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Immune response to 13-valent pneumococcal conjugate vaccine with a reduced dosing schedule

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ABSTRACT

Background: The 7-valent pneumococcal conjugate vaccine (PCV7) has demonstrated effectiveness against pneumococcal illnesses when administered as 3 infant doses plus a toddler dose (3+1 schedule) or as an abbreviated schedule of 2 infant doses plus a toddler dose (2+1 schedule). The 13-valent pneumococcal conjugate vaccine (PCV13) is approved and World Health Organization-prequalified for administration in a 2+1 schedule when used as part of routine immunization programs.
Objective: To summarize immunologic responses elicited by PCV13 administered in a 2+1 schedule and following 2 doses in a 3+1 schedule.
Methods: Studies were double-blind, randomized, active-controlled, multicenter studies except the Mexico study (open-label, single-arm). In 2+1 studies, PCV13 was administered at 2, 4, and 12 (UK) or 3, 5, and 11 (Italy) months. In 3+1 studies (Spain and Mexico), assessment was made postdose 2 of the primary series (2, 4, and 6 months). The primary immunogenicity endpoint was the proportion of participants achieving serotype-specific antipolysaccharide immunoglobulin (Ig)G concentrations $\geq$0.35 μg/mL (i.e., responders) 1 month postdose 2. Pneumococcal IgG geometric mean concentrations (GMCs), opsonophagocytic activity (OPA), and concomitant vaccine responses were assessed.
Results: PCV13 and PCV7 elicited comparable immune responses for the 7 common serotypes after 2 infant doses. The proportion of PCV13 responders postdose 2 was >85% for most of the 7 common and 6 additional serotypes, except common serotypes 6B (27.9–81.4%) and 23F (55.8–77.5%) and additional serotypes 3 (73.8–96.9%) and 6A (79.2–94.4%). Serotypes 6B and 23F elicited lower IgG GMCs postdose 2 compared with other serotypes; all serotypes demonstrated boosting posttoddler dose. All serotypes demonstrated functional activity; >95% of participants achieved OPA levels $\geq$1:8 postdose 2. Concomitant vaccine responses were similar between PCV13 and PCV7 groups.
Conclusion: Immune responses elicited by PCV13 following 2 infant doses support transition from PCV7 to PCV13 in countries using a 2+1 schedule.
Clinical trial registration numbers: UK (Study 007) NCT00384059; Italy (Study 500) NCT00366899; Spain (Study 501) NCT00368966; Spain (Study 3007) NCT00474539; and Mexico (Study 3009) NCT00708682.

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1. Introduction

The 7-valent pneumococcal conjugate vaccine (PCV7; serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to cross-reactive material 197 [CRM_{197}], a nontoxic variant of diphtheria toxin), has proven efficacy and effectiveness against pneumococcal disease. PCV7 efficacy against invasive pneumococcal diseases (IPD), pneumonia, and acute otitis media (AOM) was demonstrated in clinical trials using 3 infant doses followed by a toddler dose (3+1 schedule) [1–5]. Some countries opted to administer 2 infant doses of PCV7 (e.g., at ages 2 and 4, or 3 and 5 months) followed by a toddler dose, usually between ages 11 and 15 months (2+1 schedule). The effectiveness of PCV7 administered in 2+1 schedules against IPD, pneumonia, and otitis media has been demonstrated in multiple countries, including Belgium [6], Canada [7–9], Denmark [10], Italy [11,12], Norway [13], Poland [14], the UK [15], and Uruguay [16]. Protection of nonimmunized persons by indirect (herd) effects has been documented in countries using the 2+1 schedule [15–18]. However, because immune responses to PCV7, particularly to serotypes 6B and 23F, may be lower following 2 infant doses compared with 3 infant doses [19–28], high levels of vaccine uptake and compliance with the pediatric immunization program and a catch-up program are important to maximize herd immunity in countries with a 2+1 schedule; this could contribute to protection in vaccinated children during the interval between the second infant dose and the toddler dose.

The 13-valent pneumococcal conjugate vaccine (PCV13), which includes the PCV7 serotypes plus 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A) individually conjugated to CRM_{197}, is licensed in more than 100 countries including the USA and has received prequalification from the World Health Organization (WHO). In Europe and many countries globally, and as part of the WHO prequalification, PCV13 is approved for administration in a 2+1 schedule when part of a routine immunization program [29,30].

We reviewed immunologic responses elicited by PCV13 administered in a 2+1 schedule, based on results of clinical studies conducted in the UK (Study 007) [31] and Italy (Study 500) [32]. In addition, we reviewed data following the second dose of PCV13 administered in a 3+1 schedule from three studies: two conducted in Spain (Study 501 and Study 3007) [33–35]; and one conducted in Mexico (Study 3009) [36]. Studies were designed to determine whether immune responses following 2 infant doses support transition from PCV7 to PCV13 in countries using a 2+1 schedule. Although safety was assessed in these studies, it has been presented in detail elsewhere and is not reviewed here [31–33,35–37].

2. Methods

Methods for each study are described in detail elsewhere [31–33,35,36]. The studies from the UK (Study 007), Italy (Study 500), and Spain (Studies 501 and 3007) were randomized, double-blind, active-controlled (control PCV7), multicenter studies conducted at 9 sites in the UK, 9 sites in Italy, and 35 sites (Study 501) and 23 sites (Study 3007) in Spain [31–33,35]. The Mexican study (Study 3009) was an open-label, single-arm multicenter study conducted at 7 sites in Mexico [36].

In all but the Mexico study, participants were randomly assigned in a 1:1 ratio to receive PCV13 or PCV7; in the Mexico study, all subjects received PCV13 (Table 1) [31–33,35,36]. In all studies, PCV7 or PCV13 was administered intramuscularly, typically in the anterolateral thigh muscle of the left leg. In the 2+1 studies, PCV13 and PCV7 were administered at ages 2, 4, and 12 months (UK Study 007) or 3, 5, and 11 months (Italy Study 500) [31,32]. In the 3+1 studies PCV13 and PCV7 were administered at 2, 4, 6, and 12 months (Mexico Study 3009) and 2, 4, 6, and 15 months (Spain Studies 501 and 3007) [33,35,36]. Routine pediatric vaccines specified per protocol for each study were administered concomitantly with PCV13 (all studies) or PCV7 (all but the Mexico study) (Table 1). Concomitant vaccines were administered in a different limb than PCV13 or PCV7 [31–33,35,36].

Each study was conducted in accordance with the ethical principles that have origins in the Declaration of Helsinki, and were designed and performed in compliance with Good Clinical Practice and applicable regulatory requirements. All studies were approved by their respective institutional review boards or independent ethics committees. Written informed consent was obtained from parent(s)/legal guardian(s) of each participant before enrollment and before performance of any study-related procedure [31–33,35,36].

2.1. Assessment of immune response

2.1.1. Pneumococcal immune response

Blood was drawn 1 month after dose 2 of the infant series and 1 month after the toddler dose (for the toddler dose, only data from the 2+1 studies will be presented) [31–33,35,36]. Pneumococcal serotype-specific immunoglobulin G (IgG) concentrations were measured with a standardized double-absorption enzyme-linked immunosorbent assay (ELISA) that used a cell wall extract containing cell wall polysaccharide (CWPS) plus serotype 22F capsular polysaccharide containing CWPS2 [38,39]. Serum opsonophagocytic activity (OPA) was measured using previously described methods [40,41].

The primary pneumococcal immunogenicity endpoint in all studies was the proportion of participants vaccinated with PCV13 achieving serotype-specific antipolysaccharide IgG concentrations $\geq$0.35 μg/mL (defined by the WHO as a reference antibody concentration for assessment of vaccine against IPD when used after 3 infant doses because no standard exists following 2 infant doses) [42], at 1 month after dose 2 of the infant series [31–33,35,36]. To assess differences, 95% confidence intervals (CIs) on the difference in proportions (PCV13 minus PCV7) were calculated for each serotype. Noninferiority was determined if the lower bound of the 2-sided 95% CI for the difference was >−0.10 [31,32]. For the UK (007) [31] and Spain (501) studies [32], comparisons of IgG immune responses (i.e., IgG geometric mean concentrations [GMCs] and proportions of subjects with IgG concentrations $\geq$0.35 μg/mL) between PCV13 and PCV7 recipients were performed as post hoc analyses.

GMCs were assessed 1 month after dose 2 of the infant series, and 1 month posttoddler dose in the Italian (500) and UK (007) studies [31–33,35,36].

OPA data (proportion of participants achieving serotype-specific OPA assay levels $\geq$1:8 and serotype-specific OPA geometric mean titers [GMTs]) obtained 1 month after dose 2 of the infant series and 1 month posttoddler dose, were compared between the Italian (500) (secondary endpoint) and UK (007) studies (post hoc analysis) [31,32].

2.1.2. Concomitant vaccine immune response

Immune responses to concomitant vaccine antigens were assessed in the Italian (500), UK (007), and Spain (501 and 3007) studies; endpoints included proportions of participants who achieved prespecified antibody levels for each vaccine antigen [31,32,34,35]. Methodology to assess concomitant vaccine antigen response is presented in the Online Supplemental Content (Concomitant vaccine assessment).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.08.009.