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## Safety of 13-valent pneumococcal conjugate vaccine in infants and children: Meta-analysis of 13 clinical trials in 9 countries<sup>☆</sup>



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### ABSTRACT

**Background:** Meta-analyses enable summarization and interpretation of data across clinical trials. When applied to safety data they allow for detection of rare events. Recently, a 13-valent pneumococcal conjugate vaccine (PCV13) was approved in multiple countries worldwide for routine immunization of infants and young children. This meta-analysis was conducted to identify potentially clinically important rare safety events associated with PCV13.

**Objective:** To summarize the safety of PCV13 compared with 7-valent pneumococcal conjugate vaccine (PCV7) administered to infants and toddlers.

**Methods:** A meta-analysis was performed of integrated safety data from 13 infant studies (PCV13  $n=4729$  and PCV7  $n=2760$ ) conducted in 9 North American, European, and Asian countries. Local reactions at the vaccine injection site and systemic events were collected for 4–7 days after each dose into electronic diaries. Adverse events (AEs) were collected after each vaccination.

**Results:** Overall, rates of local reactions after any dose of the infant series were similar between PCV13 and PCV7 groups: tenderness (46.7% vs 44.8%, respectively); swelling (28.5% vs 26.9%); and redness (36.4% vs 33.9%). After the toddler dose, tenderness was significantly higher among PCV7 subjects than PCV13 subjects (54.4% vs 48.8%;  $P=0.005$ ). Frequencies of fever ( $\geq 38^\circ\text{C}$ ) were similar in both groups and mostly mild ( $\leq 39^\circ\text{C}$ ); incidence of moderate fever ( $>39^\circ\text{C}$  to  $\leq 40^\circ\text{C}$ ) with PCV13 was  $\leq 2.8\%$  after any infant dose and 5.0% after the toddler dose, compared with  $\leq 2.6\%$  and 7.3%, respectively, with PCV7. Fever  $>40^\circ\text{C}$  was uncommon in both groups. Frequencies of decreased appetite, irritability, and sleep disturbances were similar in both groups. AEs were the types of conditions and symptoms expected in infants and children, and clinically significant differences between vaccine groups were not observed.

**Conclusion:** PCV13 has a favorable safety profile similar to that of PCV7, a vaccine for which there is  $>10$  years clinical experience.

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### 1. Introduction

*Streptococcus pneumoniae* is a major cause of mortality in young children worldwide. Among children  $<5$  years of age there are  $>541,000$  deaths worldwide annually due to pneumococcal disease [1], making *S. pneumoniae* the leading cause of vaccine-preventable death in children aged  $<5$  years globally.

In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was approved for use in the USA. Although the incidence of invasive pneumococcal disease (IPD) caused by vaccine serotypes has decreased since PCV7 was licensed, the incidence of IPD due to nonvaccine serotypes increased [2]. To increase serotype coverage globally, a 13-valent pneumococcal conjugate vaccine (PCV13) that contains the PCV7 serotypes and 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A) was developed. PCV13 was recently approved in several countries worldwide for routine immunization of infants and young children [3–6].

Safety is a primary concern with any preventive therapy given to young children, particularly a vaccine that could be used worldwide. Therefore, as part of regulatory submissions for approval of PCV13, safety data from trials in infants and toddlers were pooled using meta-analysis techniques to evaluate overall safety of PCV13

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compared with the standard PCV7. This safety evaluation summarized the integrated safety analyses of PCV13 compared with PCV7 when administered to infants and young children. This analysis also evaluated acceptability of the safety profile of PCV13 as measured by incidence rates of local reactions, systemic events, and adverse events (AEs). Although individual studies provide valuable safety data, by combining data from several studies, this analysis has increased power to identify safety signals, particularly clinically important rare events.

## 2. Methods

This meta-analysis of PCV13 was based on data from 13 randomized, double-blind, multicenter studies that evaluated the safety and immunogenicity of PCV13 in healthy infants in a uniform manner (Table 1) [7–19]. All studies were phase 3 studies except for Study 003, which was a phase 1/2 study. The meta-analysis utilized individual data and was performed based on a pre-specified analysis plan, which was finalized prior to initiating the meta-analysis. This meta-analysis comprised all data available from phase 2 and 3 infant studies in the PCV13 clinical development program as of November, 18, 2008. Each study was conducted in a single country; 9 countries in North America, Europe, and Asia were included. All 13 studies evaluated the safety and immunogenicity of PCV13 when administered with other pediatric vaccines. Choice of concomitant vaccines, described in Table 1, was based upon national recommendations. Ten studies used PCV7, which was equivalent to the marketed Prevnar® vaccine (Pfizer Inc., Collegeville, PA), as a single, active comparator; and 3 studies compared different formulations or lots of PCV13. All data utilized in this analysis were contained within the Pfizer PCV13 Oracle Clinical database. As all clinical trials data were included, no selection bias was introduced. The main purpose of this meta-analysis was to identify signal events and distinguish rare events that are clinically important from rare events that are not clinically important.

### 2.1. PCV vaccinations

The PCV vaccination schedules used were based on national recommendations and varied across studies. In all studies, PCV13 or PCV7 was administered intramuscularly by injecting 0.5 mL into the left anterolateral thigh muscle. Across studies, all subjects received the same amount of PCV7 or PCV13 antigen in each dose. All vaccines were produced by the same manufacturer using a similar process. Polysorbate 80 (P80) is a nonionic detergent that is widely used in both oral and injectable medications to solubilize proteins. Most studies included in the analysis used PCV13 without P80 [7–11,13–15,18,19]. However, following a decision to produce a commercial formulation of PCV13 containing P80, later studies utilized a PCV13 formulation containing P80 [12,16,17]. Study 009 demonstrated that both the safety and immunogenicity profiles of the original clinical study formulation without P80 and the formulation with P80 were similar [12]. Studies 3000 and 3005 demonstrated that the safety and immunogenicity of three lots of PCV13 were similar [16,17].

### 2.2. Safety evaluations

Safety evaluations included use of a scripted electronic diary and collection of adverse events during clinic visits and a telephone contact. Following each dose of study vaccine, the parent or legal guardian was asked to monitor local reactions and systemic events and provide information about use of antipyretic medication to treat or prevent symptoms daily. This information was collected for 4 days after each vaccination in all studies except for studies 004 and 3005 which collected data for 7 days and Study 003 which

collected data for 15 days during the first stage and 8 days during the second stage. Monitored local reactions were redness, swelling, and tenderness at the pneumococcal conjugate vaccine injection site. Tenderness was recorded as none, present, or interfered with limb movement. If present, the diameter of swelling and redness was measured with a provided caliper. Monitored systemic events included fever (defined as a temperature of  $\geq 38.0^{\circ}\text{C}$ ), decreased appetite, decreased sleep, increased sleep, and irritability. Temperature was taken daily at bedtime and any time the subject felt feverish; the highest daily temperature was reported.

In all studies, AEs were recorded from study enrollment until 1 month after the last dose of the infant series, and from the toddler dose until 1 month after the toddler dose. Serious AEs (SAEs) were reported from study enrollment to final visit. Newly diagnosed chronic medical conditions were collected at the toddler dose and 6 months after the final study vaccination, using a telephone interview. Requirements for AE reporting were uniform across studies.

Uniform case report forms and a common electronic diary were used for collection of safety data in 12 of the 13 studies. Therefore, no bias was introduced by use of different data collection tools across studies. In Study 003, a phase 1/2 trial, local reactions and systemic events were recorded in a paper diary.

At the time this analysis was conducted, safety data were available for the infant series from all 13 studies and for the toddler dose from 9 studies [7–12,14–16]. For 6 studies follow-up safety data were available from a telephone interview conducted 6 months after the subject's last vaccination [7–9,12,14,15].

### 2.3. Analyses

The safety population was defined as all subjects who received at least 1 dose of study vaccine and had at least 1 safety evaluation reported. Separate safety populations were defined for each dose and included all subjects who were vaccinated at that dose and had data during the protocol-specified period (usually 4 or 7 days) after the respective dose. Subjects with no data for a particular dose were excluded from that analysis.

Twelve subjects, who incorrectly received the alternate study vaccine (relative to their randomized treatment assignment) and/or were randomized but not vaccinated, were excluded from analysis. Inspection of these data did not show any impact on inference (data on file).

For the integrated analysis, data from the 13 studies were pooled across all PCV13 groups, regardless of formulation or lot. This pooling was justified on the basis that data from the individual studies demonstrate the similarity of reactogenicity of PCV13 across lots and formulations. In Study 008, subjects in one group received PCV7 during the infant series and PCV13 at the toddler dose. In summaries of local reactions, systemic events, and AEs that occurred during the infants series or between the infant series and toddler series, data for subjects in this treatment group were pooled with data for subjects in the PCV7 groups and in summaries of events that occurred after the toddler dose; data for these subjects were pooled with data for the PCV13 groups.

Data for local reactions and systemic events were summarized separately for each dose in the infant series and for the toddler dose. AEs were summarized separately for each dose in the infant series, for the toddler dose, and for any time during the infant series, which includes data from any subject who is included in the dose 1, dose 2, or dose 3 safety populations. In addition, AEs were summarized for the period between the infant series and the toddler dose, and for the 6-month follow-up telephone contact. Subjects who did not have any AE data for the period summarized were not included in these summaries. AEs were categorized according to the Medical Dictionary for Regulatory Activities.

**Table 1**  
Studies included in the safety meta-analysis.

Study ID (ref.)/location	No. of patients	Infant schedule (months of age)	Toddler dose (months of age)	Randomization groups	Concomitant vaccines
003 [7]/USA	247	2, 4, 6	12–15	PCV13 ( <i>n</i> = 121)	Pediarix®
004 [8]/USA	663	2, 4, 6	12–15	PCV7 ( <i>n</i> = 126) PCV13 ( <i>n</i> = 332) PCV7 ( <i>n</i> = 331)	ActHIB® Pediarix® ActHIB® ProQuad® PedvaxHIB® VAQTA®
006 [9]/Germany	603	2, 3, 4	11–12	PCV13 ( <i>n</i> = 300) PCV7 ( <i>n</i> = 303)	Infanrix® Hexa
007 [10]/UK	278	2, 4	12	PCV13 ( <i>n</i> = 139) PCV7 ( <i>n</i> = 139)	NeisVac-C® PEDIACEL® Menitorix Pentavac®
008 [11]/France <sup>a</sup>	611	2, 3, 4	11–12	PCV13/PCV13 ( <i>n</i> = 302) PCV7/PCV13 ( <i>n</i> = 151) PCV7/PCV7 ( <i>n</i> = 158)	
009 [12]/Poland	500	2, 3, 4	11–12	PCV13 + P80 ( <i>n</i> = 250) PCV13-P80 ( <i>n</i> = 250)	Pentaxim® Engerix B® Priorix®
011 [13]/India	353	1.5, 2.5, 3.5	12	PCV13 ( <i>n</i> = 178) PCV7 ( <i>n</i> = 175)	Easyfive® Biopolio
500 [14]/Italy	604	3, 5	11	PCV13 ( <i>n</i> = 302) PCV7 ( <i>n</i> = 302)	Infanrix® Hexa
501 [15]/Spain	616	2, 4, 6	12–15	PCV13 ( <i>n</i> = 314) PCV7 ( <i>n</i> = 302)	Infanrix® Hexa Meningitec® Infanrix™-IPV + Hib Pentaxim® Engerix B® Priorix®
3000 [16]/Poland	268	2, 3, 4	11–12	PCV13 Pilot lot ( <i>n</i> = 134) <sup>b</sup> PCV13 Man lot ( <i>n</i> = 134)	
3005 [17]/USA	1699	2, 4, 6	12–15	PCV13 Pilot lot 1 ( <i>n</i> = 486) <sup>b</sup> PCV13 Pilot lot 2 ( <i>n</i> = 484) PCV13 Man lot ( <i>n</i> = 485) PCV7 ( <i>n</i> = 244) PCV13 ( <i>n</i> = 218) PCV7 ( <i>n</i> = 226)	Pediarix® ActHIB® M-M-R® II Varivax® Havrix™
3007 [18]/Spain	444	2, 4, 6	12–15	PCV13 ( <i>n</i> = 218) PCV7 ( <i>n</i> = 226)	NeisVac-C® Infanrix® Hexa Infanrix™-IPV + Hib
3008 [19]/Canada	603	2, 4, 6	12–15	PCV13 ( <i>n</i> = 300) PCV7 ( <i>n</i> = 303)	NeisVac-C® Pentacel® MMR Varivax®

<sup>a</sup> The objective of Study 008 in France was to evaluate the safety of PCV13 administered at the toddler dose to subjects who had been vaccinated with PCV7 during the 3-dose infant series. Subjects were randomly assigned to 1 of 3 vaccine groups: to receive PCV13 during the infant series and at the toddler dose (PCV13/PCV13); PCV7 during the infant series and at the toddler dose (PCV7/PCV7); or PCV7 during the infant series and PCV13 at the toddler dose (PCV7/PCV13).

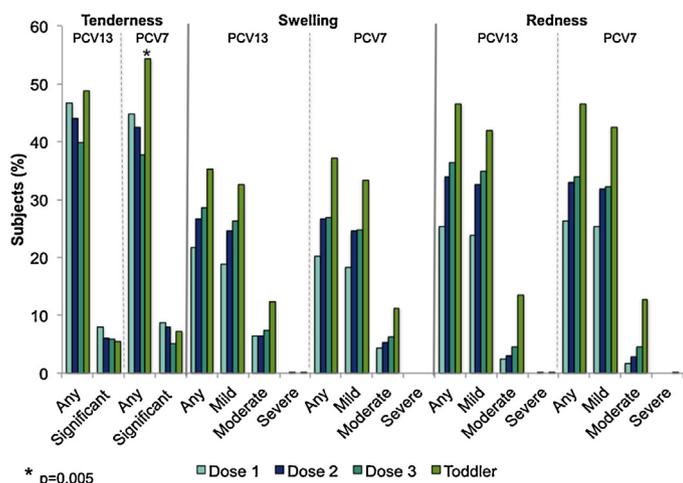
<sup>b</sup> Study 3000, conducted in Poland, compared a PCV13 pilot scale lot with a PCV13 manufacturing scale lot; Study 3005, conducted in the USA, compared 2 pilot scale lots and 1 manufacturing scale lot of PCV13 and PCV7. The 2 studies used the same lot of manufacturing scale PCV13. All the lots of PCV13 were formulated with P80. Results of both studies demonstrated that the safety and immunogenicity of the PCV13 manufacturing scale lot were similar to those of the PCV13 pilot scale lots. Man, manufacturing; P80, polysorbate 80; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

Meta-analyses of the safety data followed principles for meta-analysis of individual subject, binary data method which assumes, for each given event, that a true (and unknown) numeric difference in vaccine effect (i.e., difference in incidence) exists between subjects who received PCV13 and subjects who received PCV7. No assumption around the magnitude of this numeric difference is made, and it can be greater than, less than, or equal to zero for a difference in observed rates between regimens. For each event, it is assumed that the measured magnitude of the difference in a given study will vary above or below the true (and unknown) numeric value in a random manner.

To derive a precise estimate of the true and unknown numeric difference, a mixed effect, meta-analysis model is employed pooling individual data across studies, accounting for each study as its

own control. All data collected are utilized in assessing statistical inference between PCV13 and PCV7. Estimates for the treatment difference are weighted according to the degree of precision arising from each study, such that those with greater sample size are deemed to contribute a higher degree of information. These estimates are then used to derive a test statistic (odds ratio) and are expressed as a *P*-value to assess whether the true (and unknown) magnitude of the treatment difference is non-null. For events for which too few events were observed to allow the model to converge, the Fisher exact test was used to test for a difference between PCV13 and PCV7.

The unadjusted event counts and the percentages of subjects with an event are presented along with the model-derived *P*-value to facilitate clinical review of events for which the statistics deem



**Fig. 1.** Comparison of local reactions after each dose: (A) tenderness; (B) swelling; (C) redness. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

that a difference between PCV13 and PCV7 may exist. These findings should be viewed as a statistical screening tool and to highlight the potential need for clinical assessment of significance.

### 3. Results

#### 3.1. Subject disposition and demographics

The disposition of subjects is described in Supplemental online content subject disposition and shown in Supplemental online content Table 1.

Few withdrawals due to AEs occurred (Table 2); 23 subjects (15 PCV13 (0.3%) subjects and 8 PCV7 (0.3%) subjects) during the infant series, 16 subjects (7 PCV13 (0.3%) subjects and 9 PCV7 (0.5%) subjects) between the infant series and toddler dose, and no subjects following the toddler dose. Types of AEs most frequently resulting in withdrawal were nervous system disorders and infections and infestations (Table 2). Specific details of these patients are presented in Supplemental online text febrile convulsions and infestations. There was no statistically significant difference in model-adjusted incidence between PCV13 and PCV7 at the 0.05 (2-sided) level.

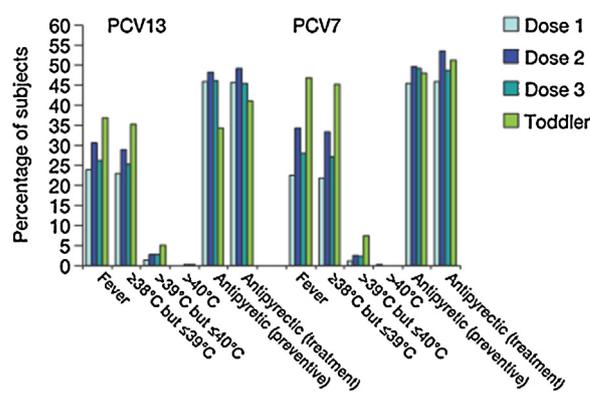
Representative demographic characteristics for the infant series population are shown in Supplemental online content Table 2.

Results of individual studies have been reported previously [7–19].

#### 3.2. Local reactions

Overall, rates of local reactions after any dose of the infant series were similar between PCV13 and PCV7 (Fig. 1). In the PCV13 group any tenderness ranged from 39.9% following dose 3 of the infant series to 48.8% after the toddler dose. In the PCV7 group any tenderness ranged from 37.7% following infant series dose 3 to 54.4% following the toddler dose. Any induration ranged from 21.8% following dose 1 to 35.3% following the toddler dose in the PCV13 group, while any induration ranged from 20.2% following dose 1 to 37.1% following the toddler dose in the PCV7 group. Any erythema ranged from 25.3% following dose 1 to 46.6% following the toddler dose in the PCV13 group and 26.2% to 46.6% following the toddler dose in the PCV7 group.

After dose 1 of the infant series, the incidences of moderate swelling ( $P=0.034$ ) and moderate redness ( $P=0.009$ ) were significantly higher among PCV13 subjects than PCV7 subjects. After dose

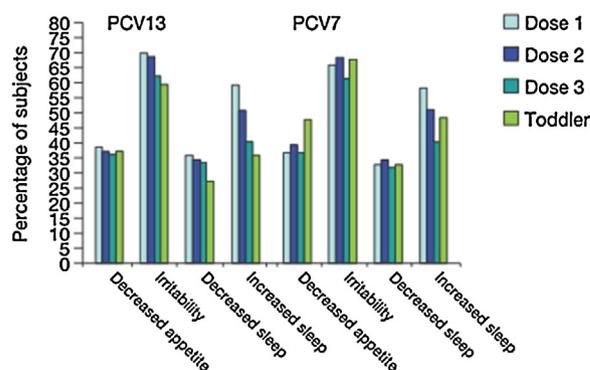


**Fig. 2.** Comparison of fever rates and antipyretic use after each dose. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

2, the incidence of significant tenderness was significantly higher among PCV7 subjects than PCV13 subjects ( $P=0.047$ ). After the toddler dose, the incidence of tenderness was significantly higher among PCV7 subjects than PCV13 subjects ( $P=0.005$ ).

#### 3.3. Systemic reactions

Frequencies of fever were similar in both groups and most were mild ( $\leq 39^\circ\text{C}$ ) (Fig. 2). In the PCV13 group any fever ranged from 23.9% following dose 1 of the infant series to 36.9% after the toddler dose. In the PCV7 group, any fever ranged from 22.5% after dose 1 of the infant series to 46.7% following the toddler dose. Severe fever ( $>40^\circ\text{C}$ ) occurred in  $\leq 0.3\%$  of subjects after any dose. Antipyretic medications were administered at similar rates in both groups with a low of 41.1% for the PCV13 group and high of 51.3% in the PCV7 group, for treatment, both occurring following the toddler dose. For prevention, the lowest frequency of use (34.2%) occurred in the PCV13 group following the toddler dose and the highest frequency of use (49.6%) occurred in the PCV7 group following dose 2. Frequencies of decreased appetite, irritability, and sleep disturbances were also similar in both groups during the infant series and following the toddler dose (Fig. 3). The lowest incidence of decreased appetite (36.3%) occurred in the PCV13 following dose 2 of the infant series, and highest incidence (48.0%) occurred in the PCV7 group after the toddler dose. Lowest (61.4%) and highest (70.0%) incidences of irritability occurred in the PCV7 and PCV13 groups, following dose 3 and dose 1, respectively. The lowest incidence of increased sleep (36.0%) occurred following the toddler dose and the highest incidence (59.2%) occurred following dose 1, both in the PCV13 group. Decreased sleep occurred at the lowest frequency in the PCV13 group (27.5%) following the toddler dose. Highest



**Fig. 3.** Comparison of systemic events after each dose. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

**Table 2**

Withdrawals due to adverse events (AEs) by System Organ Class<sup>a</sup> and pneumococcal conjugate vaccine group (includes events which are not related to vaccination as well as those that are possibly related).

N	PCV13	PCV7
	<i>n</i> = 4723 infant series; <i>n</i> = 2569 between infant and toddler dose <sup>b,c</sup> ; <i>n</i> = 2499 <sup>d</sup>	<i>n</i> = 2754 infant series; <i>n</i> = 1800 between infant and toddler dose <sup>b,c</sup> ; <i>n</i> = 1482 <sup>d</sup>
Any AE	22	17
Nervous system disorders	8	9
Infections and infestations	5	3
Skin and subcutaneous tissue disorders	2	3
Psychiatric disorders	2	2
Blood and lymphatic system disorders	3	0
General disorders/administration site disorders	2	1

<sup>a</sup> Only classes with  $\geq 2$  AEs are shown.

<sup>b</sup> AEs were collected differently for the period between the infant series and the toddler dose, than for the infant and toddler doses. At the toddler dose visit, parents/guardians were to report any new chronic medical condition and any serious AEs that had occurred since the previous visit.

<sup>c</sup> Postinfant series data are available for 9 studies.

<sup>d</sup> There were no withdrawals because of AEs during the toddler dose. AE, adverse event; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

incidence also occurred in the PCV13 group (36.0%) following dose 1.

#### 3.4. Comparative event rates 2 + 1 versus 3 + 1 dosing schedules

Two studies included in our meta-analysis utilized a 2 + 1 dosing schedule to compare immunogenicity and safety of PCV13 to PCV7. In the study conducted in Italy [4], no statistically significant differences between vaccine groups were observed after doses 1 and 2 of the infant series or after the toddler dose for local reactions. Tenderness and redness were reported slightly more following the toddler dose than following the infant series. In the case of systemic events, only one significant difference between vaccine groups occurred. Irritability following dose 1 of the infant series was significantly greater in the PCV13 group than the PCV7 group  $P \leq 0.05$ . Most cases of fever were mild in severity ( $\geq 38^\circ$  but  $\leq 39^\circ$ ). Severe fever was reported only once in the study, and occurred in one subject in the PCV7 group following the toddler dose. In a second study using the 2 + 1 schedule and conducted in the United Kingdom [22], the only instance of a significant difference in reactions was the frequency of erythematous reactions that occurred following the first dose of PCV13 than PCV7. There were no statistically significant differences between groups. While no studies utilizing a direct comparison between the 2 + 1 and 3 + 1 dosing schedules have been done, we can say that frequencies and severity of local and systemic reactions following dose 3 (toddler dose) in the studies with the 2 + 1 dosing schedule were within the expected ranges for these events seen following dose 4 (toddler dose) during the 3 + 1 studies [6–14]. See Supplemental online Tables 3 and 4 (Percent of subjects experiencing local events following the toddler dose in studies with a 2 + 1 dosing schedule versus a 3 + 1 dosing schedule and Percent of subjects experiencing systemic events following the toddler dose in studies with a 2 + 1 dosing schedule versus a 3 + 1 dosing schedule) which report frequencies of local and systemic events across the 2 + 1 and 3 + 1 studies included in our meta-analysis.

#### 3.5. Adverse events

The types of AEs reported were conditions and symptoms generally expected in these age groups, and were reported at similar frequencies in the PCV13 and PCV7 groups. Among AEs that occurred most frequently, there were no trends suggesting a tendency to increase or decrease across doses.

AEs that showed a statistically significant difference between PCV13 and PCV7 are listed in Supplemental online Tables 5 and 6. Among AEs with statistically significant differences in incidence

between groups, the higher frequency was seen more often in the PCV7 group, suggesting no concerns regarding the safety of PCV13 relative to PCV7. Furthermore, for most of these events the difference in incidence between groups was  $< 1.0\%$ , suggesting statistical findings were not due to clinically important differences.

Related AEs were reported at a low incidence. During the infant series, related AEs were reported in 5.2% and 6.6% of subjects vaccinated with PCV13 and PCV7 respectively; after the toddler dose, the incidence was 2.0% and 2.9%, respectively. The types of AEs most frequently reported as related to study vaccine were general disorders and administration site conditions, including pyrexia and injection site reactions. These are either events related to the use of concomitant vaccinations as only information for the pneumococcal vaccine injections site was collected in the electronic diaries, or events that investigators did not think were fully described in the diaries.

The incidence of SAEs reported during each period (infant series, between infant and toddler dose, toddler dose, and follow-up period) was  $\leq 4.6\%$  for each vaccine group. Infections and infestations were the most frequently reported types of SAEs. The next most common were gastrointestinal and respiratory, thoracic, and mediastinal disorders.

SAEs that the investigator considered related to study vaccine were reported for 11 subjects. Related SAEs in the PCV7 group included febrile convulsion ( $n = 2$ ), infantile spasms ( $n = 1$ ), nephroblastoma ( $n = 1$ ), and pyrexia ( $n = 1$ ). Related SAEs in the PCV13 group included febrile convulsion and pyrexia ( $n = 1$ ), pyrexia ( $n = 1$ ), bronchitis ( $n = 1$ ), inconsolable crying ( $n = 1$ ), allergy to vaccine ( $n = 1$ ), and bronchiolitis ( $n = 1$ ). Among the 7489 vaccinated infants, 3 (0.063%) vaccinated with PCV13 and 1 (0.036%) vaccinated with PCV7 died as a result of Sudden Infant Death Syndrome (SIDS) considered unrelated to study vaccine.

## 4. Discussion

By design all PCV13 safety comparisons were made with PCV7. The safety of PCV7 administered with other vaccines has been established in clinical and postmarketing studies [20,21]. One review noted in PCV7 clinical studies, the most frequently reported AEs were injection site reactions, fever, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, and rash, and that postmarketing studies confirmed the favorable safety profile [20]. Data from the US Vaccine Adverse Event Reporting System (VAERS) demonstrated that the most frequently reported conditions following use of PCV7 were fever, injection-site reactions, rashes (including urticaria), and irritability or agitation [21].

Several large randomized clinical studies have confirmed the safety of PCV13 administration in infants and toddlers [6,22–25]. This meta-analysis was conducted to further evaluate the safety of PCV13 compared with PCV7 when administered with concomitant vaccines, with an emphasis on the examination of rare events. The analysis provided a method by which the wealth of data available in PCV13 clinical trials could be used to identify signal events.

Local reactions at the injection site (tenderness, swelling, and redness) were reported at similar rates in the PCV13 and PCV7 groups, with the incidence of local reactions generally lowest after dose 1 and highest after the toddler dose. Fever was also reported at similar frequencies in both groups, with no clinically important differences between groups. Most reports of fever were mild. Severe fever occurred in  $\leq 0.3\%$  of subjects after any dose. Decreased appetite, irritability, increased sleep, and decreased sleep were reported at similar frequencies in the PCV13 and PCV7 groups, with no clinically important differences in reactogenicity between the groups. Most reported AEs were generally those expected and commonly seen in infants and toddlers, and were reported at similar frequencies in both groups. Few subjects in either group discontinued study vaccine because of AEs.

This analysis used a statistical method that was very sensitive and could detect small numerical differences between the groups. As a result of this sensitivity and the large number of comparisons made, the many significant differences noted between groups with this model must be interpreted with caution. All AEs with statistical significance between groups were reviewed to determine if further clinical evaluation was warranted. In most cases, further review was unwarranted as the actual differences were small and not clinically meaningful, and there was no clear mechanism by which a true clinical difference might be explained. For example, during the infant series eye discharge occurred significantly more frequently in the PCV13 group than the PCV7 group (0.6% vs 0.3%) but there is no clear mechanism that might explain a true clinical difference, and although the difference between groups is statistically significant it is highly unlikely that the 0.3% difference between groups is clinically significant. AEs that were examined further included anemia, seizure, immune system disorders, wheezing, pneumonia, and apnea. Upon further examination, no clinically meaningful differences were found for these AEs.

Four of the 7489 vaccinated infants with data included in the integrated safety analyses died. All 4 deaths were attributed to SIDS and were not considered related to study vaccine. The rate of SIDS observed in this analysis is consistent with the incidence in the general population [26–28].

In each of the 13 studies included in this analysis the choice of concomitant vaccines and vaccine schedule were based on national recommendations. Therefore, a variety of concomitant vaccines and vaccine schedules were employed. Consequently, this integrated analysis provides a thorough evaluation of the safety profile of PCV13.

In conclusion, based on clinical data from 13 studies, PCV13 has a favorable safety profile similar to that of PCV7, which has been the standard of care for infants and young children for >10 years. AE monitoring continues post-licensure to confirm these findings. Safety assessments continue through routine pharmacovigilance mechanisms and additional safety studies (NCT01509105).

#### Conflict of interest statement

This analysis was sponsored by Pfizer Inc. All authors are current employees of Pfizer Inc. Medical writing support for this manuscript was provided by Elaine Santiago, PharmD, at Excerpta Medica and was sponsored by Pfizer Inc.

#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2013.08.025>.

#### References

- [1] World Health Organization. Estimated Hib and pneumococcal deaths for children under 5 years of age; 2008, [http://www.who.int/immunization\\_monitoring/burden/Pneumo\\_hib\\_estimates/en/index.html](http://www.who.int/immunization_monitoring/burden/Pneumo_hib_estimates/en/index.html).
- [2] Plishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010;201:32–41.
- [3] Kieninger DM, Kueper K, Steul K, Juergens C, Ahlers N, Baker S, et al. Safety, tolerability, and immunologic noninferiority of a 13-valent pneumococcal conjugate vaccine compared to a 7-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in Germany. *Vaccine* 2010;28:4192–203.
- [4] Esposito S, Tansey S, Thompson A, Razmpour A, Liang J, Jones TR, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine compared to those of a 7-valent pneumococcal conjugate vaccine given as a three-dose series with routine vaccines in healthy infants and toddlers. *Clin Vaccine Immunol* 2010;17:1017–26.
- [5] Bryant KA, Block SL, Baker SA, Gruber WC, Scott DA. PCV13 Infant Study Group. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. *Pediatrics* 2010;125:866–75.
- [6] Yeh SH, Gurtman A, Hurley DC, Block SL, Schwartz RH, Patterson S, et al. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in infants and toddlers. *Pediatrics* 2010;126:e493–505.
- [7] A Phase I/II, 2-stage, Randomized, Double-Blind Trial of the Safety, Tolerability and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in Healthy Infants; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00205803>.
- [8] A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability and Immunologic Noninferiority of a 13-valent Pneumococcal Conjugate Vaccine Compared to a 7-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in the United States; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00373958>.
- [9] A Phase 3, Randomized, Active-Controlled, Double-blind Trial of the Safety, Tolerability, and Immunologic Non-Inferiority of a 13-valent Pneumococcal Conjugate Vaccine Compared to a 7-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Germany; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00366340>.
- [10] A Phase 3, Randomized, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in the United Kingdom; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00384059>.
- [11] A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in France; 2013, [www.clinicaltrials.gov/ct2/show/NCT00366678](http://www.clinicaltrials.gov/ct2/show/NCT00366678).
- [12] A Phase 3, Randomized, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine Manufactured With and Without Polysorbate 80 in Healthy Infants Given in a 2-, 3-, 4-, and 12-Month Schedule With Routine Pediatric Vaccinations; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00366548>.
- [13] A Phase 3, Randomised, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Paediatric Vaccinations in India; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00452790>.
- [14] A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Paediatric Vaccinations in Italy; 2013, [www.clinicaltrials.gov/ct2/show/NCT00366899](http://www.clinicaltrials.gov/ct2/show/NCT00366899).
- [15] A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Spain; 2013. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00368966>.
- [16] A Phase 3, Randomised, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of Manufacturing Scale 13-valent Pneumococcal Conjugate Vaccine; 2013. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00464945>.
- [17] A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of Three Lots of 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in the United States; 2013. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00444457>.
- [18] A Phase 3, Randomized, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With a Meningococcal C-Tetanus Toxoid

- Conjugate Vaccine and Other Routine Pediatric Vaccinations in Spain; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00474539>.
- [19] A Phase 3, Randomized, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Canada; 2013, <http://www.clinicaltrials.gov/ct2/show/NCT00475033>.
- [20] Center KJ, Strauss A. Safety experience with heptavalent pneumococcal CRM197-conjugate vaccine (Prevenar) since vaccine introduction. *Vaccine* 2009;27:3281–4.
- [21] Destefano F, Pfeifer D, Nohynek H. Safety profile of pneumococcal conjugate vaccines: systematic review of pre- and post-licensure data. *Bull World Health Organ* 2008;86:373–80.
- [22] Snape MD, Klinger CL, Daniels ED, John TM, Layton H, Rollinson L, et al. Immunogenicity and reactogenicity of a 13-valent-pneumococcal conjugate vaccine administered at 2, 4, and 12 months of age: a double-blind randomized active-controlled trial. *Pediatr Infect Dis J* 2010;29:e80–90.
- [23] Gadzinowski J, Albrecht P, Hasiac B, Konior R, Dziejuch J, Witor A, Melleliu T, et al. Phase 3 trial evaluating the immunogenicity, safety, and tolerability of manufacturing scale 13-valent pneumococcal conjugate vaccine. *Vaccine* 2011;29:2947–55.
- [24] Frenck Jr R, Thompson A, Yeh SH, London A, Sidhu M, Patterson S, et al. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in children previously immunized with 7-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2011;30:1086–91.
- [25] Grimprel E, Laudat F, Patterson S, Baker SA, Sidhu MS, Gruber WC, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13) when given as a toddler dose to children immunized with PCV7 as infants. *Vaccine* 2011;29:9675–83.
- [26] California Department of Public Health. Facts About Sudden Infant Death Syndrome (SIDS) Mortality In California, 2008; September 2010. Available at: <http://www.cdph.ca.gov/data/statistics/Documents/MO-SIDS-FactSheet-2008.pdf>.
- [27] Hauck FR, Tanabe KO. International trends in sudden infant death syndrome: stabilization of rates requires further action. *Pediatrics* 2008;122:660–6.
- [28] Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J* 2000;19:187–95.