Efficacy of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Versus That of 7-Valent PCV (PCV7) Against Nasopharyngeal Colonization of Antibiotic-Nonsusceptible *Streptococcus pneumoniae*

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**Background.** Pediatric respiratory infections caused by antibiotic-nonsusceptible *Streptococcus pneumoniae* (ANSP) continue to present an important challenge, even after introduction of 7-valent pneumococcal conjugate vaccine (PCV7). This randomized double-blind trial assessed the potential additional impact of PCV13 over PCV7 on reducing ANSP carriage.

**Methods.** Healthy infants were randomly assigned to receive PCV13 (n = 932) or PCV7 (n = 934) at ages 2, 4, 6, or 12 months. Eight nasopharyngeal specimens were collected by swabbing between ages 2 and 24 months. *S. pneumoniae* isolates were serotyped and tested for antimicrobial susceptibility by the disk-diffusion method and the Etest. Nasopharyngeal acquisition and prevalence of ANSP during ages 7–24 months were compared between the 2 vaccine groups.

**Results.** In general, new acquisition of pneumococci nonsusceptible to penicillin, erythromycin, clindamycin, penicillin plus erythromycin, and multiple drugs (≥3 antibiotics) was significantly lower in the PCV13 group compared with the PCV7 group; the main serotypes contributing to this significant decrease were serotype 19F, present in PCV13 and PCV7, and serotypes 6A and 19A, present in PCV13 only.

**Conclusions.** PCV13 has a significant added benefit over PCV7 in reducing carriage of ANSP. Because carriage determines transmission, these results suggest that PCV13 will provide protection against ANSP disease that exceeds protection provided by PCV7.

**Clinical Trials Registration.** NCT00508742.

**Keywords.** *Streptococcus pneumoniae*; pneumococcal conjugate vaccine; antibiotic-nonsusceptibility; nasopharyngeal colonization.
serotype 19A, was observed, resulting in attenuation of the overall reduction in ANSP disease [2, 5–7]. An increase in antibiotic-nonsusceptible serotype 19A carriage and disease was also observed in countries that had not introduced PCV7, coinciding with extensive antibiotic use [8]. PCV13 (which targets the PCV7 serotypes plus serotypes 1, 3, 5, 6A, 7F, and 19A) could potentially reverse this increase in disease caused by antibiotic-nonsusceptible non-PCV7 serotypes [2, 9].

Previously, this double-blind, randomized clinical study conducted in Israel assessed the impact of PCV13, compared with that of PCV7, on nasopharyngeal (NP) pneumococcal colonization, demonstrating that PCV13 resulted in lower colonization than PCV7 by S. pneumoniae with PCV13 serotypes 1, 6A, 7F, and 19A; the cross-reacting serotype 6C; and the PCV7/PCV13 serotype 19F [10]. For serotype 3 and the other 6 PCV7-serotypes, there were no significant differences between the vaccine groups. There were too few serotype 5 events to draw inference [10]. Presented here is a post hoc analysis of this study examining the impact of PCV13 and PCV7 on NP colonization of ANSP for the most commonly used antibiotics.

**METHODS**

The current analysis was part of a double-blind study comparing the immunogenicity, safety, NP acquisition, and prevalence of pneumococcal colonization in children immunized with PCV13 and PCV7 [10]. The design of this study was described in detail elsewhere [10]. In brief, healthy infants were randomly assigned to receive PCV13 or PCV7 at ages 2, 4, 6, and 12 months. PCV7 contains saccharides from pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, each individually conjugated to CRM197. PCV13 contains saccharides from the pneumococcal serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A, each individually conjugated to CRM197. The PCV13 and PCV7 formulations used in this study were identical in appearance. Concomitant pediatric vaccines were administered as recommended in Israel. Eight NP specimens for pneumococcal cultures were to be collected by swabbing at ages 2, 4, 6, 7, 12, 13, 18, and 24 months. All collected S. pneumoniae isolates were serotyped and tested for antimicrobial susceptibility. The study was conducted by a single coordinating center overseeing activities at 11 clinical sites in southern Israel. The trial was approved by the Institutional Ethics Committee of the Soroka University Medical Center and the National Ethics Committee. Written informed consent was obtained from all parent(s) or legal guardian(s) of every subject before enrollment in the study and before performance of any study-related procedures.

This post hoc analysis compared acquisition and prevalence of ANSP NP colonization between the vaccine groups. The study was conducted before the introduction of PCV13 in Israel, thus allowing an unbiased comparison of the impact of PCV13 with that of PCV7 on all ANSP isolates collected.

**NP Cultures and Laboratory Testing**

NP specimens were obtained from participants by using flexible polyethylene terephthalate–tipped swabs; swabs and cultures were prepared as previously described [10]. In brief, pneumococcal isolates were serotyped by the Quellung reaction, using antisera (Statens Serum Institut, Copenhagen, Denmark). Isolates with negative reactions to all pooled serum samples and to Omni serum were considered to be nontypeable. All isolates testing positive by the Quellung reaction to serotype 6A were further characterized by polymerase chain reaction testing to differentiate between serotypes 6A and 6C. During the study (and before unblinding), it became apparent that serotype 6C, which is structurally similar to serotype 6A, could now be distinguished from serotype 6A and should be assessed separately. Thus, although serotype 6C is not a PCV13 serotype, it was included in the assessment [11, 12].

**Antibiotic Susceptibility Testing**

Specimens were cultured at the Clinical Microbiology Laboratory of the Soroka University Medical Center. Antibiotic susceptibility testing was performed by the disk-diffusion method of Bauer and Kirby, according to National Committee for Clinical Laboratory Standards recommendations, and by the Etest (AB Biodisk; Solna, Sweden) and has been described elsewhere [13]. Nonsusceptibility among isolates was defined as a minimal inhibitory concentration (MIC) above or a zone diameter below the susceptibility breakpoint, as follows: for penicillin (for pneumococcal disease treated orally), an MIC of ≥0.125 μg/mL; for ceftriaxone, an MIC of ≥1.0 μg/mL; for erythromycin, a zone diameter of ≤21 mm; for trimethoprim-sulfamethoxazole (TMP-SMZ), a zone diameter of ≤19 mm; for tetracyclines, a zone diameter of ≤23 mm; for chloramphenicol, a zone diameter of ≤20 mm; and for clindamycin, a zone diameter of ≤19 mm. For dual nonsusceptibility to erythromycin and penicillin, an MIC of ≥0.125 μg/mL was used. Isolates nonsusceptible to ≥3 of the antibiotics assessed were defined as multidrug resistant (MDR).

**Statistical Methods**

**Outcomes**

In this post hoc analysis, the impact of PCV13 and PCV7 on ANSP carriage was assessed for all identified vaccine and nonvaccine serotypes combined, for various combinations of serotypes, and for single serotypes, using 3 outcome measures. First, since reduction in NP acquisition may be predictive of direct protection for vaccinated individuals, we assessed NP acquisition of serotypes by measuring the number of participants within each vaccine group with a new ANSP NP acquisition from the age of 7 months (ie, 1 month after completion of the infant series) to the age of 24 months, relative to the total number of participants with at least 1 culture result. A new acquisition was defined as detection of a given serotype that was not previously identified at baseline (age 2, 4, and 6 months) or at any other time before
the detection. Therefore, only 1 new acquisition was counted for each serotype per participant [13]. Second, prevalence, in contrast to acquisition, may predict indirect effects on the community, reflecting the potential transmission of the organism. Therefore, the prevalence of NP colonization with ANSP serotypes was calculated at each visit (ages 7, 12, 13, 18, and 24 months), using the number of participants with at least 1 isolate that was antibiotic nonsusceptible relative to the total number of participants with least 1 NP culture result at each given visit. Third, the cumulative prevalence of NP colonization of serotypes from 7 months to 24 months of age, reflecting the period during which individuals may transmit the organism, was assessed. The cumulative prevalence of an ANSP isolate was calculated as the number of participants with at least 1 isolate that was antibiotic nonsusceptible relative to the total number of participants who completed the study with at least 1 NP culture result at any time from age 7 months up to and including a given time point.

Statistical Analysis
The per-protocol analysis included eligible healthy infants who received the treatment to which they were randomly assigned, had at least 1 NP swab specimen for the proposed analysis, and had no other major protocol violations. For comparisons between the vaccine groups of new acquisition, prevalence, and cumulative prevalence, odds ratios (ORs; PCV13:PCV7) were derived and 2-sided 95% confidence intervals (CIs) were constructed using logistic regression. A reduction between the groups was considered statistically significant if the upper limit of the 95% CI around the OR was <1. Statistics were derived using SAS (SAS Institute, Cary, NC; version 9.2) and PROC STATXACT (Cytel, Cambridge, MA; version 8.1).

RESULTS

Participants
Between February 2008 and September 2009, 1866 healthy infants were randomly assigned to receive PCV13 (n = 932) or PCV7 (n = 934). The evaluable per-protocol population included 881 PCV13 recipients and 873 PCV7 recipients; details of the study populations were described elsewhere [10]. Most of the excluded participants (103 of 112) did not receive all pneumococcal vaccinations. The last study visit was September 2011.

Demographic Characteristics
The demographic characteristics of the per-protocol populations were similar with respect to sex (females: 51.3% and 50.2% for PCV13 and PCV7 recipients, respectively) and ethnicity (Jewish 66.2% and 65.4%, respectively; Bedouin 33.5% and 34.4%, respectively; and others 0.3% and 0.2%, respectively). The mean age (±SD) in both groups was 2.2±0.3 months at dose 1; 3.9±0.4 months at dose 2; 5.7±0.5 months at dose 3; and 12.5±0.6 months at the toddler dose [10].

S. pneumoniae Isolates and Antibiotic Nonsusceptibility
A total of 5049 pneumococcal isolates were included in the per-protocol population (from 1754 evaluable participants). The number of isolates available at the prespecified age points included 863 at 7 months (PCV13, 455; PCV7, 408), 948 at 12 months (PCV13, 489; PCV7, 459), 858 at 13 months (PCV13, 449; PCV7, 409), 965 at 18 months (PCV13, 501; PCV7, 464), and 1002 at 24 months (PCV13, 499; PCV7, 503).

For the antibiotics investigated, nonsusceptibility to penicillin (2314 of 5049 [45.8%]) and TMP-SMZ (1539 of 5049 [30.5%]) was most common among ANSP isolates; chloramphenicol nonsusceptibility was low (52 of 5049 [1.0%]), and only 1 isolate (<1%) was nonsusceptible to ceftriaxone (Supplementary Table 1). The most common vaccine serotypes that were nonsusceptible to at least 1 of the studied antibiotics were PCV13/PCV7 serotypes 6B (288 of 299 isolates), 9V (65 of 70 isolates), 14 (156 of 161 isolates), 19F (220 of 288 isolates), and 23F (157 of 160 isolates) and the PCV13-specific serotypes 6A (276 of 320 isolates) and 19A (410 of 422 isolates). For PCV7/PCV13 serotypes 4 (1 of 28 isolates) and 18C (12 of 68 isolates), and for PCV13-specific serotypes 1 (7 of 10 isolates), 3 (0 of 52), 5 (3 of 5 isolates), and 7F (10 of 20 isolates) and the cross-reacting serotype 6C (21 of 108 isolates), colonization of ANSP was low (Figure 1 and Supplementary Table 1).

The most commonly isolated antibiotic-nonsusceptible nonvaccine serotypes were serotypes 10B (89 of 102 isolates), 11A (82 of 205 isolates), 15A (72 of 183 isolates), 15B/C (280 of 424 isolates), 16F (128 of 216 isolates), 17F (87 of 102 isolates), 21 (98 of 112 isolates), 23B (48 of 106 isolates), 34 (44 of 144 isolates), and 35B (124 of 233 isolates). Nonvaccine serotypes that were frequently carried (≥60 isolates) but for which ANSP carriage was generally low included serotypes 10A (7 of 93 isolates), 23A (13 of 159 isolates), 31 (10 of 98 isolates), and 38 (28 of 105 isolates; Figure 1 and Supplementary Table 1).

Impact of PCV13 and PCV7 on ANSP

Antibiotic-Nonsusceptible Strains for Vaccine and Nonvaccine Serotypes Combined
PCV13, compared with PCV7, significantly reduced overall NP acquisition of penicillin-, erythromycin-, and clindamycin-nonsusceptible pneumococci, as well as MDR (≥3 categories) and dual penicillin and erythromycin–nonsusceptible pneumococci, but not TMP-SMZ–, tetracycline–, or chloramphenicol–nonsusceptible pneumococci (Figure 2 and Supplementary Table 2).

For the overall prevalence of antibiotic nonsusceptibility among strains at prespecified age points, there were significant reductions in the PCV13 group, compared with the PCV7 group, for penicillin, erythromycin, clindamycin, TMP-SMZ, tetracycline, MDR, and dual penicillin and erythromycin at ≥1 time point. Of interest, the difference between vaccine groups in the overall prevalence of ANSP NP colonization...
Figure 1. Overall nasopharyngeal acquisition of antibiotic-nonsusceptible *Streptococcus pneumoniae* after the infant series from 7 to 24 months of age by serotype. Multidrug resistant indicates resistance to ≥3 of the following antibiotics: chloramphenicol, clindamycin, erythromycin, trimethoprim-sulfamethoxazole (TMP-SMZ), tetracycline, and penicillin. Because of the limited number of subjects with nasopharyngeal acquisition of *S. pneumoniae* isolates that were nonsusceptible to ceftriaxone or chloramphenicol, these data are described in the text and Supplementary Table 1 only. Abbreviations: NS, nonsusceptible; S, susceptible.
Figure 2. Nasopharyngeal (NP) acquisition of antibiotic-nonsusceptible Streptococcus pneumoniae after the infant series from 7 to 24 months of age: 13-valent pneumococcal conjugate vaccine (PCV13) serotypes combined and single serotypes, by vaccine group. A, Penicillin minimum inhibitory concentration \( \geq 0.125 \) µg/mL. B, Erythromycin. C, Clindamycin. D, Trimethoprim-sulfamethoxazole (TMP-SMZ). E, Tetracycline. F, Chloramphenicol. G, Multidrug resistant (ie, resistance to \( \geq 3 \) of the following antibiotics: chloramphenicol, clindamycin, erythromycin, TMP-SMZ, tetracycline, and penicillin). H, Dual penicillin and...
was generally more pronounced at ages 13–24 months than after the primary series (ages 7 and 12 months); however, changes were less pronounced for NP acquisition by TMP-SMZ–nonsusceptible isolates (Figure 3).

The impact of PCV13 and PCV7 on the cumulative prevalence for all ANSP isolates was generally consistent with that observed for NP acquisition, with significant reductions in the PCV13 group, compared with the PCV7 group, for penicillin-, erythromycin-, clindamycin-, and dual penicillin and erythromycin–nonsusceptible serotypes but not for TMP-SMZ–, tetracycline–, or chloramphenicol-nonsusceptible isolates or MDR isolates (Supplementary Table 3).

**Antibiotic-Nonsusceptible Strains for Single Vaccine-Type Serotypes**

For new acquisition and cumulative prevalence, the main antibiotic-nonsusceptible single serotypes contributing to the significant decrease in the PCV13 group, compared with the PCV7 group, were PCV13/PCV7 serotype 19F and the PCV13-specific serotypes 6A and 19A. Significant reductions in the PCV13 group, compared with the PCV7 group, were observed for the antibiotic-nonsusceptible serotypes 19A and 19F, for the majority of antibiotics, and for serotype 6A, for penicillin, erythromycin, and dual penicillin and erythromycin (Supplementary Tables 2 and 3).

For PCV7/PCV13 serotypes 4 and 18C, the PCV13-specific serotypes 1, 3, 5, and 7F, and the cross-reacting serotype 6C, overall colonization was infrequent and colonization by antibiotic-nonsusceptible strains was absent or rare.

**Antibiotic-Nonsusceptible Strains for PCV13 Serotypes Combined**

For PCV13 serotypes combined, NP acquisition of penicillin-, erythromycin-, clindamycin-, TMP-SMZ–, and tetracycline-nonsusceptible isolates, as well MDR and dual penicillin and erythromycin–nonsusceptible isolates, was significantly more common in the PCV13 group, compared with the PCV7 group (Figure 2 and Supplementary Table 2). PCV13 had a similar impact on cumulative prevalence for these antibiotics; however, although tetracycline-nonsusceptible isolates were less common in the PCV13 group, this difference was not statistically significant (Supplementary Table 3).

**Antibiotic-Nonsusceptible Strains for Nonvaccine Serotypes**

For nonvaccine serotypes combined and for select nonvaccine serotypes (i.e., 11A, 15A, 15B/C, 16F, 21, 35B, 35F, and 38), both as individual serotypes and combined, there was no difference in the proportion of participants with NP acquisition or the cumulative prevalence of ANSP isolates between the PCV13 and PCV7 vaccine groups for any of the antibiotics (Figure 2 and Supplementary Tables 2 and 3) or for the prevalence of antibiotic-susceptible select single serotypes (data not shown).

**DISCUSSION**

This randomized double-blind study showed that PCV13, compared with PCV7, reduced the overall colonization of ANSP for the majority of antibiotics and antibiotic combinations investigated. The antibiotics chosen for this assessment were those commonly used to assess pneumococcal nonsusceptibility. The most common nonsusceptibility was to penicillin and TMP-SMZ, followed by erythromycin, tetracycline, and clindamycin. Dual penicillin and erythromycin nonsusceptibility and MDR were also common. Chloramphenicol nonsusceptibility was rare, and nonsusceptibility to ceftriaxone was not detected.

The most commonly carried ANSP isolates were PCV7/PCV13 serotypes 6B, 9V, 14, 19F, and 23F and PCV13-specific serotypes 6A and 19A. These serotypes represent the most commonly observed antibiotic resistant serotypes globally [14]. Of the most commonly isolated nonvaccine serotypes (>60 isolates each), those having the highest proportion of nonsusceptible isolates were 10B, 11A, 15A, 15B/C, 16F, 17F, 21, 23B, 34, 35B, and 38. Serotypes 10A, 23A, and 31 were commonly carried but showed a low frequency of nonsusceptibility. In this study, nonvaccine serotypes 11A, 15A, 15B/C, 16F, 21, 35B, 35F, and 38 were selected for single-serotype and combined analyses. These nonvaccine serotypes were chosen because of a tendency for increased prevalence after widespread uptake of PCV7 (serotype replacement) [15–19]. Our study showed that all of these preselected nonvaccine serotypes were frequently carried, with the exception of serotype 35F.

Significant reduction in ANSP acquisition or carriage was most commonly seen in relationship to a reduction of serotypes 19A, 19F, and 6A in the PCV13 group, compared with the PCV7 group. Here, as discussed in the primary article for this study [10], immune responses against these 3 serotypes were significantly higher after PCV13 receipt, compared with after PCV7 receipt. This included serotype 19F, which may explain the significantly increased impact of PCV13, compared with PCV7, against this PCV7/PCV13 serotype [10]. Although it is unknown why the PCV7/PCV13 serotype 19F elicited higher IgG geometric mean concentrations in the PCV13 group than in PCV7 group, changes made to optimize the manufacturing of serotype 19F in PCV13, compared with PCV7, may be involved or PCV13 may have enhanced activity against serotype 19F, owing to cross-reactive antibodies induced by 19A [10].

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**Figure 2 continued.** Erythromycin. Penicillin nonsusceptibility was determined for mean inhibitory concentration of >0.125 µg/mL. *NP acquisition was statistically significantly lower in the PCV13 group if the upper limit of the 2-sided 95% confidence interval (CI) of the odds ratio (OR) was <1. Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; VT, vaccine serotype.
Figure 3. Prevalence of antibiotic nonsusceptibility for all serotypes combined at prespecified time points, by vaccine group. A, Penicillin. B, Erythromycin. C, Clindamycin. D, Trimethoprim-sulfamethoxazole (TMP-SMZ). E, Tetracycline. F, Multidrug resistant (ie, resistance to ≥3 of the following antibiotics: chloramphenicol, clindamycin, erythromycin, TMP-SMZ, tetracycline, and penicillin). G, Dual penicillin and erythromycin. Penicillin nonsusceptibility was determined for a mean inhibitory concentration of ≥0.125 µg/mL. Differences between the vaccine groups were considered statistically significant if the upper bound of the 2-sided 95% confidence interval (CI) of the odds ratio (OR) was <1. Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.
For PCV7/PCV13 serotypes 6B, 9V, 14, and 23F, although there was colonization of nonsusceptible strains in both vaccine groups, no statistically significant differences were observed between the study groups for any of the antibiotics; immune responses were similar (for serotypes 6B, 9V, and 14) or significantly lower (for serotype 23) after PCV13 receipt, compared with after PCV7 receipt, which may explain the lack of impact of PCV13 versus that of PCV7 on the ANSP serotypes [10]. For PCV7/PCV13 serotypes 4 and 18C, PCV13-specific serotypes 1, 3, 5, and 7F, and the cross-reacting serotype 6C, overall colonization in both vaccine groups was infrequent, and colonization of antibiotic-nonsusceptible strains was zero or rare.

Why some serotypes are infrequent colonizers is unknown. The inability to culture specific pneumococcal serotypes from the nasopharynx is possibly a function of their density and duration of colonization [17, 20], given that all invasive serotypes are presumed to be carried, at least transiently, before invasion. In the literature, several serotypes have been reported as infrequent colonizers, including serotypes 1, 4, 5, and 7F [15, 17]. NP colonization is a dynamic process in terms of the turnover of colonizing serotypes. Several factors that influence colonization, particularly colonization by antibiotic-nonsusceptible strains, include natural exposure, antibiotic use, ethnic factors, geographical location, socioeconomic factors (e.g., overcrowded living conditions), age, maturation of the immune system, smoking, and health, as well as innate immunological mechanisms for mucosal clearance that contribute to protection (i.e., the role of interleukin 17A–producing T-helper type 17 (Th17) CD4+ T cells, which are considered important effectors against S. pneumoniae colonization and subsequent disease) [21].

Of interest, the difference between vaccine groups in the prevalence of ANSP NP colonization was generally more pronounced at ages 13–24 months than after the primary series, with the exception of isolates nonsusceptible to TMP-SMZ (one of the most common antibiotics for which pneumococci are nonsusceptible). Whether this more pronounced effect at ages 13–24 months is caused by the booster dose eliciting higher antibody concentrations, which may further reduce NP colonization [22], and/or by antibody maturation with time and age [23], which has a direct effect on the magnitude of antibody responses to T-cell–dependent protein antigens, has not been completely elucidated. Because there is no known antibody concentration threshold of protection against acquisition of carriage, it is generally accepted that higher antibody concentrations, especially functional antibody titers, may achieve a higher protection against carriage [22]. Indeed, when looking at the current study, antibodies against the most important PCV13 ANSP serotypes rose significantly after the booster dose, as measured by both an enzyme-linked immunosorbent assay and an opsonophagocytic assay [10, 21].

The impact of a booster dose on NP carriage is of particular interest for World Health Organization (WHO) considerations of vaccine schedules for developing countries, where regimens with and those without booster doses (2+1 doses vs 3+0 doses) are considered [24]. The WHO concluded that, despite differences in immunogenicity, evidence suggests that the clinical outcomes between these regimens may be minimal in the presence of herd protection. This study suggests an added benefit elicited by the booster dose, although maturation of antibodies with age could provide an additional potential explanation for the enhanced reduction of NP carriage. An open-label study conducted in Israel, which compared the PCV7 3+1 schedule (n = 177), administered at 2, 4, 6, and 12 months of age, with the 3+0 schedule (n = 176), administered at 2, 4, and 6 months of age, showed that, although the booster dose for the 3+0 group resulted in reduced geometric mean concentrations in the second year of life, vaccine-type NP carriage in the 3+0 group was similar to that of the 3+1 group at least up to age 2.5 years. The latter study was smaller than this study, which may explain the differences in outcome [25].

In the relatively short time since widespread introduction of PCV13 in 2010, the impact on invasive pneumococcal disease [26–32], pneumonia [33–35], otitis media [36, 37], and carriage [10, 38] were suggested for PCV13-specific serotypes 1, 6A, 7F, and 19A. This reduction was accompanied by a reduction in ANSP disease. However, as in other ecological studies dealing with antibiotic resistance, many factors, including alterations of antibiotic use, fluctuation in the severity of viral seasonality, and geographical differences, may influence interpretation of the results [5]. The current study, owing to its double-blinded and randomized design, excluded these potential biases and demonstrated beyond a doubt the significant and independent role of PCV13 in further reducing carriage of ANSP beyond PCV7.

One limitation of this study is the conservative approach in defining new NP acquisition, as only 1 new acquisition was counted for each serotype per participant. Thus, there is the possibility that ANSP NP acquisitions occurred more frequently than detected in this study. However, this limitation existed for both arms of the study.

By increasing the spectrum of PCVs with additional serotypes that show high prevalence of nonsusceptibility to a variety of antibiotics, antibiotic resistance can be reduced through 2 additional mechanisms beyond the direct reduction of carriage and disease by ANSP [39]. First, a further reduction of disease beyond that achieved by PCV7 may be associated with less frequent use of antibiotics, as overuse is the main promoter of resistance. Second, a reduction of ANSP carriage will result in a reduction of the spread of the organisms to nonvaccinated children and adults and will thus reduce the incidence of ANSP disease in populations beyond vaccinated children (through herd protection) [40].

PCV13 has a significant added benefit over PCV7 in reducing carriage of ANSP. Disease caused by ANSP is a global problem. Widespread use of PCVs is likely to further reduce the worldwide...
burden of ANSP disease, reduce antibiotic use, and preserve options for antibiotic selection. Ongoing surveillance to monitor emerging nonvaccine strains and antibiotic susceptibility will remain an important tool in targeting future intervention strategies.

**Supplementary Data**

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**References**


