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RESEARCH PAPER

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Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine administered in a prime-boost regimen among Chinese infants: a randomized, double blind phase III clinical trial

Wenjuan Wang[a*], Qi Liang[a*], Jiahong Zhu[b], Junxia Zhang[c], Junsheng Chen[d], Sulan Xie[e], Yuemei Hu[a], and Guifan Li[f]

[a]Vaccine Clinical Evaluation Department, Jiangsu Provincial Center for Disease Control and Prevention, Jiangsu, China; [b]Department of Acute Infectious Disease Control and Prevention, Lianshui County Center for Disease Control and Prevention, Jiangsu, China; [c]Department of Acute Infectious Disease Control and Prevention, Huaiyin District Center for Disease Control and Prevention, Jiangsu, China; [d]Vice Director, Hongze District Center for Disease Control and Prevention, Jiangsu, China; [e]Administration Office, Hongze District Center for Disease Control and Prevention, Jiangsu, China; [f]Registration Department, Beijing Minhai Biotechnology Co., LTD., Beijing, China

ABSTRACT

This study aimed to evaluate the immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13). In total, 1200 infants were randomized into two groups with a 1:1 allocation and received a three-dose series of tested PCV13 or control PCV13 at ages 2, 4 and 6 months, respectively, and a booster dose at 12–15 months. Blood samples were collected before and 30 days after primary and booster vaccination. Serotype-specific antibodies were measured using ELISA for immunoglobulin G (IgG) and OPA for functional antibodies. Safety data were collected for 30 days after each inoculation. Results showed that post primary vaccination seropositive rates of all 13 serotypes except type 3 were not significantly different between two groups. The seropositive rate for type 3 in Group T was significantly higher than Group C ($P < .0001$). For all 13 serotypes except type 7 F, the GMCs in Group T were significantly higher than Group C. The GMC for type 7 F in Group T ($P < .0009$) was significantly lower than Group C. The frequencies of overall adverse events ($P = .0064$) and solicited adverse reactions ($P = .0019$) in Group T were significantly lower than Group C. Post booster vaccination, seropositive rates for all serotypes in Group T were 100.00%. For all serotypes except type 23 F, IgG GMCs in Group T were significantly higher than Group C. Totally, 21 subjects reported SAEs and all but one were considered irrelevant or probably irrelevant to vaccination. In conclusion, the tested PCV13 showed non-inferior immunogenicity and had a good safety profile compared with control vaccine.

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Introduction

Streptococcus pneumococcal is the major pathogenic bacteria of human pneumoniae, meningitis, bacteremia and otitis media. Invasive pneumococcal disease (IPD) is related with significant morbidity and mortality.[1–3] Streptococcus pneumoniae is genetically diverse, with more than 90 distinct capsular polysaccharides which have already been identified.[4,5] Before pneumococcal conjugate vaccines (PCVs) were prevalently introduced in 2000, 700,000 deaths and 14 million cases of diseases in children under 5 years old were caused by Streptococcus pneumoniae every year.[6] A variety of related pneumococcal vaccines have been developed to prevent pneumococcal infection and proved to be probably cost effective in some regions.[7] It is of great importance to improve vaccine coverage to eliminate the burden of pneumococcal infection. Currently, several pneumococcal conjugate vaccines (such as PCV7,10,13,15) are used to prevent infants against pneumococcal infection. After introduction of PCV-13, there was significant decrease of IPD due to vaccine-related serotype.[8,9]

In China, Beijing Minhai Biotechnology Co., LTD. had developed a new PCV13 and obtained official approval for clinical trials in June, 2014. An open-label phase 1 trial had been performed among 80 adults and children aged from 2 months to 55 years, in which the safety and tolerability of the new PCV13 had been preliminarily proved. In this study, we evaluated its immunogenicity and safety administered among healthy infants aged 2 months compared with a control PCV13. The results were described hereinafter.

Materials and methods

Ethics statement

Ethic approval (Approval No.: JSJK2015-A002-02) had been granted by the Institutional Review Board of Jiangsu Provincial Center for Disease Control and Prevention. Written informed consent had been obtained before each participant's entry into the study. The research was performed in compliance with the principles of the Declaration of Helsinki, and followed the

CONTACT Yuemei Hu 993832717@qq.com Jiangsu Provincial Center for Disease Control and Prevention, NO. 172 Jiangsu Rd., Gulou District, Nanjing, Jiangsu 210009, China; Guifan Li guifan@sohu.com Beijing Minhai Biotechnology Co., LTD., NO. 35 Simiao Rd., Daxing Biomedical Industrial Base, Daxing District, Beijing 102600, China

*These authors contributed equally to this work.

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standards of Good Clinical Practice and Chinese regulatory requirements stipulated by the National Medical Products Administration (NMPA).

Study design and participants

This was a randomized, double blind, positive-controlled phase III clinical trial of a new PCV13 administered in a prime-boost regimen (Clinical Trials.gov identifier: NCT02494999). It was conducted in three study sites-Lianshui County, Huaiyin District and Hongze District, Jiangsu Province, China, between June 2016 and December 2018. Eligible participants were healthy infants, aged 42–77 days. Those who (1) were preterm infants or low birth weight infants, (2) had any administration history of pneumococcal polysaccharide or conjugate vaccine, (3) had a medical history of culture-confirmed invasive disease caused by Streptococcus pneumonia, (4) had allergic history or serious adverse reaction history after vaccination, (5) with congenital malformation, developmental disorder, genetic defects or severe malnutrition, (6) with epilepsy, seizure or mental disease, (7) were known or suspected immune deficiency or immune suppression, (8) were diagnosed coagulation abnormalities or significant bruising or blood clotting disorder, (9) had immunosuppressive therapy, cytotoxic therapy, inhaled corticosteroids within 6 months prior to the study entry were excluded from the study.

A total of 1200 infants were randomly assigned at 1:1 ratio into two study groups- Group T received tested PCV13 and Group C received positive control PCV13 separately. Eligible participants were vaccinated three doses intramuscularly at Months 0, 2, and 4 and a booster dose at Month 10. Baseline demographics was collected during enrollment interview.

Vaccines

The tested PCV13 (batch number 20170301) was produced by Beijing Minhai Biotechnology Co., LTD and the positive control PCV13 (Prevnar 13, batch number TS15224N73146) was manufactured by Pfizer Pharmaceuticals. Both of them contained 0.125 mg of aluminum as aluminum phosphate adjuvant and were supplied in prefilled 0.5 mL syringes. In tested PCV13, each 0.5 mL dose contained 1.8 μg pneumococcal polysaccharide serotype 1, 2.1 μg pneumococcal polysaccharide serotypes 3 and 4, 1.75 μg pneumococcal polysaccharide serotypes 5 and 7 F, 1.85 μg pneumococcal polysaccharide serotype 6A, 4.4 μg pneumococcal polysaccharide serotype 6B, 2.3 μg pneumococcal polysaccharide serotype 9 V, 1.35 μg pneumococcal polysaccharide serotype 14, 3.65 μg pneumococcal polysaccharide serotype 18 C, 1.6 μg pneumococcal polysaccharide serotype 19A, 1.25 μg pneumococcal polysaccharide serotype 19 F and 2.35 μg pneumococcal polysaccharide serotype 23 F; and serotypes 1, 5, 6A, 9 V, 19A, 19 F, and 23 F capsular polysaccharide were conjugated to a tetanus toxoid carrier protein while serotypes 3, 4, 6B, 7 F, 14 and 18 C were conjugated to a diphtheria toxoid carrier protein. Unlike tested PCV13, control PCV13 contained 2.2 μg pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A,7 F, 9 V, 14, 18 C, 19A, 19 F, and 23 F and 4.4 μg pneumococcal polysaccharide serotype 6B per 0.5 mL dose; and each of the polysaccharides was covalently conjugated to CRM 197, a nontoxic variant of diphtheria toxin.

Immunogenicity assessment

Serum samples were collected at four different time points: immediately before the first dose, 30 days after the third dose, immediately before the booster dose, and 30 days after the booster vaccination. For all participants serum concentrations of anticapsular polysaccharide immunoglobulin G (IgG) for each of the 13 pneumococcal serotypes were measured at the previously mentioned time points, using the standardized enzyme-linked immunosorbent assay (ELISA) method.[10] In addition, the opsonophagocytic assay (OPA)[11] for each serotype were performed to test functional antibodies within a subset comprising of approximate 100 participants in each group (around 200 infants in total).

Safety assessment

Each participant had been observed for 30 minutes after each dose of inoculation. Any immediate and noted adverse events (AEs) were recorded by investigators on safety diary cards at site. Parents or legal guardians of each participant were trained how to observe and document local reactions (redness, pain, induration, rash, swelling, and pruritus), systemic reactions (decreased appetite, fever, diarrhea, cough, crying, vomiting and fatigue) and axillary temperatures for 7 days after leaving the site. Additionally, other AEs within 30 days after each dose together with concomitant medications to treat or to prevent symptoms were also collected. All AEs were assessed by trained investigators and classified according to the guidelines predefined in the study protocol. Serious adverse events (SAEs) had been collected throughout the research period until one month after booster immunization.

Statistical analysis

Full analysis set (FAS) complied with the principles of intent-to-treat (ITT) and comprised all participants who received at least one dose of vaccine and one follow-up visit. Per-protocol analysis set (PPS) comprised ITT participants who completed all study visits and had available serological data. Immunogenicity analysis consisted of all participants who belonged to PPS. Safety analysis set (SS) included participants who received at least one dose of study vaccines and whose safety data were recorded.

The primary immunogenicity endpoints were the proportion of participants reaching the serotype-specific IgG concentration threshold of 0.35 μg/mL (seropositive rate) and the geometric mean IgG concentration (GMC) measured 30 days after the primary series. To evaluate differences between two groups, the sequential testing of the non-inferiority of tested PCV13 for each pneumococcal serotype had been performed. If the lower limit of the two-sided 97.5% confidence interval (CI) calculated using the exact binomial method for the difference in proportion (Group T-Group C), was >-10%, or the lower bound of the two-sided 97.5% CI of the IgG GMC ratio

(Group T/Group C), was >0.5, the non-inferiority would be declared. Only after all of 13 serotypes had been confirmed to be non-inferior would the tested PCV13 be assumed noninferior to the control PCV13. On the premise of noninferiority, if the lower limit of the two-sided 97.5% CI was >0%, or the lower bound of the two-sided 97.5% CI of the IgG GMC ratio >1, the superiority for each serotype would be declared.

The secondary immunogenicity endpoints were the proportion of participants reaching the serotype-specific IgG concentration threshold of 1.0 μg/mL 30 days after the primary and booster immunization, the IgG GMC measured 30 days after the booster dose and the geometric mean IgG antibody increase (GMI) 30 days after the primary and booster immunization. In addition, the proportions of participants reaching the OPA titer threshold of 1:8 and the geometric mean OPA titer (GMT) after primary and booster immunization in predefined subgroups were also served as secondary immunogenicity end points.

All statistical analyses were performed by an independent statistician using SAS 9.3 software. Chi-square test and two-sided Fisher's exact test were used to compare the seropositive rates, the incidences of local and systemic ARs for each dose, respectively, and for all in total as well. The GMC and GMT of each serotype between two groups were compared using paired Student's *t*-test. A *p* value equal to or < 0.05 indicated a statistically significant difference.

Results

Participant characteristics

Of 1277 infants assessed for eligibility in the trial, 1200 healthy infants were enrolled and randomly assigned into one of two study groups- Group T and Group C. In each 600 participants received the first dose of tested PCV13 or control PCV13 respectively. In sum, 1122 (93.5%) children completed primary vaccination: 558 (93.0%) children in Group T and 564 (94.0%) children in Group C; 1040 (86.7%) children completed booster vaccination: 517 (86.2%) children in Group T and 523 (87.2%) children in Group C (Figure 1). Rates of drop out in the following visits were similar between the two groups. The baseline demographics including age, sex, body length, weight, and axillary temperature were equally comparable (Table 1).

At baseline, seropositive rates of Group T and Group C, ranging from 6.59% to 96.42%, were similar for twelve serotypes (all except serotype 19 F-Group T was significantly lower than Group C). IgG GMCs between two groups had no significant difference for eleven serotypes (all except serotype 1 and serotype 5-Group T was significantly lower than Group C, 0.14 VS. 0.17 and 0.09 VS. 0.12) (Table 2). The percentages of participants with IgG GMC≥1.0 μg/mL were similar for all 13 serotypes (Supplementary Table 1). The percentages of participants with OPA≥1:8 (range 3.88%~69.90%) between two groups were similar for twelve serotypes (all except

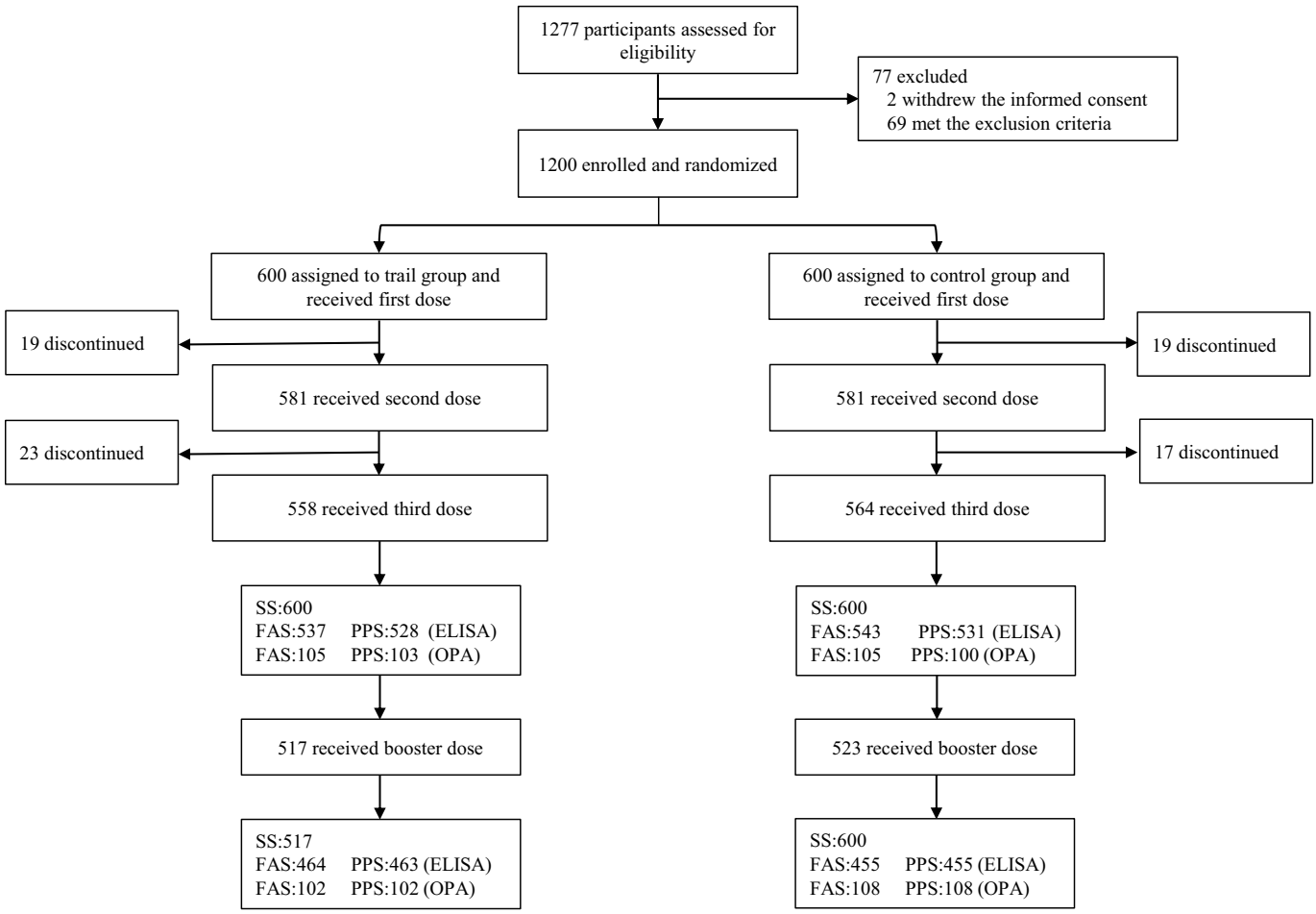

Figure 1. Screening, randomization, and inclusion in safety and immunogenicity analyses.

Table 1. Baseline demographics of study population.

Characteristics	Group T	Group C	Total	*P*
Age at first dose (days)	59.75 ± 10.42	59.45 ± 10.27	59.60 ± 10.34	.6136
Age at booster dose (months)	13.11 ± 0.61	13.11 ± 0.61	13.11 ± 0.61	.8571
Sex at first dose				
Male	321 (53.50)	327 (54.50)	648 (54.00)	.7282
Female	279 (46.50)	273 (45.50)	552 (46.00)	
Sex at booster dose				
Male	277 (53.58)	281 (53.73)	558 (53.65)	.9613
Female	240 (46.42)	242 (46.27)	482 (46.35)	
Body length at first dose (cm)	58.83 ± 2.69	58.80 ± 2.59	58.81 ± 2.64	.8698
Body length at booster dose (cm)	77.18 ± 2.87	77.00 ± 2.95	77.09 ± 2.91	.2985
Weight at first dose (kg)	5.88 ± 0.81	5.85 ± 0.76	5.87 ± 0.79	.4815
Weight at booster dose (kg)	10.12 ± 1.18	10.01 ± 1.17	10.06 ± 1.17	.1230
Axillary temperature before first dose (°C)	36.71 ± 0.23	36.71 ± 0.23	36.71 ± 0.23	.9799
Axillary temperature before booster dose (°C)	36.64 ± 0.32	36.65 ± 0.31	36.64 ± 0.31	.8319

Data are mean ± SD or n(%).

serotype 19A-Group T was significantly higher than Group C, 40.78% VS. 26.00%) (Table 3). OPA GMTs between two groups had no significant difference for eleven serotypes (all except serotype 14 and serotype 19A-Group T was significantly higher than Group C, 27.71 VS. 15.23, 6.01 VS. 4.06) (Supplementary Table 2). In general levels of serotype-specific antibodies were comparable between two study groups.

Anti-pneumococcal IgG response

One month post primary vaccination (Month 5), seropositive rates of Group T and Group C were at least 93.41% for all serotypes in two groups, which had no significant difference for twelve serotypes (all except serotype 3-Group T was higher than Group C, 100.00% vs. 93.41%). For twelve serotypes IgG GMCs of Group T were higher than those of Group C and the differences were statistically significant (all *P* values <.05); while for serotype 7 F IgG GMC of Group T was significantly lower than Group C (5.60 vs. 6.54). For eleven serotypes IgG GMIs of Group T were higher than those of Group C (all *P* values <.05) while there were no significant difference for serotype 7 F and serotype 14 (Table 2). Percentages of participants in Group T with IgG GMC ≥1.0 μg/mL for five serotypes-serotype 3, 4, 5, 9 V, and 23 F were significantly higher than those in Group C (all *P* values <.05) (Supplementary Table 1).

Prebooster vaccination (Month 10), for two serotypes-3 and 4 both seropositive rates in Group T were significantly higher than Group C, for serotype 7 F seropositive rate in Group T was significantly lower than Group C (98.06% vs. 100.00%). For eight serotypes-3, 4, 5, 6B, 9 V,19A, 19 F, and 23 F, IgG GMCs of Group T were higher than Group C and for two serotypes-7 F and 14 IgG GMCs in Group T were significantly lower than Group C (Table 4). For eight serotypes-4, 5, 6A, 6B, 9 V, 19A, 19 F, and 23 F percentages of participants with IgG GMC ≥1.0 μg/mL in Group T were significantly higher than Group C, for two serotypes-7 F and 18 C percentages of participants with IgG GMC ≥1.0 μg/mL in Group T were significantly lower than Group C (all *P* values <.05) (Supplementary Table 1).

Post booster vaccination (Month 11), seropositive rates for all serotypes of Group T were 100.00% while seropositive rates for three serotypes-3, 6A, 18 C of Group C were 99.56%, 99.78%, and 99.78% separately. All differences of seropositive rates between two groups were not statistically significant. For 12 serotypes IgG GMCs of Group T were significantly higher than those of Group C (all *P* values <.05); only for serotype 23 F there was no significant difference when IgG GMCs of two groups were compared. For twelve serotypes IgG GMIs of Group T were higher than those of Group C (all *P* values <.05); only for serotype 23 F IgG GMI of Group T was lower than that of Group C (Table 4). Percentages of participants in Group T with IgG GMC ≥1.0 μg/mL for four serotypes- serotype 3, 4, 5, and 18 C were significantly higher than those in Group C (all *P* values <.05) (Supplementary Table 1).

OPA responses

Post primary vaccination (Month 5), there were no significant differences when comparing percentages of participants with OPA≥1:8 (range 96.00%~100.00%) between two groups (Table 3). For four serotypes-1, 3, 4, and 5, OPA GMTs of Group T were higher than those of Group C and for five serotypes-6A, 6B, 7 F, 19A, and 23 F OPA GMTs of Group T were lower than those of Group C (all *P* values <.05). For four serotypes-1, 3, 4, and 5, OPA GMIs of Group T were higher than those of Group C and for five serotypes-6A, 7 F, 14, 18 C, and 19A OPA GMIs of Group T were lower than those of Group C (all *P* values <.05) (Supplementary Table 2).

There was no significant difference between two groups when percentages of participants with OPA≥1:8 before (range 90.20%~100.00%) and 30 days after (range 96.30%~100.00%) booster vaccination for all serotypes were compared (Table 3). Before booster vaccination (Month 10), for four serotypes-3, 4, 5, and 19 F OPA GMTs of Group T were higher than Group C and three serotypes-6A, 7 F and 23 F OPA GMTs of Group T were lower than Group C (all *P* values equal to or <0.0193). Post booster vaccination (Month 11), for four serotypes-3, 5, 9 V, and 14 OPA GMTs of Group T were higher than Group C and for another four serotypes-6A, 6B, 18 C, 23 F OPA GMTs of Group T were lower than those of Group C(all *P* values equal to or <0.0181). For two serotypes-7 and 14 OPA GMIs of Group T were higher than Group C and for three serotypes-5, 6A, and 19 F OPA GMIs of Group T were lower than those of Group C (all *P* values <.05) (Supplementary Table 3).

Table 2. Type-specific seropositive rates, GMC and GMI pre- and postprimary vaccination.

		Preprimary vaccination				Postprimary vaccination					
Serotype	Group	Seropositive rate n, % (95% CI)	*P*	GMC (95% CI)	*P*	Seropositive rate n, % (95% CI)	*P*	GMC (95% CI)	*P*	GMI (95% CI)	*P*
1	T	135,25.57 (21.90–29.51)	.1649	0.14 (0.12–0.16)	**.0368**	528, 100.0 (99.30–100.0)	.3185	5.90 (5.53–6.31)	**<.0001**	42.12 (35.42–50.08)	**<.0001**
	C	156,29.38 (25.53–33.45)		0.17 (0.15–0.20)		530,99.81 (98.96–100.0)		4.28 (4.02–4.56)		24.60 (21.21–28.53)	
3	T	39,7.39 (5.30–9.96)	.6119	0.10 (0.08–0.11)	.2561	528, 100.0 (99.30–100.0)	**<.0001**	2.06 (1.96–2.16)	**<.0001**	21.62 (18.98–24.62)	**<.0001**
	C	35, 6.59 (4.63–9.05)		0.10 (0.09–0.12)		496,93.41 (90.95–95.37)		0.85 (0.80–0.89)		8.11 (7.18–9.16)	
4	T	66,12.50 (9.80–15.63)	.5477	0.07 (0.06–0.08)	.0515	528, 100.0 (99.30–100.0)	.2496	4.88 (4.54–5.24)	**<.0001**	70.62 (58.18–85.73)	**<.0001**
	C	73,13.75 (10.93–16.97)		0.09 (0.07–0.10)		528,99.44 (98.36–99.88)		2.25 (2.12–2.39)		25.95 (21.93–30.69)	
5	T	81,15.34 (12.37–18.70)	.5178	0.09 (0.08–0.11)	**.0092**	528, 100.0 (99.30–100.0)	.1343	2.79 (2.63–2.96)	**<.0001**	30.51 (25.60–36.36)	**<.0001**
	C	74,13.94 (11.10–17.18)		0.12 (0.11–0.14)		527,99.25 (98.08–99.79)		2.00 (1.89–2.12)		16.56 (14.23–19.26)	
6A	T	223,42.23 (37.98–46.58)	.8171	0.22 (0.19–0.25)	.2446	523,99.05 (97.80–99.69)	.2521	4.35 (4.02–4.70)	**.0038**	19.81 (16.64–23.58)	**.0218**
	C	228,42.94 (38.68–47.27)		0.25 (0.22–0.28)		529,99.62 (98.65–99.95)		3.74 (3.49–4.00)		15.13 (13.02–17.59)	
6B	T	377,71.40(67.34–75.22)	.9536	0.48(0.44–0.53)	.8761	525,99.43(98.35–99.88)	.7101	5.09(4.68–5.54)	**.0001**	10.49(9.22–11.95)	**.0066**
	C	380,71.56(67.52–75.37)		0.49(0.45–0.53)		527,99.25(98.08–99.79)		4.04(3.75–4.35)		8.24(7.34–9.26)	
7 F	T	255,48.30(43.96–52.65)	.8757	0.29(0.26–0.32)	.4635	527,99.81(98.95–100.0)	.9968	5.60(5.27–5.95)	**.0009**	19.58(17.24–22.24)	.2656
	C	259,48.78(44.45–53.12)		0.30(0.27–0.33)		530,99.81(98.96–100.0)		6.54(6.11–7.00)		21.64(19.16–24.45)	
9 V	T	292,55.30(50.95–59.60)	.9676	0.32(0.28–0.35)	.3977	527,99.81(98.95–100.0)	.9968	5.90(5.49–6.34)	**<.0001**	18.69(16.34–21.37)	**<.0001**
	C	293,55.18(50.84–59.46)		0.29(0.26–0.33)		530,99.81(98.96–100.0)		3.15(2.95–3.36)		10.71(9.32–12.31)	
14	T	505,95.64(93.54–97.22)	.5166	1.48(1.35–1.62)	.9427	528, 100.0(99.30–100.0)	1.0000	21.72(19.86–23.76)	**.0023**	14.69(12.63–17.09)	.0733
	C	512,96.42(94.47–97.83)		1.47(1.35–1.60)		531,100.0(99.31–100.0)		18.06(16.71–19.52)		12.27(10.80–13.94)	
18 C	T	282,53.41(49.05–57.73)	.7400	0.28(0.25–0.31)	.7550	522,98.86(97.54–99.58)	.5193	4.54(4.17–4.94)	**.0002**	16.31(13.89–19.15)	**.0272**
	C	289,54.43(50.08–58.72)		0.29(0.25–0.32)		527,99.25(98.08–99.79)		3.65(3.38–3.94)		12.76(11.01–14.79)	
19A	T	503,95.27(93.09–96.91)	.9836	0.93(0.85–1.01)	.0723	528, 100.0(99.30–100.0)	1.0000	6.33(5.92–6.78)	**<.0001**	6.83(6.08–7.67)	**<.0001**
	C	506,95.29(93.13–96.93)		1.03(0.96–1.10)		531,100.0(99.31–100.0)		4.98(4.67–5.30)		4.84(4.37–5.36)	
19 F	T	476,90.15(87.29–92.56)	**.0401**	0.81(0.75–0.87)	.5138	528, 100.0(99.30–100.0)	1.0000	10.95(10.23–11.71)	**<.0001**	13.50(12.18–14.96)	**<.0001**
	C	497,93.60(91.17–95.53)		0.84(0.79–0.89)		531,100.0(99.31–100.0)		5.43(5.12–5.77)		6.48(5.92–7.10)	
23 F	T	265,50.19(45.84–54.54)	.4437	0.34(0.32–0.37)	.8197	527,99.81(98.95–100.0)	.9968	7.38(6.77–8.03)	**<.0001**	21.44(18.84–24.39)	**<.0001**
	C	279,52.54(48.20–56.86)		0.35(0.32–0.38)		530,99.81(98.96–100.0)		4.49(4.13–4.87)		12.85(11.22–14.71)	

GMC = geometric mean concentration; IgG = immunoglobulin G; n = number of subjects with a determinate IgG antibody concentration for the given serotype;
Seropositive rates = percentage of IgG responders (IgG ≥0.35 µg/mL).
The *P* value in bold font means there is a significant difference between those two groups.

Table 3. Type-specific seropositive rates, GMC and GMI pre- and postbooster vaccination.

		Prebooster vaccination				Postbooster vaccination					
Serotype	Group	Seropositive rate n, % (95% CI)	*P*	GMC (95% CI)	*P*	Seropositive rate n, % (95% CI)	*P*	GMC (95% CI)	*P*	GMI (95% CI)	*P*
1	T	459,99.14(97.80–99.76)	1.0000	1.32(1.25–1.40)	.0507	463,100.0(99.21–100.0)	1.0000	8.15(7.64–8.68)	**.0022**	6.16(5.80–6.55)	**<.0001**
	C	452,99.34(98.09–99.86)		1.43(1.36–1.50)		455,100.0(99.19–100.0)		6.99(6.50–7.53)		4.90(4.62–5.21)	
3	T	301,65.01(60.47–69.36)	**.0001**	0.44(0.42–0.47)	**<.0001**	463,100.0(99.21–100.0)	.2454	2.96(2.79–3.14)	**<.0001**	6.67(6.30–7.07)	**<.0001**
	C	238,52.31(47.61–56.98)		0.37(0.35–0.39)		453,99.56(98.42–99.95)		1.78(1.66–1.90)		4.78(4.54–5.03)	
4	T	434,93.74(91.13–95.77)	**.0144**	0.96(0.90–1.03)	**<.0001**	463,100.0(99.21–100.0)	1.0000	6.40(5.94–6.89)	**<.0001**	6.66(6.23–7.11)	**<.0001**
	C	406,89.23(86.01–91.93)		0.74(0.70–0.78)		455,100.0(99.19–100.0)		3.95(3.65–4.27)		5.33(5.00–5.68)	
5	T	449,96.98(94.98–98.34)	.5726	0.91(0.87–0.95)	**.0389**	463,100.0(99.21–100.0)	1.0000	4.18(3.95–4.43)	**<.0001**	4.59(4.39–4.81)	**<.0001**
	C	444,97.58(95.72–98.79)		0.85(0.82–0.89)		455,100.0(99.19–100.0)		3.18(2.97–3.40)		3.74(3.54–3.94)	
6A	T	453,97.84(96.06–98.96)	.6608	1.35(1.28–1.44)	.0989	463,100.0(99.21–100.0)	.4956	8.45(7.83–9.13)	**.0002**	6.24(5.86–6.65)	**.0033**
	C	447,98.24(96.57–99.24)		1.26(1.19–1.34)		454,99.78(98.78–99.99)		6.89(6.38–7.44)		5.45(5.12–5.81)	
6B	T	461,99.57(98.45–99.95)	1.0000	1.96(1.85–2.07)	**.0092**	463,100.0(99.21–100.0)	1.0000	13.41(12.43–14.47)	**.0004**	6.86(6.45–7.29)	**.0314**
	C	454,99.78(98.78–99.99)		1.76(1.66–1.86)		455,100.0(99.19–100.0)		10.93(10.05–11.89)		6.22(5.83–6.64)	
7 F	T	454,98.06(96.34–99.11)	**.0038**	1.26(1.20–1.32)	**<.0001**	463,100.0(99.21–100.0)	1.0000	8.06(7.61–8.53)	**.0114**	6.42(6.03–6.83)	**<.0001**
	C	455,100.0(99.19–100.0)		1.97(1.87–2.08)		455,100.0(99.19–100.0)		7.19(6.72–7.69)		3.65(3.45–3.85)	
9 V	T	455,98.27(96.62–99.25)	.0616	1.19(1.12–1.27)	**.0004**	463,100.0(99.21–100.0)	1.0000	10.42(9.72–11.17)	**<.0001**	8.73(8.21–9.29)	**<.0001**
	C	438,96.26(94.09–97.81)		1.02(0.96–1.09)		455,100.0(99.19–100.0)		5.68(5.27–6.11)		5.56(5.25–5.88)	
14	T	463,100.0(99.21–100.0)	1.0000	5.23(4.92–5.56)	**.0003**	463,100.0(99.21–100.0)	1.0000	34.21(32.25–36.28)	**<.0001**	6.54(6.14–6.96)	**<.0001**
	C	455,100.0(99.19–100.0)		6.10(5.77–6.45)		455,100.0(99.19–100.0)		20.43(19.14–21.82)		3.35(3.15–3.56)	
18 C	T	430,92.87(90.14–95.04)	.6491	0.89(0.83–0.95)	.1095	463,100.0(99.21–100.0)	.4956	5.97(5.61–6.36)	**.0029**	6.75(6.32–7.21)	**<.0001**
	C	426,93.63(90.97–95.69)		0.96(0.90–1.02)		454,99.78(98.78–99.99)		5.13(4.75–5.55)		5.37(5.06–5.70)	
19A	T	461,99.57(98.45–99.95)	.4995	2.47(2.31–2.64)	**.0497**	463,100.0(99.21–100.0)	1.0000	18.74(17.52–20.05)	**<.0001**	7.58(7.07–8.14)	**<.0001**
	C	455,100.0(99.19–100.0)		2.25(2.09–2.41)		455,100.0(99.19–100.0)		12.95(12.04–13.94)		5.77(5.38–6.19)	
19 F	T	463,100.0(99.21–100.0)	1.0000	3.04(2.86–3.23)	**<.0001**	463,100.0(99.21–100.0)	1.0000	19.77(18.55–21.07)	**<.0001**	6.51(6.08–6.97)	**<.0001**
	C	455,100.0(99.19–100.0)		2.22(2.10–2.35)		455,100.0(99.19–100.0)		9.95(9.28–10.67)		4.48(4.19–4.80)	
23 F	T	461,99.57(98.45–99.95)	.1049	1.93(1.81–2.06)	**.0032**	463,100.0(99.21–100.0)	1.0000	10.54(9.83–11.31)	.3278	5.46(5.14–5.81)	**<.0001**
	C	448,98.46(96.86–99.38)		1.67(1.56–1.79)		455,100.0(99.19–100.0)		11.12(10.25–12.06)		6.66(6.22–7.13)	

GMC = geometric mean concentration; IgG = immunoglobulin G; n = number of subjects with a determinate IgG antibody concentration for the given serotype;
Seropositive rates = percentage of IgG responders (IgG ≥0.35 μg/mL)
The *P* value in bold font means there is a significant difference between those two groups.

Table 4. Percentage of participants with OPA≥1:8 pre- and postprimary and booster vaccination.

		Preprimary vaccination		Postprimary vaccination		Prebooster vaccination		Postbooster vaccination	
Serotype	Group	Percentage n, % (95% CI)	*P*	Percentage n, % (95% CI)	*P*	Percentage n, % (95% CI)	*P*	Percentage n, % (95% CI)	*P*
1	T	4,3.88(1.07–9.65)	.7453	102,99.03(94.71–99.98)	1.0000	92,90.20(82.71–95.20)	.8931	102,100.0(96.45–100.0)	1.0000
	C	5,5.00(1.64–11.28)		99,99.00(94.55–99.97)		98,90.74(83.63–95.47)		108,100.0(96.64–100.0)	
3	T	27,26.21(18.04–35.80)	.3821	103,100.0(96.48–100.0)	1.0000	102,100.0(96.45–100.0)	1.0000	102,100.0(96.45–100.0)	1.0000
	C	21,21.00(13.49–30.29)		100,100.0(96.38–100.0)		107,99.07(94.95–99.98)		108,100.0(96.64–100.0)	
4	T	9,8.74(4.07–15.94)	.4455	103,100.0(96.48–100.0)	1.0000	102,100.0(96.45–100.0)	1.0000	102,100.0(96.45–100.0)	1.0000
	C	12,12.00(6.36–20.02)		100,100.0(96.38–100.0)		108,100.0(96.64–100.0)		108,100.0(96.64–100.0)	
5	T	10,9.71(4.75–17.13)	.1998	103,100.0(96.48–100.0)	1.0000	101,99.02(94.66–99.98)	1.0000	102,100.0(96.45–100.0)	1.0000
	C	5,5.00(1.64–11.28)		100,100.0(96.38–100.0)		107,99.07(94.95–99.98)		108,100.0(96.64–100.0)	
6A	T	33,32.04(23.18–41.96)	.6549	100,97.09(91.72–99.40)	.2465	101,99.02(94.66–99.98)	1.0000	101,99.02(94.66–99.98)	.4857
	C	35,35.00(25.73–45.18)		100,100.0(96.38–100.0)		107,99.07(94.95–99.98)		108,100.0(96.64–100.0)	
6B	T	55,53.40(43.30–63.29)	.7324	103,100.0(96.48–100.0)	.4926	102,100.0(96.45–100.0)	.2470	102,100.0(96.45–100.0)	.1220
	C	51,51.00(40.80–61.14)		99,99.00(94.55–99.97)		105,97.22(92.10–99.42)		104,96.30(90.79–98.98)	
7 F	T	31,30.10(21.45–39.92)	.5161	103,100.0(96.48–100.0)	1.0000	101,99.02(94.66–99.98)	.4857	102,100.0(96.45–100.0)	1.0000
	C	26,26.00(17.74–35.73)		100,100.0(96.38–100.0)		108,100.0(96.64–100.0)		108,100.0(96.64–100.0)	
9 V	T	16,15.53(9.15–24.00)	.2382	103,100.0(96.48–100.0)	.4926	102,100.0(96.45–100.0)	1.0000	102,100.0(96.45–100.0)	1.0000
	C	10,10.00(4.90–17.62)		99,99.00(94.55–99.97)		108,100.0(96.64–100.0)		108,100.0(96.64–100.0)	
14	T	72,69.90(60.08–78.55)	.3712	102,99.03(94.71–99.98)	1.0000	98,96.08(90.26–98.92)	.4347	102,100.0(96.45–100.0)	1.0000
	C	64,64.00(53.79–73.36)		100,100.0(96.38–100.0)		106,98.15(93.47–99.77)		108,100.0(96.64–100.0)	
18 C	T	36,34.95(25.82–44.98)	.2865	102,99.03(94.71–99.98)	1.0000	102,100.0(96.45–100.0)	1.0000	102,100.0(96.45–100.0)	1.0000
	C	28,28.00(19.48–37.87)		99,99.00(94.55–99.97)		108,100.0(96.64–100.0)		108,100.0(96.64–100.0)	
19A	T	42,40.78(31.20–50.90)	**.0257**	102,99.03(94.71–99.98)	1.0000	102,100.0(96.45–100.0)	1.0000	102,100.0(96.45–100.0)	1.0000
	C	26,26.00(17.74–35.73)		100,100.0(96.38–100.0)		107,99.07(94.95–99.98)		108,100.0(96.64–100.0)	
19 F	T	34,33.01(24.06–42.97)	.0793	102,99.03(94.71–99.98)	1.0000	101,99.02(94.66–99.98)	.2132	102,100.0(96.45–100.0)	.2470
	C	22,22.00(14.33–31.39)		99,99.00(94.55–99.97)		103,95.37(89.53–98.48)		105,97.22(92.10–99.42)	
23 F	T	20,19.42(12.28–28.38)	.9398	101,98.06(93.16–99.76)	.4404	100,98.04(93.10–99.76)	1.0000	101,99.02(94.66–99.98)	.6220
	C	19,19.00(11.84–28.07)		96,96.00(90.07–98.90)		105,97.22(92.10–99.42)		105,97.22(92.10–99.42)	

The *P* value in bold font means there is a significant difference between those two groups.

Table 5. Overall profiles of adverse events after primary and booster vaccination.

	Postprimary vaccination			Postbooster vaccination		
Event n (%)	Group T (N = 600)	Group C (N = 600)	*P*	Group T (N = 517)	Group C (N = 523)	*P*
Serious adverse events	5(0.83)	13(2.17)	.0938	1(0.19)	2(0.38)	1.0000
Overall adverse events	458(76.33)	497(82.83)	**.0064**	207(40.04)	253(48.37)	**.0073**
Unsolicited adverse reactions	84(14.00)	68(11.33)	.1928	12(2.32)	12(2.29)	1.0000
Solicited adverse reactions	432(72.00)	479(79.83)	**.0019**	199(38.49)	249(47.61)	**.0032**
Grade 3	21(3.50)	22(3.67)	1.0000	11(2.13)	21(4.02)	.1049
Injection-site adverse reactions	262(43.67)	296(49.33)	.0561	97(18.76)	101(19.31)	.8745
Grade 3	17(2.83)	16(2.67)	1.0000	9(1.74)	13(2.49)	.5191
Redness	216(36.00)	256(42.67)	**.0211**	76(14.70)	88(16.83)	.3509
Grade 3	13(2.17)	15(2.50)	.8488	7(1.35)	10(1.91)	.6263
Pain	31(5.17)	18(3.00)	.0791	8(1.55)	12(2.29)	.4994
Induration	151(25.17)	129(21.50)	.1517	46(8.90)	37(7.07)	.3039
Grade 3	10(1.67)	5(0.83)	.2987	4(0.77)	7(1.34)	.5467
Rash	2(0.33)	2(0.33)	1.0000	1(0.19)	4(0.76)	.3738
Grade 3	0(0.00)	0(0.00)	1.0000	0(0.00)	1(0.19)	1.0000
Swelling	74(12.33)	146(24.33)	**<.0001**	39(7.54)	47(8.99)	.4315
Grade 3	9(1.50)	6(1.00)	.6049	4(0.77)	9(1.72)	.2639
Pruritus	0(0.00)	1(0.17)	1.0000	1(0.19)	1(0.19)	1.0000
Systemic adverse reactions	357(59.50)	388(64.67)	.0742	146(28.24)	199(38.05)	**.0008**
Grade 3	4(0.67)	6(1.00)	.7529	2(0.39)	8(1.53)	.1077
Decreased appetite	20(3.33)	23(3.83)	.7565	8(1.55)	5(0.96)	.4186
Fever	317(52.83)	357(59.50)	**.0232**	132(25.53)	185(35.37)	**.0006**
Grade 3	3(0.50)	4(0.67)	1.0000	2(0.39)	8(1.53)	.1077
Diarrhea	45(7.50)	50(8.33)	.6691	11(2.13)	10(1.91)	.8292
Grade 3	1(0.17)	1(0.17)	1.0000	0(0.00)	0(0.00)	1.0000
Cough	58(9.67)	58(9.67)	1.0000	3(0.58)	11(2.10)	.0558
Crying	86(14.33)	99(16.50)	.3374	17(3.29)	32(6.12)	**.0396**
Grade 3	0(0.00)	1(0.17)	1.0000	0(0.00)	0(0.00)	1.0000
Vomiting	19(3.17)	32(5.33)	.0850	2(0.39)	5(0.96)	.4516
Fatigue	23(3.83)	20(3.33)	.7565	2(0.39)	10(1.91)	**.0375**

For the computation of frequencies, the numerators were numbers of the subjects who occurred adverse events.

Safety analysis

Overall, after primary immunization solicited adverse reactions (ARs) were reported in 72.00% of participants in Group T and 79.83% in Group C- the difference between two groups was statistically significant (*P* = .0019). In Group T 17 subjects had Grade 3 injection-site ARs (redness, induration and swelling) and 4 subjects had Grade 3 systemic ARs (fever and diarrhea) while in Group C 16 subjects had Grade 3 injection-site ARs (redness, induration and swelling) and 6 subjects had Grade 3 systemic ARs (fever,

diarrhea and crying). Fewer subjects in Group T reported common ARs (redness, swelling and fever) than those in Group C (all P values <.05). All adverse events (AEs) were mild and mainly classified in Grade 1 and Grade 2. No Grade 4 AE was reported. Five subjects in Group T reported SAEs and thirteen in Group C. None of the SAEs were considered related to study vaccines (Table 5).

As for safety after each inoculation, the frequencies of overall AEs after the first dose were 52.50% in Group T and 58.50% in Group C respectively-the difference was statistically significant (P = .0420). After the second dose solicited ARs (43.55% vs. 49.91%, P = .0342) reported in Group T were significantly fewer than Group C while unsolicited ARs (6.88% vs. 3.79%, P = .0258) and pain (2.58% vs. 0.86%, P = .0397) occurred more frequently in Group T than in Group C. Participants who reported swelling after each dose of primary immunization in Group T were fewer than Group C (4.83% vs. 11.00% P = .0001, 5.85% vs. 9.12% 0.0443, 3.58% vs. 9.40% 0.0001, respectively) (Supplementary Table 4).

After booster immunization there was a significantly difference of the frequency of solicited ARs between Group T and Group C (38.49% vs. 47.61%, P = .0032). In Group T 11 subjects had Grade 3 solicited ARs while in Group C 21 subjects had Grade 3 solicited ARs – the difference was not statistically significant. All AEs were mainly Grade 1 and Grade 2 and no Grade 4 AE occurred. One subject in Group T reported SAE and two in Group C. The one case of SAE in Group T, diagnosed as febrile convulsion and acute upper respiratory tract infection, was considered relevant to study vaccines (Table 5).

Discussion

The results reported establish the immunologic noninferiority and comparable safety of tested PCV13 relative to positive control PCV13 given as a 3-dose series at ages 2, 4, and 6 months respectively, with an additional dose administered at 12–15 months. One month post primary vaccination (Month 5), for serotype 3 seropositive rate in Group T was significantly higher than Group C (100.00% vs. 93.41, P < .0001) and for the other 12 serotypes seropositive rates in two groups were similar. For 12 serotypes IgG GMCs of Group T were significantly higher than Group C(all P values equal to or <0.0038); for serotype 7 F IgG GMC of Group T was lower than Group C (P = .0009). Hence, for all serotypes seropositive rates of Group T were noninferior to those of Group C. Meanwhile, for all serotypes IgG GMC of Group T were noninferior to those of Group C. Based on the noninferiority, for serotype 3 seropositive rate of Group T was declared superior to Group C. For all serotypes except 7 F IgG GMCs of Group T were also tested to be superior to Group C. These probably had relation with different carrier proteins contained in the two study vaccines but the exact mechanism underlying for the difference of the immunogenicity is still unclear to our knowledge.

After combining the immunogenicity data at four different time points – immediately before the first dose, 30 days after the third dose, immediately before the booster dose, and 30 days after the booster vaccination, we found an overall increase-decrease-reincrease trend of the anti-pneumococcal IgG response in both groups. This indicated that levels of type-specific serological antibodies waned after primary immunization as time went by and booster immunization elicited prospective immunity enhancement. As for control PCV13, among 13 serotypes seropositive rates for serotype 3 were lowest and IgG GMCs for serotype 14 were highest both after primary series and after booster vaccination. There were higher immunogenic levels after booster vaccination than after primary series. These data were in line with findings of previous studies among healthy infants in prime-boost regimens.[12]

On the other hand, the frequencies of overall AEs and solicited ARs post primary immunization in Group T were significantly lower than Group C. The most common injection-site ARs were redness, induration and swelling; the frequencies of redness and swelling reported in Group T were both significantly lower than those in Group C. The most common systemic AR was fever and significantly fewer participants reported fever in Group T than Group C. None unsolicited adverse events were related with vaccination assessed by clinical investigator. Post booster immunization the frequencies of overall AEs, solicited ARs and systemic ARs in Group T were significantly lower than Group C. As for AE symptoms, the frequencies of fever, crying and fatigue in Group T were also significantly lower than Group C. Consequently the tested PCV showed better safety profile post booster immunization, which might be attributed to its less total content of pneumococcal polysaccharide in each 0.5 mL dose (28.25 μg vs. 30.8 μg). Similarly with results of other trials among Chinese infants, AEs were mainly mild to moderate and were reported more frequently after the first dose than any other dose.[13,14] Totally 21 subjects reported SAEs during the whole research period. All SAE cases except one were assessed irrelevant or probably irrelevant to study vaccines.

This study had two notable advantages. Firstly, it was a rigorous comparative study of PCV13 because it had chosen Prevnar 13 as positive control. The 2, 4, 6 + 12-month dosing schedule was the same as the administration schedule approved in China which allowed for direct comparison between two study vaccines. Secondly, for each serotype not only IgG binding but also functional antibody responses were examined in this study, which provided additional data of immunologic support among Chinese infants.

To put our study results in perspective, some limitations have to be addressed. First, the persistent immunogenicity of tested PCV 13 remains unknown. A 5-year follow-up study is in process among a subset of our study population. Second, in order to investigate the long-term safety surveillance systems are also needed to monitor rare adverse events or diseases after immunization. Additionally, all 1200 subjects in our study were healthy infants from Jiangsu Province, China. In the future clinical trials may be performed among larger populations with different demographic characteristics such as races or nutrient status of children.

In conclusion, in this study the tested PCV13 showed noninferior immunogenicity and had a good safety profile in prime-booster regimen compared with control vaccine. It could be a promising vaccine to prevent infants against

pneumococcal disease attributable to pneumococcal serotypes contained in the vaccine.

Abbreviations

CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
GMC	geometric mean concentration
GMI	geometric mean increase
GMT	geometric mean titre
OPA	opsonophagocytic assays
FAS	full analysis set
PCV13	13-Valent pneumococcal conjugate vaccine
PPS	per-protocol set
SAE	serious adverse event
SS	safety set

Disclosure statement

Guifan Li is an employee of Beijing Minhai Biotechnology Co., LTD. All other authors have no conflicts.

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Author contributions

Y.H. and G.L. designed the trial and the study protocol, Q.L. and G. L. contributed to the critical review and revision of the report. W.W., Q. L., J.Z., J.Z., J.C., S.X., H.M. led and participated in the site work, including the recruitment, follow-up. W.W. and Q.L. contributed to the data collection, data management, and statistical analysis and wrote the paper.

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