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A toddler PCV booster dose following 3 infancy priming doses increases circulating serotype-specific IGG levels but does not increase protection against carriage

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ABSTRACT

Background: We compared PCV7 serological response and protection against carriage in infants receiving 3 doses (2, 4, 6 months; 3+0 schedule) to those receiving a booster (12 months; 3+1).
Methods: A prospective, randomized controlled study, conducted between 2005 and 2008, before PCVs were implemented in Israel. Healthy infants were randomized 1:1:1 to receive 3+1, 3+0 and 0+2 (control group; 12, 18 months doses). Nasopharyngeal/oropharyngeal swabs were obtained at all visits. Serum serotype-specific IgG concentrations and opsonic activities (OPA) were measured at 2, 7, 13 and 19 months. This study was registered with Current Controlled Trials, Ltd. ISRCTN28445844.
Results: Overall, 544 infants were enrolled: 3+1 (n = 178), 3+0 (n = 178) and 0+2 (n = 188).

Post-priming (7 months), antibody concentrations were similar in both groups, except for serotype 18C (higher in 3+0). Post-booster (13, 19 months), ELISA and OPA levels were significantly higher in 3+1 than in 3+0 group.

Nasopharyngeal/oropharyngeal cultures were positive for *Streptococcus pneumoniae* in 2673 (54.3%) visits. Acquisition rates (vaccine and non-vaccine serotypes) were similar for 3+1 and 3+0 groups at 7–30 months and for 0+2 group at 19–30 months.
Conclusions: PCV7 booster after 3 priming doses increased substantially IgG concentrations but did not further reduced vaccine-serotype nasopharyngeal acquisition, suggesting that protection from pneumococcal carriage does not depend primarily on serum IgG.

1. Introduction

The 7-valent CRM_{197} pneumococcal conjugate vaccine (PCV7) was licensed in the US in the early 2000s for use as 3 infant doses and a booster in second year of life (3+1 schedule) [1]. Subsequently, many countries introduced pneumococcal conjugate vaccines (PCVs) into their national immunization program (NIP) [2,3]. However, considerations regarding the high cost of PCVs and the growing number of injections in infant vaccination regimens led many countries to choose different (reduced) schedules with no toddler dose (3+0) and 2 infant doses with a toddler booster dose (2+1) [4].

Schedules with a lower number of doses often elicit lower immune response compared to the original 3+1 schedule [5–11]. Furthermore, a higher nasopharyngeal carriage rate with decreasing number of PCV doses in infants was observed in several studies [6,12,13]. However, the clinical consequences of the immunologic differences are not entirely clear and are subject to debate [10,11]. Systematic reviews support a 3+0 schedule, which in various studies was typically used in infants at 6, 10, and 14 weeks or 2, 4, and 6 months schedules (the latter was often studied compared with a booster toddler dose as a 3+1 schedule) [10,14].

Abbreviations: 7VT+6A, pneumococcal serotypes included in PCV7 and serotype 6A; MCHCs, Mother-and-Child Health Centers; MOPA, multiplexed opsonophagocytosis assay; NIP, national immunization program; OPA, opsonic activities; PCVs, pneumococcal conjugate vaccines; PCV7, 7-valent CRM_{197} pneumococcal conjugate vaccine; PCV13, 13-valent conjugate vaccine.

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Reduction in nasopharyngeal carriage of pneumococcal serotypes included in PCV7 and serotype 6A (7VT+6A) plays an important role in the success of immunization programs, by reducing transmission to susceptible subjects, resulting in indirect (herd) protection [15,16]. In the US, a near total elimination of 7VT+6A was observed in all ages in the PCV7 era [17]. Several studies have shown that a 3+0 regimen was also associated with carriage reduction [8,13,18–20]. Furthermore, after the introduction of the 3+0 PCV7 regimen to the NIP in Australia, indirect protection was demonstrated [21]. However, these reports do not enable comparison of the 3+0 and 3+1 regimens, and to determine whether the 3+0 regimen is equivalent to the 3+1 regimen in its ability to induce and maintain reduction in 7VT+6A pneumococcal serotypes in the community. Furthermore, a recent study from Australia suggested that after 13-valent conjugated vaccine (PCV13) introduction with the 3+0 regimen, a lower herd protection than expected was observed, prompting a change to a 3+1 regimen [22].

We conducted a prospective randomized controlled study prior to PCV7 implementation in Israel to examine the added value of the booster dose in protecting against carriage in toddlers who had received 3 infancy doses by comparing the effect of the 3+0 and 3+1 responses on acquisition and prevalence of pneumococcal carriage in infants and toddlers. We also included in this group of children those who were not vaccinated in the first year of life, but received a 2-dose regimen at 12 and 18 months (0+2), to assess the toddler-only schedule on carriage, as this schedule only protects directly against infections caused by vaccine-serotypes in toddlers and does not protect directly against infections in infants.

2. Methods

2.1. Setting

Two ethnic groups whose socioeconomic conditions and lifestyles differ inhabit Southern Israel (the Negev region): the Jewish and the Bedouin populations. The Bedouin population, formerly desert nomads, in transition to a western lifestyle, is characterized by overcrowding, lower levels of education, lower income and larger family size than the Jewish population [23]. Pneumococcal nasopharyngeal carriage is usually higher among Bedouin infants than among Jewish infants [24]. Approximately 95% of all routine immunizations in Israel are given in public sector Mother-and-Child Health Centers (MCHCs). In the present study, we selected 7 MCHCs, 4 serving the Jewish population and 3 serving the Bedouin population (yearly birth cohorts of ~1400 and ~1700, respectively).

PCV7 was licensed in Israel in 2006 and became publicly available in 2007. However, in southern Israel, only <10% and <25% of children received the vaccine before 2008 and between 2008 and mid-2009, respectively. In July 2009, PCV7 was implemented in the Israeli NIP.

2.2. Participants

Healthy infants were enrolled at the age of 2 months (±3 weeks). Exclusion criteria were: prematurity (<35 weeks); fever (>38 °C); congenital abnormalities; metabolic disorders; coagulation disorders; use of immune-modifying drugs; allergy to ≥1 vaccine constituents; hypotonic-hyporesponsiveness or persistent inconsolable crying after any prior vaccine; and HIV infection.

The study was approved by the Ethics Committees of the Soroka University Medical Center, Maccabi Health Services and the Ministry of Health and was registered with Current Controlled Trials, Ltd. ISRCTN28445844.

2.3. Study design

This open-label study was initiated in August 2005. Enrollment was conducted through March 2008, and the last follow-up visit was in March 2009, before the implementation of PCV7 in the Israeli NIP. We invited ~3100 eligible infants who belonged to the study MCHCs to take part in the study. The parents of 1141 infants were willing to consider participation in the study, and eventually 733 infants were enrolled [12]. After an informed consent was obtained, subjects were randomized 1:1:1:1 to receive 3 PCV7 doses at 2, 4, 6 months and a 4th toddler dose at 12 months, (3+1; n = 178); 3 PCV7 doses at 2, 4, 6 months with no additional toddler doses (3+0; n = 178); and no dose during infancy but 2 doses in the second year at 12, 18 months (control group, 0+2; n = 188) (Fig. 1) [12]. The third group, originally studied as a "catch-up" schedule for the purpose of PCV7 national immunization plan introduction [12] was chosen as a control group for both the 3+1 and 3+0 groups, since they did not receive any PCV7 dose during their first year of life. An additional 189 subjects were enrolled to a 2+1 arm (presented in a previous article) [12].

The study vaccine was Prevenar™ (Wyeth Vaccines; Collegeville, PA, USA) containing 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) individually conjugated to CRM_{197}; lots used were no. A94431D, B08636C, 808672K and C659732), All infants received concomitant vaccines.

Blood (2–4 mL) was drawn at ages 2, 7, 13 and 19 months, transferred refrigerated within 8 h to the laboratory, separated within 24 h and kept at −70 °C until processed. In group 0+2, subjects were randomized (1:1) to give blood samples at 2 months or at 7 months of age, but all gave blood at 13 and 19 months.

Nasopharyngeal and oropharyngeal swabs were obtained at each visit using transport swabs (nasopharyngeal – MW173 Amies transport medium, Transwab, Medical Wire and Equipment, Potley, UK; oropharyngeal – Culture-Swab Transport System, Venturi Transystem®, Copan Innovation, Italy). The swabs were kept at room temperature and processed within 16 h. Results of the oropharyngeal swabs for positive pneumococcal culture were used only if the nasopharyngeal swabs were culture-negative. Pneumococcal identification and serotyping were performed as previously described [25].

2.4. Serologic assays

Serum serotype-specific pneumococcal anti-capsular IgG concentrations for PCV7 serotypes (4, 6A, 6B, 9V, 14, 18C, 19F and 23F) were measured using ELISA at the Department of Applied Immunology & Endocrinology, Kinder und Jugendklinik Universitatsklinikum Erlangen, Germany, after double absorption with C-polysaccharide and pneumococcal serotype 22F polysaccharide [5,26–28].

The opsonic activities of anti-pneumococcal antibodies were measured against PCV7 serotypes by a fourfold multiplexed opsonophagocytosis assay (MOPA) as previously described [29], with minor modifications [30].

Serum samples from which enough serum volume was available (n = 281) were submitted also to MOPA assay (in addition to ELISA assay). For those samples, ELISA GMCs were compared to MOPA GMTs. Since serotype 6A antigen is not a part of PCV7, serotype 6A MOPA was compared to serotype 6B ELISA antibodies.

2.5. Data and statistical analysis

Data were analyzed with SPSS 18.0 software for Windows (Chicago, IL, USA). Contingency table analyses were performed using χ^2 test or Fisher's exact test. Continuous variables were analyzed using the *t*-test or ANOVA procedures. Correction for ethnicity

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