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Long-term antibody persistence study (3 years after last dose) of the 7-valent pneumococcal conjugate vaccine in young children in China

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ABSTRACT

Background: In a previous study, Chinese infants were vaccinated with 7-valent pneumococcal conjugate vaccine (PCV7) ⩾7 days before routine diphtheria, tetanus, and acellular pertussis vaccine (DTaP); PCV7 administered concomitantly with DTaP (PCV7 + DTaP); or DTaP alone. This study examined antibody persistence at a single time point 3 years after the last vaccination.
Methods: Children who participated in the prior PCV7 study were eligible to participate. A single blood sample was drawn at enrollment. Immunoglobulin G (IgG) geometric mean concentrations (GMCs) specific to the PCV7 serotypes and percentages of subjects with IgG ⩾0.35 μg/mL were compared for subjects receiving PCV7 versus PCV7 + DTaP (concomitant) and for PCV7 or PCV7 + DTaP (concomitant) versus DTaP alone. IgG concentrations at 3 years after the last vaccination were also compared with those after the infant series and toddler dose.
Results: Three years after the last vaccination with PCV7 or PCV7 + DTaP (concomitant), IgG GMCs for most PCV7 serotypes were lower than after the infant series or toddler dose but remained above prevaccination concentrations. IgG GMC were similar between the PCV7 and PCV7 + DTaP (concomitant) groups for 5 out of 7 serotypes but serotypes 4 and 19F were significantly lower in the PCV7 + DTaP (concomitant) recipients. Three years after the last vaccination, IgG GMCs were significantly higher for 6 of 7 PCV7 serotypes among those receiving PCV7 or PCV7 + DTaP (concomitant) compared with recipients of DTaP alone. Among subjects receiving DTaP alone, serotype-specific antibody concentrations were significantly higher for all serotypes 3 years after the last vaccination compared with after the infant series.
Conclusion: Three years after PCV7 vaccination, serotype-specific antibodies were lower than after the primary infant series but higher than prevaccination levels and higher among subjects who received PCV7 compared with those who did not. The immune response was comparable in children who received PCV7 with and without concomitant DTaP.
Clinical Trial Registration: NCT01298544

1. Introduction

Streptococcus pneumoniae is a leading cause of acute otitis media, pneumonia, and invasive disease in children globally [1,2]. In China, pneumococcal disease remains a significant cause of morbidity and mortality in children <5 years of age [3]. A 7-valent pneumococcal conjugate vaccine (PCV7) containing the capsular polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F

Abbreviations: DTaP, routine diphtheria, tetanus, and acellular pertussis; GMC, geometric mean concentration; GMFC, geometric mean fold change; IgG, immunoglobulin G; PCV7, 7-valent pneumococcal conjugate vaccine.

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was approved for use in China in 2008 [4]. During the period of the study, PCV7 was available in the private market in China but had not been incorporated into the routine infant immunization schedule.

Licensure of PCV7 for use in China was based on a clinical study conducted by Li and colleagues in Chinese infants that assessed the immunogenicity and safety of PCV7 in conjunction with the routine diphtheria, tetanus, and acellular pertussis vaccine (DTaP) [5]. Infants were randomized to receive 1 of 3 dosing schedules at 3, 4, and 5 months of age (infant series): PCV7 ⩾7 days before DTaP, PCV7 concomitant with DTaP, or DTaP alone. All infants vaccinated with PCV7 received a toddler dose between 12 and 15 months of age [5].

This postlicensure study assessed antibody persistence in children who participated in the original clinical study of PCV7 conducted by Li and colleagues. The objectives were to assess persistence of serotype-specific antibodies at a single time point 3 years after the last vaccination among children who received PCV7 with or without concomitant DTaP vaccination, and to assess serotype-specific antibody levels after 3 years in children receiving PCV7 versus DTaP alone.

2. Methods

2.1. Study design and subjects

This study enrolled children who had participated in the PCV7 study described above [5], were in general good health, and had parental consent for participation. The study investigator was responsible for contacting all former participants by telephone. Data were collected at least 3 years after the last vaccination and were derived from analysis of a single blood sample drawn at enrollment. No vaccines were administered during this study. Subjects were evaluated according to the vaccine group to which they were assigned in the original trial: PCV7 administered ⩾7 days before DTaP (PCV7), PCV7 + DTaP administered concomitantly (PCV7 + DTaP), or DTaP alone.

Subjects were excluded for vaccination with any pneumococcal vaccine in the period between completion of the initial study and enrollment in the post-licensure study, or if they had a history of pneumococcal disease; immunodeficiency; receipt of blood products, including immunoglobulin, within 12 weeks of the study start; or any acute or chronic medical condition deemed by the study investigator to be injurious to the subject or a source of potential bias for the study. Subjects who did not receive PCV7 during the initial trial were offered PCV7 after their participation in this study. This study was conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

2.2. Immunogenicity evaluations

The primary immunogenicity objective was to evaluate immunoglobulin G (IgG) concentrations specific to the 7 pneumococcal vaccine serotypes 3 years after administration of the toddler dose of PCV7 with or without concomitant DTaP. The secondary immunogenicity objective was to compare IgG concentrations specific to the PCV7 serotypes in children who received PCV7 or PCV7 + DTaP versus DTaP only. For antibody assessment, a 5-mL blood sample was collected at enrollment. The standardized WHO ELISA was performed as describe using the international reference standard serum, 89SF, to calculate all ELISA results, [6,7]. The assays were carried out in double-absorbent assay conditions with pneumococcal cell wall polysaccharide (CWPS) and serotype 22F pneumococcal polysaccharide (CWPS2),

Table 1
Disposition of study subjects.

Subjects	Vaccination schedule		
	PCV7	PCV7 + DTaP	DTaP
Enrolled in prior registration study, n	300	296	204
Completed the prior registration study, n (%)	236 (78.7)	238 (80.4)	178 (87.3)
Screened for antibody persistence study	123	121	91
Assessed ⩾3 y after the last vaccination, n (%)	123 (52.1)	121 (50.8)	91 (51.1)
Age at blood draw, years			
Mean (SD)	5.04 (0.144)	5.04 (0.157)	5.04 (0.151)
Minimum, maximum	4.7, 5.4	4.7, 5.4	4.7, 5.4

DTaP = routine diphtheria, tetanus, and acellular pertussis; PCV7 = 7-valent pneumococcal conjugate vaccine; SD = standard deviation.

Table 2
Pneumococcal IgG GMCs (μg/mL) 3 years after the last vaccination with PCV7 or PCV7 + DTaP (concomitant).

Serotype	PCV7 n = 120–123[a] GMC[b] (95% CI[c])	PCV7 + DTaP n = 120–121[a] GMC[b] (95% CI[c])	PCV7 + DTaP/PCV7 Ratio[d] (95% CI[e])	PCV7 or PCV7 + DTaP n = 241–244[a] GMC[b] (95% CI[c])	DTaP n = 84–91[a] GMC[b] (95% CI[c])	PCV7 or PCV7 + DTaP/DTaP Ratio[d] (95% CI[e])
4	0.98 (0.77, 1.23)	0.66 (0.52, 0.84)	0.68 (0.48, 0.94)	0.8 (0.68, 0.95)	0.41 (0.29, 0.58)	1.97 (1.39, 2.8)
6B	11.35 (9.71, 13.27)	9.24 (7.66, 11.16)	0.81 (0.64, 1.04)	10.26 (9.08, 11.59)	3.37 (2.76, 4.13)	3.04 (2.41, 3.84)
9V	1.35 (1.13, 1.62)	1.29 (1.08, 1.54)	0.95 (0.74, 1.23)	1.32 (1.16, 1.5)	1.05 (0.83, 1.32)	1.26 (0.98, 1.62)
14	4.5 (3.38, 5.98)	3.02 (2.25, 4.05)	0.67 (0.45, 1.01)	3.69 (3.01, 4.53)	0.55 (0.4, 0.76)	6.66 (4.53, 9.79)
18C	0.8 (0.66, 0.97)	0.77 (0.6, 0.98)	0.96 (0.7, 1.31)	0.78 (0.67, 0.92)	0.34 (0.24, 0.47)	2.34 (1.68, 3.24)
19F	10.14 (8.06, 12.75)	5.67 (4.5, 7.14)	0.56 (0.4, 0.77)	7.6 (6.44, 8.97)	1.7 (1.35, 2.15)	4.47 (3.29, 6.07)
23F	3.31 (2.8, 3.91)	2.71 (2.26, 3.25)	0.82 (0.64, 1.05)	2.99 (2.65, 3.39)	1.44 (1.17, 1.76)	2.08 (1.65, 2.63)

CI = confidence interval; DTaP = routine diphtheria, tetanus, and acellular pertussis; GMC = geometric mean concentration; IgG = immunoglobulin G; PCV7 = 7-valent pneumococcal conjugate vaccine.

[a] Number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] GMCs were calculated using all subjects with available data for the specified blood draw.
[c] CIs are back transformations of confidence levels based on the Student *t* distribution for the mean logarithm of the concentrations.
[d] Ratios of GMCs are calculated by back transforming the ratio difference between vaccine groups on the logarithmic scale.
[e] CIs for the ratio are back transformations of a CI based on the Student *t* distribution for the difference of the logarithms of the measures.