Clinical Research

Safety of a 2-dose primary series of 13-valent pneumococcal conjugate vaccine in Indonesian infants

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ABSTRACT

BACKGROUND In 2017, the Indonesian Technical Advisory Group on Immunization recommended a safety monitoring demonstration program for the 13-valent pneumococcal conjugate vaccine (PCV13) in West Lombok and East Lombok, West Nusa Tenggara to evaluate the 2-dose primary series (2 and 3 months of age) for serious adverse events (SAEs), adverse events, systemic events, and local reactions.

METHODS A total of 1,083 infants from 10 primary healthcare centers were analyzed, with 687 receiving the first dose and 396 receiving the second dose. Based on the national immunization program, they received PCV13 + DTwP-HB-Hib + OPV (n = 544), PCV13 + DTwP-HB-Hib (n = 101), or PCV13 only (n = 403). They were monitored for 30 min after vaccination for any immediate SAEs, and parents were given a diary card to record safety information prospectively for 28 days.

RESULTS No immediate SAEs were observed, and no SAEs were reported during 28 days after vaccination. Reports of local reactions and systemic events predominated on days 1–3 post-vaccination. Severe fever (axillary temperature >39.0°C) was uncommon (<2% of all infants). Most irritability was mild to moderate. Local pain was more frequent after the first dose than after the second dose. It was distributed evenly across mild, moderate, and severe classifications, while redness and swelling were mostly mild to moderate.

CONCLUSIONS The PCV13 primary series demonstration program in Indonesia confirmed tolerable local and systemic reactions.

KEYWORDS adverse effects, conjugate vaccine, Indonesia, infant, pneumococcal vaccines, safety

The World Health Organization recommends a 3-dose series for pneumococcal conjugate vaccine (PCV) administration in infants involving either 3 primary doses (3p + 0 schedule) or 2 primary doses with a booster (2p + 1 schedule). In choosing between the 3p + 0 and 2p + 1 schedules, national health authorities should consider factors such as the age-specific epidemiology of pneumococcal disease, likely vaccine uptake, and timeliness of vaccine doses.[1] The introduction of PCV into national immunization programs (NIPs) has resulted in significant reductions in clinical pneumonia and vaccine-serotype defined outcomes such as invasive pneumococcal disease or nasopharyngeal carriage.[2] Pneumonia imposes a substantial disease burden on children in Indonesia. A systematic analysis from 2019 showed that the incidence of pneumonia in Indonesian children under 5 years of age ranged from 487 per 1,000 population in 2000 to

326 per 1,000 population in 2015.[3] The acceptable safety profiles for the 13-valent pneumococcal conjugate vaccine (PCV13) from extensive clinical trials in infants and children have been comprehensively reviewed.[4] By 2020, 159 countries had included a PCV in their NIPs.[5,6] PCV13 has been approved in Indonesia since 2011 for children aged 6 weeks to 5 years and adults aged more than 50 years.[7]

In 2017, the Indonesian Technical Advisory Group on Immunization recommended a vaccine safety monitoring project (demonstration program) in West Nusa Tenggara (i.e., West Lombok and East Lombok).[5,8] The Indonesian government includes hepatitis B, BCG, polio (oral poliovirus vaccine [OPV] and inactivated polio vaccine [IPV]), DTwP-HB-Hib, and measles vaccination in the NIP.[9] The schedule is a 2-dose primary series at 2 and 3 months of age, followed by a booster dose at 12 months. Within the NIP, the demonstration program studied a 2-dose PCV13 primary series associated with DTwP-HB-Hib and OPV. In 2018–2019, PCV13 introduction was expanded to Bangka Belitung (i.e., Pangkal Pinang, Bangka, and Center Bangka) and the remaining districts of West Nusa Tenggara (i.e., Center Lombok, North Lombok, and Mataram).[10,11] Monitoring was conducted between 2019 and 2021 to evaluate the impact of the provincial immunization program in West Nusa Tenggara, Bangka Belitung, and certain districts in West Java and East Java. As of 2022, PCV13 has been included in the Indonesian NIP.

Co-administration of PCV with other pediatric combination vaccines such as DTaP-HBV-IPV/Hib has been assessed. In a clinical study of infants vaccinated at 2, 3, and 4 months of age, mild fever (38.0–39.0°C) was reported at higher rates (ranging from 28.3–42.3%) among infants who received 7-valent pneumococcal conjugate vaccine (PCV7) concomitantly with DTaP-HBV-IPV/Hib compared with infants receiving DTaP-HBV-IPV/Hib alone (ranging from 15.6–32.1%). Fever >39.0°C occurred only in a few cases and to the same extent in both groups (PCV7 + DTaP-HBV-IPV/Hib: 0.8 to 1.7%; DTaP-HBV-IPV/Hib alone: 1.6–4.1%).[12] In another study, when PCV13 was administered concomitantly with DTaP-HBV-IPV/Hib, the rates of mild fever (38.0–39.0°C, ranging from 43.5–46.8%) were similar to those after the concomitant administration of PCV7 and DTaP-HBV-IPV/Hib (ranging from 36.6–48.4%). Moderate fever rates (39.0–40.0°C) were slightly higher in the PCV13 co-administration group (ranging from 3.7–8.8%) compared with the PCV7 group (ranging from 1.4–4.4%), but there were no high fevers (>40.0°C) in either group during the primary series.[13] In clinical trials involving concomitant administration of PCV13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed.[7]

The demonstration program sought to characterize the safety of PCV13 in the 2-dose primary series at 2 and 3 months of age. Based on community co-administration practices, children received either PCV13 + DTwP-HB-Hib + OPV, PCV13 + DTwP-HB-Hib, or PCV13 only. Local reactions and systemic events, adverse events, and serious adverse events (SAEs) were described after the first or second dose. This study aimed to evaluate whether immediate SAEs occurred within 30 min of receiving PCV13 vaccination as part of the primary series. Other objectives included evaluating local reactions or systemic events, adverse events, or SAEs observed within 28 days post-vaccination after either the first or second dose.

METHODS

This observational study recruited infants from primary healthcare centers. Although the schedule recommended PCV13 co-administration with DTwP-HB-Hib and OPV, infants in the demonstration program were administered PCV13 + DTwP-HB-Hib + OPV, PCV13 + DTwP-HB-Hib, or PCV13 at the time of the study team's visit based on the infant's immunization status for the other pediatric vaccines and parental consideration. Consequently, the vaccination group for each infant was not pre-planned, and the number of individuals per group was determined spontaneously. PCV13 was administered in the left leg and DTwP-HB-Hib vaccine in the right leg.[11]

Each 0.5 ml dose of PCV13 (Pfizer Inc., USA) contained 2.2 µg of pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F and 4.4 µg of pneumococcal polysaccharide serotype 6B. Each serotype was individually conjugated to CRM197 carrier protein and adsorbed on aluminum phosphate (0.125 mg aluminum).

For sample size calculation, an SAE rate of 2% was assumed; thus, with 1,100 infants enrolled, there was a 94% probability of observing the 95% confidence interval of the SAE rate with a precision (half-width) of ≤1%. No statistical analyses were performed among the co-administered vaccines received (PCV13 + DTwP-HB-Hib + OPV, PCV13 + DTwP-HB-Hib, or PCV13 only)

based on dose group (first or second dose) or time period (defined as within days 1–3, 4–7, and 8–28) and severity of outcome (mild, moderate, or severe) across local reactions (pain, redness, and swelling) or systemic events (fever or irritability). The Ethics Committee of the Faculty of Medicine, Universitas Indonesia granted the ethical approval (No: 0279/UN2.F1/ETIK/2018).

Enrollment and study procedures

Subjects were recruited from 10 primary healthcare centers in West Lombok (Narmada, Perampuan, Gerung, Gunung Sari, and Kediri) and East Lombok (Keruak, Lepak, Batuyang, Denggen, and Terara). Inclusion criteria were infants under the age of 6 months who received either a first dose (aged 2 months) or a second dose (aged 3 months) of the PCV13 primary series as part of the demonstration program, signed informed consent from the parents and/or legal guardian, and the ability and agreement of the parents and/or legal guardian to fill out the diary card. Exclusion criteria included immunocompromised patients with a known or suspected immunodeficiency or those receiving immunosuppressive therapy, such as cytotoxic agents or systemic corticosteroids (e.g., for cancer, HIV infection, or autoimmune disease).

At enrollment, the parents were provided with a diary and digital thermometer and trained on the prospective recording of local reactions, systemic events, adverse events, or SAEs in the diary card. Infants were evaluated for 30 min after vaccination for any immediate SAEs. Following immunization, the study team conducted follow-up visits on days 3 and 28. Diary cards were collected from the parents at the next visit to the primary healthcare center. The study team evaluated the subjects at home and recorded the relevant data from the diary card if the parents could not attend the follow-up visit.

An SAE was defined as any untoward medical occurrence at any dose that resulted in death or was life-threatening. The term "life-threatening" in the definition of "SAE" referred to an event in which the patient was at risk of death at the time of the event (it did not refer to an event, which hypothetically, might have caused death if it was more severe), which required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. A systemic event was defined as the occurrence of one or several symptom(s) (solicited or unsolicited) within 28 days of vaccination, namely fever (axillary temperature ≥38.0°C) and irritability. Fever was classified into three levels: mild (38.0–38.5°C), moderate (38.5–39.0°C), and severe (>39.0°C). The intensity of irritability was graded as mild (infant cried more than usual but at a normal pitch), moderate (unusual high-pitched crying), or severe (inconsolable crying lasting >3 hours). A local reaction was defined as the occurrence of one or more reactions (solicited or unsolicited) at the PCV13 vaccination site. Local pain, redness, swelling, and any other local reaction at the PCV13 vaccination site, were all monitored. The severity of local pain was classified into mild (reacted when the site was touched), moderate (cried when the site was touched), or severe (cried when the limb was moved). Redness and swelling were measured with a plastic bangle (gauge) and classified as mild (reaction completely contained within the smaller circle, <2.5 cm), moderate (largest diameter of the reaction included between the two circles, 2.5–5 cm), or severe (reaction beyond the largest circle, >5 cm).

Data analysis

For subjects who returned the diary card, descriptive analysis to determine the number and percentage of subjects that reported adverse events was conducted for each vaccination group (PCV13 + DTwP-HB-Hib + OPV, PCV13 + DTwP-HB-Hib, and PCV13 only). The results were collated from the returned diary cards, entered into a study database in Microsoft Excel, and analyzed using SPSS software version 15.0 (SPSS Inc., USA). It was then classified by severity (mild, moderate, or severe) and time period after PCV13 vaccination.

The local reactions and systemic events percentages were reviewed for the three vaccination groups based on dose and period and presented by severity within an outcome across both local reactions and systemic events (Table 1). Given that local reactions and systemic events occurred within days of vaccination, the systemic event or local reaction frequency curves were presented for the PCV13-only group by combining the results from the first dose with those of the second dose to provide insights into the patterns of daily local reactions and systemic event over the first 9 to 12 days (Figure 1). Daily results were presented graphically for local reactions and systemic events for the first 30 min, followed by the subsequent days until the percentage values for each of the three severity subcategories fell to 0%.

RESULTS

Of 1,100 subjects enrolled, 1,083 (98.5%) completed the dairy cards, and 17 did not. Safety was evaluated in 1,048 subjects, with 544 receiving PCV13 + DTwP-HB-Hib + OPV, 101 receiving PCV13 + DTwP-HB-Hib, and 403 receiving PCV13 only. On the other hand, there were 35 subjects excluded in the calculation of the local reactions and systemic events because they received other concomitant vaccines, namely PCV13 + BCG (n = 6), PCV13 + OPV (n = 4), and PCV13 + BCG + OPV (n = 25).

Among the 1,083 subjects, 687 received the first dose, and 396 received the second dose. The mean (range) age was 2.7 (2–7) months old in the first dose group and 3.8 (2–9) months old in the second dose group. Females accounted for 45.0% of the subjects in the first dose and 51.8% in the second dose groups. The mean (range) weights were 5.8 (2.2–9.8) kg and 6.4 (2.2–10.5) kg, respectively. In the first dose group, 34 subjects (4.9%) had a medical condition before enrollment, and 22 (3.2%) used concomitant drugs, while the percentages were higher in the second dose group (6.6% and 3.8%, respectively).

Local reactions

Local reactions predominated in days 1–3 in each vaccination group (Table 1). Local pain reports were distributed evenly across the mild, moderate, or severe categories, but it was more frequently reported after the first dose, compared with the second dose, whether

Table 1. Local reactions and systemic events in infants vaccinated by PCV13

Group	PCV13 + DTwP-HB-Hib + OPV						PCV13 + DTwP-HB-Hib						PCV13 only					
	First dose, % (N = 343)			Second dose, % (N = 201)			First dose, % (N = 51)			Second dose, % (N = 50)			First dose, % (N = 270)			Second dose, % (N = 133)		
Period, days	1–3	4–7	8–28	1–3	4–7	8–28	1–3	4–7	8–28	1–3	4–7	8–28	1–3	4–7	8–28	1–3	4–7	8–28
Local pain																		
Mild	27.7	0	0	4.5	0	0	15.7	0	0	12.0	0	0	28.9	0	0	4.5	1.5	0
Moderate	22.4	0	0	1.5	1.0	0	23.5	0	0	2.0	0	0	20.0	0	0	3.8	0	0
Severe	39.9	0	0	0.5	1.0	0	31.4	0	0	0	2.0	0	29.3	0	0	0.8	0	0
Any	90.1	0	0	6.5	2.0	0	70.6	0	0	14.0	2.0	0	78.1	0	0	9.0	1.5	0
Redness																		
Mild	58.0	0	0	53.2	0	0	37.3	0	0	56.0	0	0	33.3	0	0	43.6	0	0
Moderate	7.9	0	0	7.0	0	0	13.7	0	0	8.0	0	0	9.3	0	0	6.8	0	0
Severe	1.7	0	0	2.0	0	0	2.0	0	0	2.0	0	0	3.3	0	0	5.3	0	0
Any	67.6	0	0	62.2	0	0	52.9	0	0	66.0	0	0	45.9	0	0	55.6	0	0
Swelling																		
Mild	28.6	0	0	23.9	0	0	23.5	0	0	24.0	0	0	28.9	0	0	21.8	0	0
Moderate	5.5	0	0	5.0	0	0	11.8	0	0	10.0	0	0	8.5	0	0	7.5	0	0
Severe	1.5	0	0	2.0	0	0	0	0	0	0	0	0	2.2	0	0	3.0	0	0
Any	35.6	0	0	30.8	0	0	35.3	0	0	34.0	0	0	39.6	0	0	32.3	0	0
Fever																		
Mild	6.4	0.9	0	4.5	0	0	5.9	0	0	12.0	0	0	3.0	1.9	0	5.3	2.3	0
Moderate	5.5	0.9	0	1.5	1.5	0	0	0	0	2.0	0	0	4.1	0	0	3.8	0.8	0
Severe	0.3	0.6	0	0.5	1.0	0	0	2.0	0	0	2.0	0	1.5	0.4	0	0.8	0	0
Any	12.2	2.3	0	6.5	2.5	0	5.9	2.0	0	14.0	2.0	0	8.5	2.2	0	9.8	3.0	0
Irritability																		
Mild	50.7	0	0	50.2	0	0	33.3	0	0	46.0	0	0	38.1	0	0	36.8	0	0
Moderate	21.3	0	0	12.9	0	0	23.5	0	0	8.0	0	0	14.1	0	0	15.0	0	0
Severe	0.6	0	0	1.5	0	0	2.0	0	0	4.0	0	0	1.1	0	0	3.0	0	0
Any	72.6	0	0	64.7	0	0	58.8	0	0	58.0	0	0	53.3	0	0	54.9	0	0

DTwP-HB-Hib=pediatric pentavalent combination vaccine; OPV=oral poliovirus vaccine; PCV13=13-valent pneumococcal conjugate vaccine

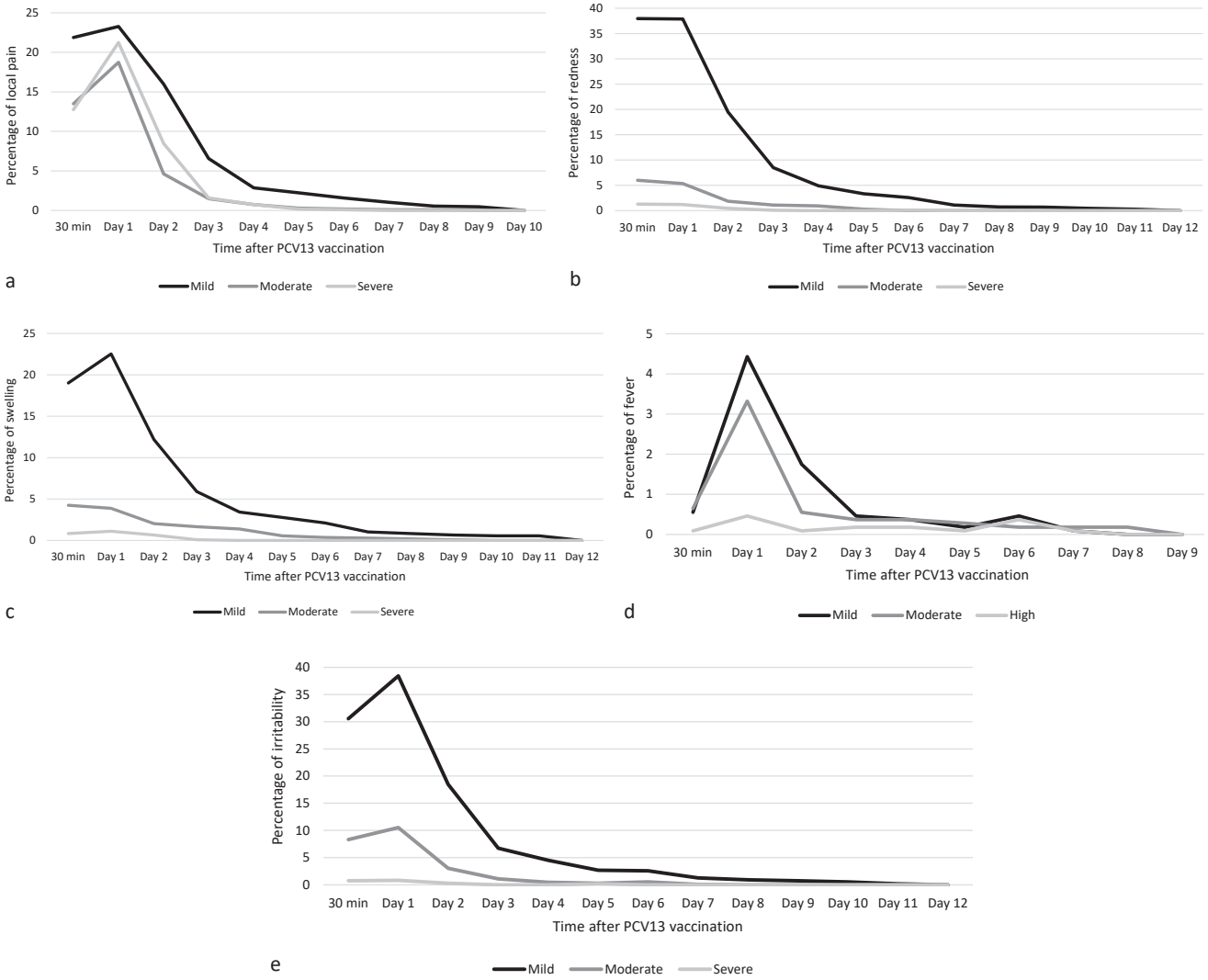

Figure 1. Proportion of subjects with reported local reactions and systemic events. (a) Local pain; (b) redness; (c) swelling; (d) fever; (e) irritability. Data from the PCV13-only vaccination group including the first and second doses (N = 403). PCV13=13-valent pneumococcal conjugate vaccine

for PCV13 + DTwP-HB-Hib + OPV (90.1% *versus* 6.5%), PCV13 + DTwP-HB-Hib (70.6% *versus* 14.0%), or PCV13 only (78.1% *versus* 9.0%). In the second dose group, any local pain continued to days 4–7, ranging from 1.5 to 2.0%, with similar proportions by severity (Table 1). In the daily reports for the PCV13-only group, local pain frequency was about 20% on day 1, regardless of severity, and decreased to <5% by days 3 and 4 (Figure 1a).

Redness and swelling were mostly mild to moderate, and the frequency was similar between the first and second doses in all concomitant vaccination groups (Table 1). Any redness was restricted to days 1–3, and there was a higher predominance after the second dose for PCV13 + DTwP-HB-Hib (52.9% after the first dose and 66.0% after the second dose) and PCV13 only (45.9% and 55.6%, respectively) (Table 1). In the daily reports (PCV13 only), mild redness was mostly observed within 30 min of immunization through day 1, persisting through days 7–9 in a small number of subjects, while moderate to severe redness resolved within 3 to 4 days (Figure 1b). Swelling was primarily observed within the first 3 days post-vaccination, with frequency rates of 35.3 to 39.6% after the first dose and 30.8 to 34.0% after the second dose. Most reports were classified as mild (21.8 to 28.9%) or moderate (5.0 to 11.8%), with severe swelling being reported infrequently whether after the first dose (0 to 2.2%) or the second dose (0 to 3.0%) (Table 1). Based on daily reports (PCV13 only), mild swelling declined from an initial peak within 30 min of immunization on day 1. Although a few subjects still experienced mild or

Table 2. Adverse events of PCV13 vaccine

Adverse events	First dose, % (N = 687)	Second dose, % (N = 396)	Total, % (N = 1,083)
Convulsion	0.1	0	0.1
Cough	1.6	1.5	1.6
Cough and diarrhea	0.1	0	0.1
Cough and runny nose	1.7	1.0	1.5
Cough, runny nose, and fatigue	0	0.3	0.1
Cough, runny nose, and itchiness	0.1	0	0.1
Diarrhea	1.2	2.0	1.5
Diarrhea and vomiting	0.3	0.3	0.3
Fatigue	0.1	0	0.1
Fatigue and runny nose	0.1	0	0.1
Runny nose	0.9	1.3	1.0
Runny nose and diarrhea	0.3	0	0.2
Vomiting	1.3	0.5	1.0
Total	8.0	6.8	7.6

moderate swelling up to 5–7 days after vaccination, no severe swelling was reported after days 2–3 (Figure 1c).

Systemic events

Almost all fevers were reported within the first 3 days post-vaccination, with a higher occurrence after the second dose in the PCV13 + DTwP-HB-Hib and PCV13-only groups, particularly in the PCV13 + DTwP-HB-Hib group, both in terms of frequency (14.0%) and severity (2% of infants, particularly on days 4–7) (Table 1). Severe fever was uncommon (≤2% of all infants) after the first or second dose and during days 1–3 or 4–7 (Table 1). Based on daily reports of the PCV13-only group, a peak in fever was noted on day 1, with no fever reported after day 8 (Figure 1d). Any irritability was commonly reported after the first dose (53.3 to 72.6%) or the second dose (54.9 to 64.7%). Mild to moderate irritability was common but only reported in days 1–3, and severe irritability was occasional (<4.0%) (Table 1). Based on daily reports (PCV13 only), mild and moderate irritability peaked on day 1 and subsided by day 7 (Figure 1e).

Adverse events and SAEs

Adverse events (frequency) included cough (1.6%), diarrhea (1.5%), and cough and runny nose (1.5%) (Table 2). No SAEs were reported in any of the three groups, either within 30 min after PCV13 vaccination or during the 28-day observation period.

DISCUSSION

PCVs are administered concurrently with other vaccines during infancy, primarily to facilitate new vaccine introduction and enhance uptake rates. In the Indonesia demonstration program, infants received either PCV13 + DTwP-HB-Hib + OPV (n = 544), PCV13 + DTwP-HB-Hib (n = 101), or PCV13 only (n = 403) depending on the community co-administration practices. Adverse events, including both local reactions and systematic events, were monitored for 28 days after vaccination. During the study period, no SAEs were found in any participants. The local and systemic reactions were consistent with the clinical trial data provided on the Indonesian National Regulatory Agency's approved product label, which describes injection site pain, redness, and swelling as very common (frequency ≥10%) reactions to PCV13 administration.[7]

A study of the safety profile after DTwP-HB-Hib vaccination in infants in West Nusa Tenggara, Bali, Yogyakarta, and West Java adopted a similar methodology, with a 3-dose primary series of vaccination. The proportion of patients experiencing local reactions, namely local discomfort (31.1%) or swelling (12.8%), was lower than in the PCV13 demonstration program.[14] As for systemic events, fever was observed in <10% of the subjects following DTwP-HB-Hib first or second dose, which is consistent with the PCV13 demonstration program; however, irritability (12.7%) was lower in the DTwP-HB-Hib study. Similar to the PCV13 demonstration program results, no SAEs were observed during the observation period.[14]

In the demonstration program, despite the high frequency of local pain after the first dose, other local reactions and systemic events were of lower frequency and milder intensity. Pain is notoriously difficult to describe, quantify, and standardize, particularly in children.[15] In preverbal children, pain is assessed by an adult observer based on a subjective interpretation of the child's behavioral responses.[15] While subjective interpretations in the first dose group would have been expected to lead to an equally high frequency of

reported pain from the second dose group, this was not observed. Likewise, though expectation might lead to a lack of objectivity, except for local pain, from the other local reactions or systemic events there was a comparable frequency of reported safety signals between the PCV13 first and second dose groups.

This study had several limitations. Subjects in the PCV13 first and second dose groups were different; thus, the after-vaccination responses might not be expected to be similar. The daily card report instructions were delivered by healthcare professionals with diverse backgrounds and experiences, which may have made reporting conformity difficult. Furthermore, this observational study did not perform statistical analyses between dose groups by outcome or intensity.

In conclusion, no SAEs were reported after the PCV13 first and second doses, and vaccination resulted in tolerable systemic events or local reactions. The demonstration program confirmed the safety of the primary series of PCV13 when administered to Indonesian infants according to the NIP schedule.

Conflict of Interest

The authors affirm no conflict of interest in this study. Mark Andrew Fletcher is a full-time employee of Pfizer Inc. and may hold stock or stock options.

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