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Comparability of antibody response to a booster dose of 7-valent pneumococcal conjugate vaccine in infants primed with either 2 or 3 doses

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ABSTRACT

In this cohort study we compared IgG antibody levels between infants immunized with 7-valent CRM197-conjugated pneumococcal vaccine (PCV-7) at 2, 4 and 11 months and at 2, 3, 4 and 11 months of age, as measured by double adsorption ELISA. Pre- and post-booster levels following the 2 + 1- and 3 + 1-dose schedule were comparable for 5 out of 7 serotypes except for serotypes 6B and 19F. The proportion of children reaching post-booster antibody thresholds were comparable except for 6B (≥1.0 μg/ml and ≥5.0 μg/ml) and 19F (≥5.0 μg/ml). Surveillance studies are warranted for vaccine impact on 6B and 19F disease cases after reduced-dose PCV-7 schedules.

1. Introduction

Streptococcus pneumonia is a leading cause of bacterial infections in children in the first years of life with clinical syndromes varying from non-invasive respiratory disease (pneumonia, otitis media) to invasive pneumococcal disease (IPD; sepsis, bacteremia and meningitis) [1]. In 2000, the CRM197-conjugated 7-valent pneumococcal vaccine (PCV-7) was licensed in the USA for infants for prevention of IPD and recommended in a 3 + 1 vaccination schedule with 3 primary doses in the first 6 months of life, followed by a booster dose in the second year of life. Clinically, protection against IPD after less than 4 doses was already observed in the licensure study for CRM197-conjugated PCV-7, the Northern California Kaiser Permanente study [2]. In this study, clinical efficacy against vaccine serotype IPD in the intention to treat analysis was high (93.9%) despite the fact that only 58% of the children had received the full PCV-7 schedule. Furthermore, protection by reduced-dose schedules in preventing vaccine serotype IPD in vaccinees was observed in a large case–control study from the USA showing high effectiveness with a 2 + 1-dose (98%, 95% confidence interval: 75–100%) and even a 2-dose schedule (96%, 95% confidence interval: 88–99%) during a period of vaccine shortage [3]. Increasingly crowded immunization programs have prompted exploration of PCV-7 schedules with fewer doses and at present over half of the European countries have already implemented a 2 + 1-dose schedule, also to allow for programmatic differences and to reduce costs [4–6].

For non-inferiority comparison between pneumococcal conjugate vaccines, an individual anticapsular serum IgG antibody concentration of 0.35 μg/ml 1 month after the primary series in infants was estimated to be associated with clinical efficacy against IPD, at least in industrialized countries like the USA [7]. In non-western countries and high-risk populations this threshold may be higher and more around 1.0 μg/ml [8]. However, threshold protective antibody levels are not well understood and seem to differ per serotype. The levels needed to prevent carriage are higher and were suggested to be around 5.0 μg/ml which is considerably higher than what is thought to be required for prevention of invasive disease [2,8,9]. Higher levels may also be required for pneumonia and otitis media compared with IPD [10,11].

A non-randomized immunogenicity study in the UK comparing a 2 + 1- and 3 + 1-dose schedule showed no consistent distinct differences between both vaccine schedules as measured by geo-

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metric mean concentrations (GMC) per vaccine serotype [12]. In a recent immunogenicity study in Iceland, post-primary differences in IgG GMCs were found for several serotypes following 2 or 3 primary vaccinations, yet after the booster dose the only difference observed was for serotype 18C [13]. However, since both the UK and Iceland study were performed with experimental 9-valent CRM197-conjugated pneumococcal vaccines that may have different immunogenic capacity compared with the currently licensed PCV-7, potential differences between a 2 + 1- and 3 + 1-dose schedule may have been masked [12,13]. In 2005, in a single cohort of infants receiving a 2 + 1 PCV-7 schedule, Kaythy et al. demonstrated low pre-booster levels for serotypes 6B and 23F [14]. Following the booster vaccination however, no differences were seen.

Since immunogenicity studies comparing 2- and 3-dose primary schedules with the licensed 7-valent CRM197 pneumococcal conjugate vaccine in infants are scarce, we evaluated individual serotype responses with the currently used PCV-7 in a 2 + 1- and 3 + 1-dose schedule in infants with primary vaccination at 2 and 4 months or 2, 3 and 4 months of age and a booster dose at 11 months of age.

2. Subjects and methods

2.1. Study design

For this study we derived data from two separate cohorts in the Netherlands. The first study was a randomized controlled trial investigating the effects of reduced-dose PCV-7 schedules on pneumococcal carriage in the first 2 years of life (ISRCTN25571720) [15]. The participants were born between June and December 2005, 1 year before nationwide implementation of PCV-7 in June 2006. Infants younger than 12 weeks, not yet immunized and living in the study region were eligible for inclusion. Exclusion criteria were known immunodeficiency, craniofacial or chromosomal abnormalities, language barrier or expected relocation within the follow-up period [15]. Infants were randomized to receive 2 primary doses of PCV-7 at 2 and 4 months of age, followed by a booster dose at 11 months of age or no PCV-7 vaccinations (controls). Infants were included in the immunogenicity arm of the study on voluntary basis with blood sampling immediately before nasopharyngeal swabs were taken. Blood samples from infants receiving 2 primary doses without a booster dose of PCV-7 were collected at 12 months of age and included in the current analysis as pre-booster samples. Blood samples from infants receiving 2 + 1 doses were also collected at 12 months of age, 1 month after the booster dose at 11 months and included in the analysis as post-booster samples. No baseline differences were found in children who participated in the immunogenicity subset and infants participating in the main carriage trial.

The second group of infants participated in a serological immune-surveillance study on pertussis vaccination (ISRCTN97785537). The infants received a 3 + 1-dose PCV-7 schedule at the age of 2, 3, 4 and 11 months, according the Dutch national immunization program (NIP) which was implemented for all newborns from April 2006, without a catch-up program for older children [16]. Infants in good general health eligible for the fourth DTP-IPV-Hib vaccination were qualified for inclusion. Exclusion criteria were known immunodeficiency, a history of any neurologic disorder (including epilepsy) or previous vaccination with any other vaccine than those used in the NIP. We obtained blood samples at 11 months (included as pre-booster samples in the current analysis) and 1 month after the booster dose at age 12 months (included as post-booster samples in the current analysis) from infants born from April to July 2006. Inclusion was restricted to infants born within the first 3 months after PCV-7 introduction in the NIP.

From both studies blood samples from high-risk infants for hepatitis B that had concomitantly received Hepatitis B immunizations were excluded from analysis. Post-booster blood samples obtained outside the estimated range of 21–42 days after receiving the booster dose were excluded. For both schedules comparable percentages of blood samples were eligible for analyses.

2.2. Study vaccines

In both studies the licensed 7-valent CRM197-conjugated pneumococcal vaccine (Wyeth Pharmaceuticals) was administered, concomitantly with DTP-IPV-Hib immunizations. Since the vaccines of the 3 + 1-dose schedule were administered as part of the Dutch NIP, different lot numbers were use in the two studies. Of note is that in January 2006, the DTaP-IPV-Hib vaccine (Infanrix-IPV-Hib™, GlaxoSmithKline) in the Dutch NIP was replaced by a comparable DTaP-IPV-Hib vaccine containing additional *B. pertussis* proteins (Pediacel™, Sanofi Pasteur MSD) [17]. Therefore, priming DTaP-IPV-Hib vaccinations differed between both study cohorts. Both cohorts received Pediacel™ as a booster dose.

Informed consent was obtained from the parents or guardians of all study participants. Studies were approved by a national ethics committee.

2.3. Laboratory measurements

After collection blood was stored at 4 °C. Serum was separated within 24 h and stored at −20 °C until assayed. Serum IgG antibody levels were measured to the 7 vaccine pneumococcal polysaccharides 4, 6B, 9V, 14, 18C, 19F and 23F. All sera were assayed in the laboratory for infectious diseases of the National Institute for Public Health and the Environment in Bilthoven with ELISA using double adsorption with cell wall polysaccharide and 22F polysaccharide [18].

2.4. Statistical analysis

Results of IgG antibody levels are expressed in Geometric Mean Concentration (GMC) with 95% confidence interval (95% CI). Statistical differences in IgG GMC values were assessed by log transformed unpaired *t*-test. Differences in percentages of subjects with antibody levels ≥0.35 μg/ml, ≥1.0 μg/ml and ≥5.0 μg/ml were calculated using Fisher's exact test. All reported *p*-values are 2-sided, *p*-values < 0.05 were considered significant. The study sample sizes enabled an estimation of pneumococcal GMCs with 95% CI within 1.4-fold and detection of a 2-fold difference for comparing schedules with 80% power at a 5% significance level [12]. Analyses were performed with SPSS 15.0.

3. Results

3.1. Study participants

We collected 80 pre-booster and 72 post-booster serum samples from infants receiving the 2 + 1-dose schedule and 98 pre-booster and 90 post-booster serum samples from infants receiving the 3 + 1-dose schedule.

For the pre-booster serum samples baseline characteristics of the participants (gender, age at time of blood collection) were comparable between the two vaccination schedules. For the post-booster samples, infants receiving the 3 + 1-dose schedule were up to 1 month older at the time of the booster vaccination compared to the infants receiving the 2 + 1-dose schedule (mean age 12.1 months vs. 11.3 months; $p < 0.001$).