

Nasopharyngeal (NP) carriage of commonly carried *Streptococcus pneumoniae* serotypes (mainly 6B, 19F, and 23F) before or at the time of pneumococcal conjugate vaccine (PCV) administration is associated with lower serotype-specific immune responses to the carried serotype after the 2-dose or 3-dose primary infant series and/or after the booster dose compared with responses to noncolonizing serotypes in carriers and to the same serotypes in noncarriers [1–5]. This hyporesponsiveness has been observed not only after carriage but also after revaccination with meningococcal and pneumococcal plain polysaccharide vaccines in pediatric and adult

populations and in children with previous invasive pneumococcal disease (IPD) subsequently vaccinated with the 7-valent PCV (PCV7) [6–10]. Reduced serologic response could have clinical implications, especially regarding presentation of mucosal disease and future NP carriage acquisition. Serum antibody concentrations higher than the threshold of 0.35 µg/mL associated with protection against IPD are required to prevent NP acquisition and mucosal disease such as otitis media [11, 12]. In addition, antibody levels required for protection against NP acquisition vary across serotypes [13–17].

The current analyses investigated the effect of acquisition of a range of commonly carried *S. pneumoniae* serotypes—including serotypes cross-reacting with those in the PCV—on immune responses at predefined time points after the 3-dose infant series and toddler dose. In addition, we assessed the relationship between the timing of serotype acquisition and the number of previously administered doses and immune responses. Data from a large randomized study of PCV7 and 13-valent PCV (PCV13) in Israel were analyzed [18]. There were sufficient NP colonization and immunogenicity data to assess serotypes 6B, 9V, 14, 18C, 19F, and 23F, which are contained in PCV7 and PCV13, and serotypes 6A and 19A, which are contained in PCV13 only.

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METHODS

Study Design

This post hoc analysis investigated data from a double-blind study conducted from February 2008 through September 2011 comparing immunogenicity, safety, and pneumococcal NP acquisition in children immunized with PCV7 and PCV13; details have been described previously [18]. In brief, healthy Israeli infants from Jewish and Bedouin ethnic populations were randomly assigned to receive PCV7 or PCV13 at ages 2, 4, 6, and 12 months. Blood samples for determination of antipolysaccharide antibody concentrations were drawn at ages 7 and 13 months. Five NP swabs for pneumococcal cultures at ages 2, 4, 6, 7, and 12 months were utilized.

The study was conducted by 1 coordinating center that oversaw study 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) or legal guardian(s) of each subject before enrollment and before performance of any study-related procedures.

NP Cultures and Blood Sampling

Nasopharyngeal swabs at ages 2, 4, and 6 months (at the time of doses 1, 2, and 3 of the infant series), at age 7 months (1 month after dose 3), and at age 12 months (at the time of the toddler dose [dose 4]) were utilized. All *S. pneumoniae* isolates were serotyped by the Quellung reaction [18]. Serum concentrations of anticapsular-binding immunoglobulin G (IgG) antibodies for each pneumococcal serotype included in PCV13 were determined in micrograms per milliliter using standardized enzyme-linked immunosorbent assays (ELISAs) [18].

Statistical Analysis

For the infant series, subjects were categorized by serotype-specific acquisition at predefined time points: before dose 1, between doses 1 and 2, and between doses 2 and 3. "New acquisition" was defined as positive NP culture after negative carriage at previous visits; "no new acquisition" was defined as negative NP culture at all visits included in the series studied. Only serotypes with a sample size of ≥ 30 new acquisitions during the infant series were selected for analysis.

Only subjects who received 3 doses of PCV7 or PCV13 during the infant series were included in the analysis. Data for the PCV7/PCV13 common serotypes were combined from the PCV7 and PCV13 groups, and data for PCV13-unique serotypes were assessed from the PCV13 group only. Serotype-specific IgG geometric mean concentrations (GMCs) 1 month after the infant series for subgroups with new acquisition of a specific serotype at predefined time points were estimated with 95% confidence intervals. IgG GMCs were compared between subgroup with new acquisition of a serotype at predefined time

points and subgroup with no new acquisition of that serotype during the infant series.

For toddler dose (dose 4) assessments, serotype-specific new acquisitions were categorized as occurring before dose 1, between doses 1 and 2, between doses 2 and 3, or between doses 3 and 4; there was also a category for no new acquisition from month 2 through month 12. Only subjects who received 4 doses of PCV7 or PCV13 were included in the analysis. Serotype-specific IgG GMCs 1 month after the toddler dose for the subgroup with new acquisition of a serotype at predefined time points were compared with the subgroup with no new acquisition of that serotype throughout the study.

The effect of cross-reaction between serotypes 19A and 19F as well as serotypes 6B and 6A was assessed. In the combined PCV7/PCV13 group, serotype 19F immune responses (IgG GMC) were evaluated by serotype 19A acquisition, and serotype 6B immune responses (IgG GMC) were evaluated by serotype 6A acquisition. In the PCV13 group, serotype 19A immune response by serotype 19F acquisition and serotype 6A response by serotype 6B acquisition were assessed.

P values from the Wilcoxon test were used and adjusted with false discovery rate owing to multicomparison adjustment (across all comparisons).

RESULTS

Participants and Demographic Characteristics

Healthy infants ($N = 1866$) were randomized to receive either PCV13 or PCV7 at 2, 4, 6, and 12 months of age [18]: 1787 subjects received 3 doses of PCV13 ($n = 897$) or PCV7 ($n = 890$) during the infant series, and 1757 subjects received 4 doses of PCV13 ($n = 875$) or 4 doses of PCV7 ($n = 882$) throughout the study. Only serotypes 6B, 9V, 14, 18C, 19F, and 23F from the combined PCV13/PCV7 groups and serotypes 6A and 19A from the PCV13 group were selected for this hyporesponsiveness investigation because the sample size of acquisition during the infant series was sufficiently meaningful (≥ 30 new acquisitions during the infant series) to proceed with further categorization by each time point.

The analysis population size differed by serotype because the analysis requires both carriage data and validated IgG data available for that serotype. For serotypes 6B, 9V, 14, 18C, 19F, and 23F, the total number of subjects in combined PCV13 and PCV7 groups was 1548, 1564, 1554, 1561, 1539, and 1555, respectively, in the post-infant series analyses and 1584, 1586, 1582, 1585, 1572, and 1588 in the post-toddler dose analyses. For serotypes 6A and 19A, the total number of subjects in PCV13 groups was 762 and 764, respectively, after the infant series and 794 and 787 after the toddler dose. Serotype-specific new acquisition at the infant-series blood draw and new acquisition at the toddler-dose blood draw were removed from the analyses because it is unknown if the acquisition was closer to the previous vaccination visit or the blood draw visit.

Association Between New NP Acquisition During Predefined Time Points and IgG GMCs After the Infant Series and After the Toddler Dose

Serotypes 6A, 6B, 18C, 19F, and 23F

Data for these serotypes were derived from the entire study population, except for serotype 6A (PCV13 recipients only). The pattern of hyporesponsiveness to timing of acquisition by number of previously administered doses was generally similar for these 5 serotypes: GMC at 7 months of age (1 month after 3 infant doses) was lowest when acquisition of the respective serotype occurred before dose 1 and gradually increased when acquisition was between doses 1 and 2 and then between doses 2 and 3 (Figure 1A; Supplementary Table 1). However, IgG GMC at 7 months of age for all of these serotypes was highest in children who never acquired the respective serotypes before dose 3. One exception was serotype 23F, for which GMC was nonsignificantly higher when the serotype was acquired between vaccine doses 2 and 3. Some differences in IgG GMCs among those who had not acquired the respective serotypes did not reach statistical significance when compared with those acquiring the respective serotypes between doses 1 and 2 (serotype 23F) and between doses 2 and 3 (serotypes 6A, 18C, and 23F).

All post-toddler dose IgG GMCs (1 month after dose 4) in subjects who acquired the respective serotype at any time before the toddler dose were lower than those not acquiring the serotype from months 2 to 12 (Figure 1B; Supplementary Table 1). The difference was not statistically significant for the following acquisition time points: before dose 1 for serotypes 18C and 23F, between doses 1 and 2 for serotype 6A, between doses 2 and 3 for serotypes 18C and 23F, and between doses 3 and 4 for serotype 18C.

Serotypes 9V, 14, and 19A

The data for serotypes 9V and 14 were derived from the entire study population; data for serotype 19A were analyzed for subjects receiving PCV13 only. For these 3 serotypes, no significant reduction in IgG GMC after the infant series or toddler dose was found in relation to acquisition of the respective serotypes during any time point apart from after the toddler dose for serotype 14 (Figure 2A and 2B; Supplementary Table 1).

Cross-reactivity Between Serotypes 6A and 6B or Serotypes 19A and 19F

No significant reduction in IgG GMCs (hyporesponsiveness) after the infant series or after the toddler dose (dose 4) was observed at any acquisition time point for the respective cross-reactive serotypes (serotypes 6B for 6A, 6A for 6B; serotypes 19F for 19A, 19A for 19F) with the exception of hyporesponsiveness to serotype 19F among those with 19A acquisition between doses 3 and 4 (Figure 3A and 3B; Supplementary Table 2). However, higher IgG GMCs in the post-infant series and post-toddler dose were consistently observed among subjects who carried the respective cross-reacting serotypes before dose 1 compared with

any other acquisition time point or compared with no new acquisition of the serotype throughout the study. For serotype 19A, the post-infant series IgG GMC was significantly higher among subjects exposed to serotype 19F before dose 1 than among those not exposed to serotype 19F during the infant series. Additionally, the post-toddler dose serotype 19A IgG GMC was significantly higher among subjects exposed to serotype 19F before dose 1 than among those not exposed to serotype 19F throughout the study. Acquisition of serotype 19A between doses 3 and 4 was associated with significantly lower 19F IgG GMCs than no acquisition of the serotype from month 2 through 12. For serotype 6A IgG GMC, acquisition of serotype 6B was not associated with any statistical difference. For serotype 6B, the post-toddler dose IgG GMC was significantly higher among those who acquired serotype 6A before dose 1 than those not acquiring the serotype from month 2 through month 12.

DISCUSSION

This large, randomized, double-blind study [18] offered an adequate sample size to assess the effect of NP acquisition on IgG immune responses after the infant series and after the toddler dose for commonly carried PCV7 serotypes (serotypes 6B, 9V, 14, 18C, 19F, and 23F) when PCV13 and PCV7 groups were combined and for serotypes 6A and 19A in the PCV13 group. Additionally, the relationship between the timing of serotype acquisition and immune responses was investigated. Carriage of other vaccine serotypes (1, 3, 4, 5, and 7F) was not sufficiently prevalent to be studied.

The data from this study generally support prior research, which showed that for the limited number of pneumococcal serotypes studied (mainly serotypes 6B, 19F, and 23F), PCVs elicit lower immune responses (hyporesponsiveness) if carried by infants before vaccination. Both lower GMCs and lower percentages of subjects with responses above threshold have been observed across infant populations from multiple countries [1–5]. However, the current study provides novel additional data, including expanding the findings on hyporesponsiveness to serotypes 6A and 18C.

The pattern of hyporesponsiveness varied by timing of acquisition in relation to the number of previously administered doses. The pattern was similar for serotypes 6A, 6B, 18C, 19F, and 23F; for these serotypes, the IgG GMCs at 7 months (after 3 infant doses) were generally lowest if acquisition of the respective serotype occurred before dose 1, and highest if the respective serotype was not acquired before dose 3. All post-toddler dose IgG GMCs in subjects who had acquired the respective serotype before the toddler dose were lower than those not acquiring these 5 serotypes from months 2 through 12.

This is the first analysis of whether carriage of cross-reactive serotypes (serotype 6B for 6A, 6A for 6B; 19A for 19F; 19F for 19A) is associated with hyporesponsiveness. No significant reduction in IgG GMCs was observed after the infant series and

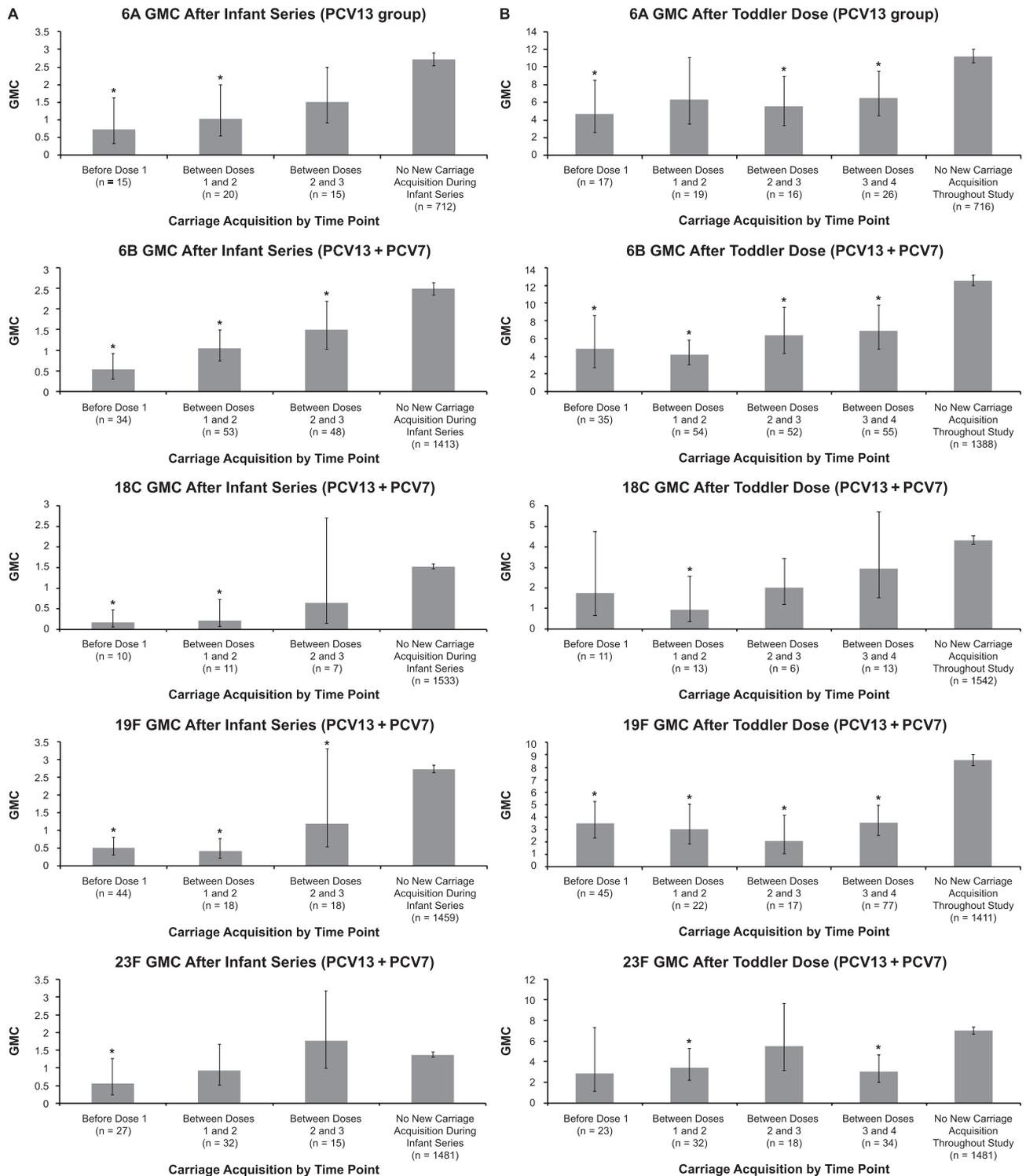


Figure 1. Serotype-specific immunoglobulin G geometric mean concentrations (GMCs) for serotypes 6A, 6B, 18C, 19F, and 23F among subjects with serotype-specific acquisition measured at predefined time points for 1 month after the infant series (asterisks indicate that the GMC is statistically significantly lower than that for no new carriage acquisition during the infant series) (A) and 1 month after the toddler dose (asterisks indicate that the GMC is statistically significantly lower than that for no carriage from month 2 through month 12) (B). Corresponding data are presented numerically in [Supplementary Table 1](#). Abbreviations: GMC, geometric mean concentration; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

after the toddler dose (dose 4) at any acquisition time point for cross-reactive serotypes. The highest IgG GMCs were generally observed after both the infant series and toddler dose in subjects

who carried the respective cross-reacting serotypes before dose 1 compared with any other acquisition time point or who had no acquisition of the serotype from months 2 through 12.

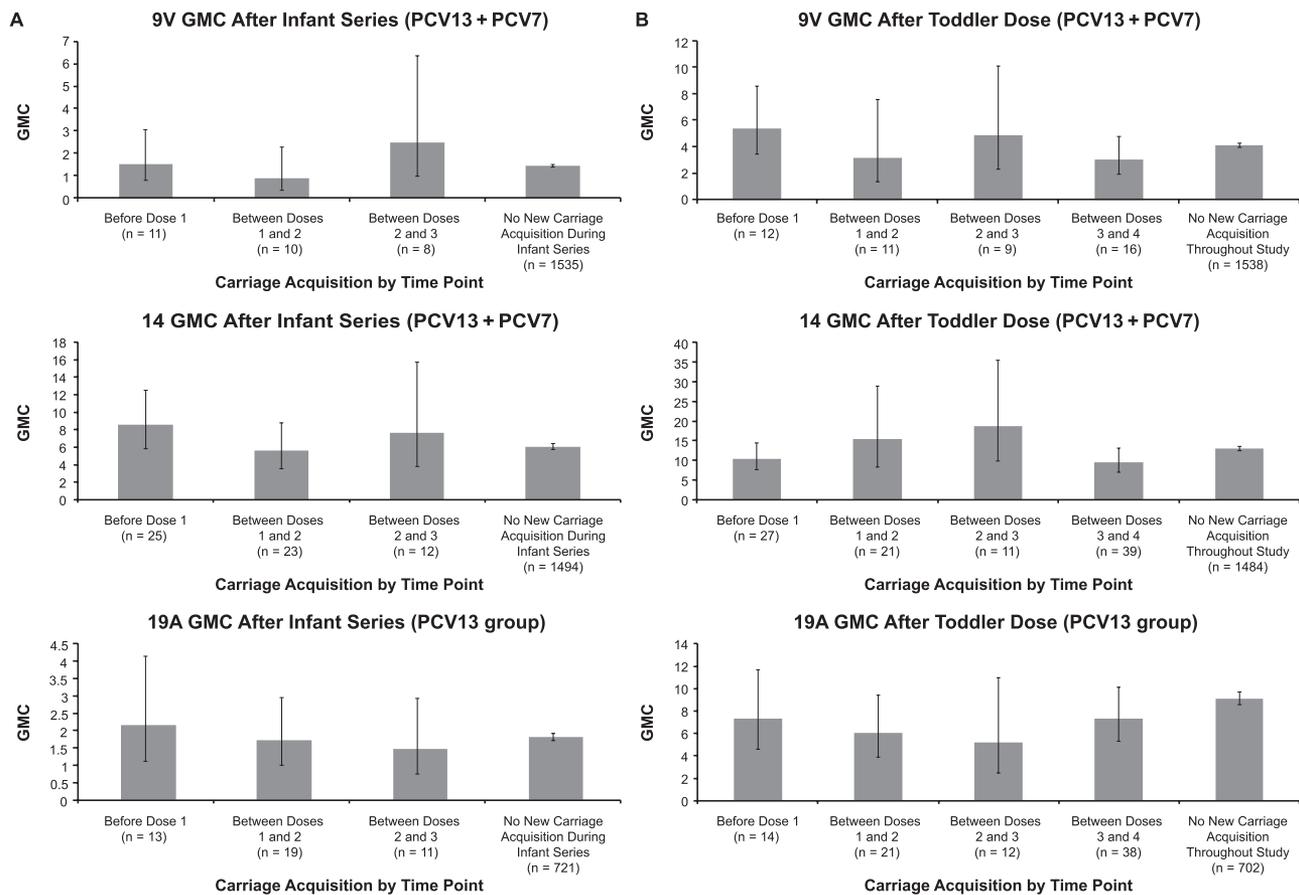


Figure 2. Serotype-specific immunoglobulin G geometric mean concentrations for serotypes 9V, 14, and 19A among subjects with serotype-specific acquisition measured at predefined time points for 1 month after the infant series (A) and 1 month after the toddler dose (B). Corresponding data are presented numerically in [Supplementary Table 1](#). Abbreviations: GMC, geometric mean concentration; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

Not all serotypes, when colonized, demonstrated hyporesponsiveness. The serotypes that were not associated with hyporesponsiveness were serotypes 19A, 14, and 9V when assessed before or after any dose during the infant series or after the toddler dose. This possibly results from structural diversity between pneumococcal epitopes [9] despite cross-reactivity.

For carried serotypes not associated with hyporesponsiveness, the mechanism remains unknown. As described previously, hyporesponsiveness after vaccination has also been observed after revaccination with meningococcal and pneumococcal plain polysaccharide vaccines in pediatric and adult populations, and among children diagnosed with IPD who did not reach the protective threshold of antibodies against the pathogenic serotype after vaccination [6–10]. A number of mechanisms have been proposed to explain this phenomenon, all of which are associated with the effect of the polysaccharide load on immune response [9]. For NP colonization, it has been suggested that the polysaccharide could be systemically absorbed [1]. The circulation of high loads of pneumococcal polysaccharide could prevent serotype-specific B lymphocyte differentiation in the marginal zone of the spleen and lymph nodes, thereby inducing B-cell fatigue or unresponsiveness that may

persist for several months [1, 3]. Polysaccharide antigens induce a T-cell-independent immune response, stimulating but not replenishing memory cells, thus resulting in overall depletion of the memory cell pool and a lower response on reexposure to the same polysaccharide antigen on vaccination [9]. However, we cannot provide a reason for the phenomenon observed with cross-reacting serotypes (6B vs 6A and 19F vs 19A) that explains why early carriage with the cross-reacting serotypes was associated with increased response to immunization.

Other factors that may play a role in immune response include genetic factors [1]. For example, antibody responses to the hepatitis B virus vaccine are affected by certain genes, and the host gut microbiome has been associated with the magnitude of response to influenza vaccine [19]. Moreover, environmental factors, such as overcrowding, nutritional status (including breastfeeding), and infection history, may influence vaccine response [3, 9, 19]. The effect of circulating antibodies (eg, high concentrations of maternal antibodies to pneumococcus or to the cross-reacting material carrier protein or antibodies elicited in infants who have pneumococcal NP colonization) may be associated with lower immune responses to the conjugated polysaccharides [1]. Last, immune responses may be influenced by

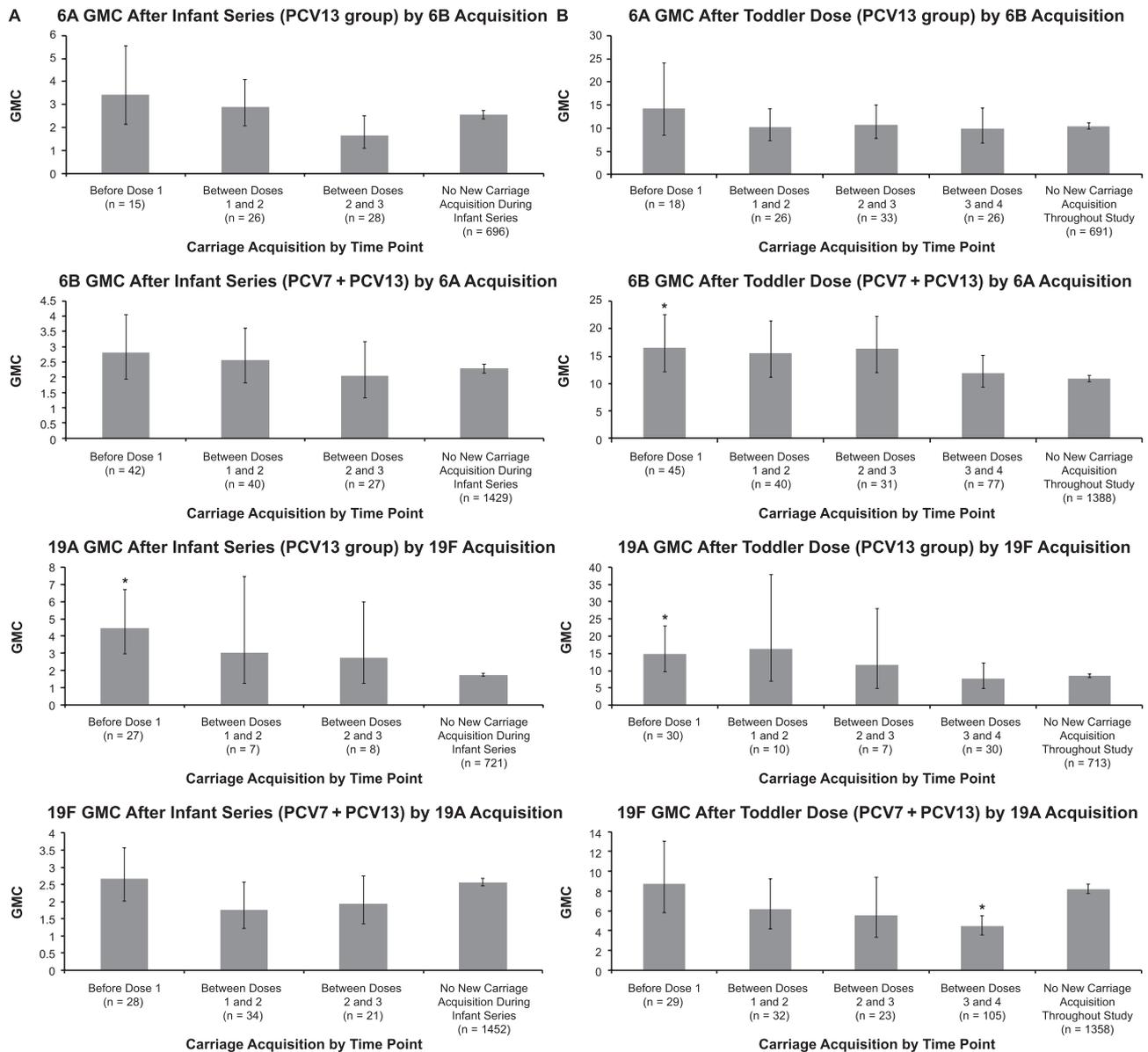


Figure 3. Immunoglobulin G geometric mean concentrations assessed at 1 month after the infant series (A) and 1 month after the toddler dose (B) for serotype 6A by serotype 6B acquisition, serotype 6B by serotype 6A acquisition, serotype 19A by serotype 19F acquisition, and serotype 19F by serotype 19A acquisition (asterisks indicate values that are significantly higher than those for no new carriage acquisition from month 2 through month 12). Corresponding data are presented numerically in [Supplementary Table 2](#). Abbreviations: GMC, geometric mean concentration; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

innate immunologic mechanisms for mucosal clearance, including the role of interleukin 17A-producing Th17 CD4⁺ cells, which are considered important effectors against *S. pneumoniae* colonization and subsequent disease [9, 19–22].

This study had some limitations, including that it did not examine the effect of vaccine-serotype colonization on the functionality of serotype-specific antibody as measured by the opsonophagocytosis assay (OPA). However, prior published results from this study showed a high correlation between IgG concentrations measured by ELISA (as shown in the present study) and more functional OPA assay [23], suggesting that binding antibody levels measured using ELISA would be

similarly associated with protection against NP acquisition of *S. pneumoniae* as the functional antibody levels measured using OPA. Another limitation is that short-term carriage episodes may have been missed, leading to overrepresentation of serotypes associated with more long-term colonization. Future studies should address whether serotypes with a tendency for prolonged colonization are differentially associated with hyporesponsiveness.

Interest has been raised about the effect of hyporesponsiveness on vaccine efficacy of the carried serotype regarding protection against the more common mucosal pneumococcal diseases, such as acute otitis media and pneumonia, in which higher IgG

concentrations may be required than are necessary to protect against IPD but for which the exact threshold is unknown [1]. In settings with high rates of NP colonization by vaccine serotypes, a greater proportion of children may be suboptimally protected against IPD. Since its introduction, PCV13 has been shown to have substantial public health benefits in vaccine-type disease reduction for vaccinated and unvaccinated individuals [24], presumably due to both the direct protection of vaccinated subjects and interruption of transmission of vaccine serotypes leading to elimination of these serotypes in the community [24]. The implication of reduced immune response following NP colonization may become less important following widespread use of PCVs and subsequent reduction of vaccine serotype pneumococcal disease and NP colonization, with reduction of transmission of vaccine serotypes leading to elimination of these serotypes in the community [3].

CONCLUSIONS

This analysis clearly shows that acquisition of some, but not all, serotypes was significantly associated with a lowered immune response to the carried serotype. Time of acquisition seems to play an important role, with acquisition before dose 1 having the strongest association with immune response. Although the clinical significance has not yet been fully elucidated, the novel insights acquired in this study add to our understanding of the immunology of polysaccharide capsule and will be useful when planning studies with next-generation PCVs, especially those with increasing complexity. The effect may be diminished in countries where widespread vaccination has generally decreased NP colonization, with reduced transmission of pneumococci and less vaccine-type pneumococcal disease.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Dagan R, Givon-Lavi N, Greenberg D, Fritzell B, Siegrist CA. Nasopharyngeal carriage of *Streptococcus pneumoniae* shortly before vaccination with a

- pneumococcal conjugate vaccine causes serotype-specific hyporesponsiveness in early infancy. *J Infect Dis* **2010**; 201:1570–9.
2. Vakevainen M, Soinen A, Lucero M, et al. Serotype-specific hyporesponsiveness to pneumococcal conjugate vaccine in infants carrying pneumococcus at the time of vaccination. *J Pediatr* **2010**; 157:778–83.e771.
3. Madhi SA, Violari A, Klugman KP, et al; CIPRA 4 Team. Inferior quantitative and qualitative immune responses to pneumococcal conjugate vaccine in infants with nasopharyngeal colonization by *Streptococcus pneumoniae* during the primary series of immunization. *Vaccine* **2011**; 29:6994–7001.
4. Rodenburg GD, van Gils EJ, Veenhoven RH, et al. Lower immunoglobulin G antibody responses to pneumococcal conjugate vaccination at the age of 2 years after previous nasopharyngeal carriage of *Streptococcus pneumoniae*. *J Pediatr* **2011**; 159:965–70.e961.
5. Ojal J, Hammit LL, Gaiho J, Scott JAG, Goldblatt D. Pneumococcal conjugate vaccine induced IgG and nasopharyngeal carriage of pneumococci: hyporesponsiveness and immune correlates of protection for carriage. *Vaccine* **2017**; 35:4652–7.
6. Pichichero ME. Immunological paralysis to pneumococcal polysaccharide in man. *Lancet* **1985**; 2:468–71.
7. Borrow R, Stanford E, Waight P, et al. Serotype-specific immune unresponsiveness to pneumococcal conjugate vaccine following invasive pneumococcal disease. *Infect Immun* **2008**; 76:5305–9.
8. Sigurdardottir ST, Center KJ, Davidsdottir K, et al. Decreased immune response to pneumococcal conjugate vaccine after 23-valent pneumococcal polysaccharide vaccine in children. *Vaccine* **2014**; 32:417–24.
9. Papadatou I, Spoulou V. Pneumococcal vaccination in high-risk individuals: are we doing it right? *Clin Vaccine Immunol* **2016**; 23:388–95.
10. Granoff DM, Pollard AJ. Reconsideration of the use of meningococcal polysaccharide vaccine. *Pediatr Infect Dis J* **2007**; 26:716–22.
11. Jokinen JT, Ahman H, Kilpi TM, Mäkelä PH, Käyhty MH. Concentration of antipneumococcal antibodies as a serological correlate of protection: an application to acute otitis media. *J Infect Dis* **2004**; 190:545–50.
12. Siber GR, Chang I, Baker S, et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. *Vaccine* **2007**; 25:3816–26.
13. Dagan R, Givon-Lavi N, Fraser D, Lipsitch M, Siber GR, Kohberger R. Serum serotype-specific pneumococcal anticapsular immunoglobulin G concentrations after immunization with a 9-valent conjugate pneumococcal vaccine correlate with nasopharyngeal acquisition of pneumococcus. *J Infect Dis* **2005**; 192:367–76.
14. Dagan R, Juergens C, Trammel J, et al. Modeling pneumococcal nasopharyngeal acquisition as a function of anticapsular serum antibody concentrations after pneumococcal conjugate vaccine administration. *Vaccine* **2016**; 34:4313–20.
15. Goldblatt D, Hussain M, Andrews N, et al. Antibody responses to nasopharyngeal carriage of *Streptococcus pneumoniae* in adults: a longitudinal household study. *J Infect Dis* **2005**; 192:387–93.
16. Andrews NJ, Waight PA, Burbidge P, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. *Lancet Infect Dis* **2014**; 14:839–46.
17. Voysey M, Fanshawe TR, Kelly DF, et al. Serotype-specific correlates of protection for pneumococcal carriage: an analysis of immunity in 19 countries. *Clin Infect Dis* **2018**; 66:913–20.
18. Dagan R, Patterson S, Juergens C, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. *Clin Infect Dis* **2013**; 57:952–62.
19. Lipsitch M, Li LM, Patterson S, et al. Serotype-specific immune responses to pneumococcal conjugate vaccine among children are significantly correlated by individual: analysis of randomized controlled trial data. *Vaccine* **2018**; 36:473–8.
20. Gray C, Ahmed MS, Mubarak A, et al. Activation of memory Th17 cells by domain 4 pneumolysin in human nasopharynx-associated lymphoid tissue and its association with pneumococcal carriage. *Mucosal Immunol* **2014**; 7:705–17.
21. Lundgren A, Bhuiyan TR, Novak D, et al. Characterization of Th17 responses to *Streptococcus pneumoniae* in humans: comparisons between adults and children in a developed and a developing country. *Vaccine* **2012**; 30:3897–907.
22. Le Polain de Waroux O, Flasche S, Prieto-Merino D, Edmunds WJ. Age-dependent prevalence of nasopharyngeal carriage of *Streptococcus pneumoniae* before conjugate vaccine introduction: a prediction model based on a meta-analysis. *PLoS One* **2014**; 9:e86136.
23. Juergens C, Patterson S, Trammel J, et al. Post hoc analysis of a randomized double-blind trial of the correlation of functional and binding antibody responses elicited by 13-valent and 7-valent pneumococcal conjugate vaccines and association with nasopharyngeal colonization. *Clin Vaccine Immunol* **2014**; 21:1277–81.
24. Klugman K, Dagan R, Malley R, Whitney CG. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin SA, Orenstein WA, Offit PA, Edwards KM, eds. *Vaccines*, 7th ed. Philadelphia, PA: Elsevier, **2018**:773–815.