Article

Not peer-reviewed version

# Safety and Immunogenicity of SII's 10-Valent Pneumococcal Conjugate Vaccine (PCV10-SII) in Vietnamese Children Aged from 6 Weeks to 24 Months: An Open-Label, Single-Arm Bridging Study

Vu Tung Son , Bui Dang The Anh , Vu Ngoc Hoan , Hoang Van Than , Bui Kim Linh , La Thi Huong Giang , Nguyen Tien Manh , Luong Thi Thu Thao , Hoang Xuan Cuong , Dao Truong Giang , Do Tuan Dat , Le Thi Huong Giang , Pham Van Hung *

Posted Date: 11 March 2026

doi: 10.20944/preprints202603.0834.v1

Keywords: PNEUMOSIL®; pneumococcal conjugate vaccines; Vietnam; vaccine safety; immunogenicity

*Article*

# Safety and Immunogenicity of SII's 10-valent Pneumococcal Conjugate Vaccine (PCV10-SII) in Vietnamese Children Aged from 6 weeks to 24 months: An Open-Label, Single-Arm Bridging Study

**Vu Tung Son [1], Bui Dang The Anh [1], Vu Ngoc Hoan [1], Hoang Van Than [1], Bui Kim Linh [1], La Thi Huong Giang [1], Nguyen Tien Manh [1], Luong Thi Thu Thao [1], Hoang Xuan Cuong [2], Dao Truong Giang [3], Do Tuan Dat [4], Le Thi Huong Giang [4] and Pham Van Hung [4,*]**

[1] Department of Military Epidemiology, Vietnam Military Medical University, Hanoi 100000, Vietnam
[2] Southern Branch, Vietnam Military Medical University (VMMU), Ho Chi Minh City 700000, Vietnam
[3] Department of Gastroenterology and Hepatology, Military Hospital 103, Vietnam Military Medical University, Hanoi, Vietnam
[4] The Company for Vaccine and Biological Production No.1 (VABIOTECH), Ministry of Health, Hanoi 100000, Vietnam
* Correspondence: hungpv@vabiotech.com.vn (P.V. Hung); Tel.: +84-24-3972-9166

**Abstract**

Background: Pneumococcal conjugate vaccines (PCVs) prevent severe disease in children, but high costs limit access. PNEUMOSIL®, a 10-valent PCV prequalified by World Health Organization (WHO) in 2019, offers a cost-effective alternative. This study assessed its safety and immunogenicity in Vietnamese children aged 6 weeks–24 months. Methods: An open-label, single-arm study enrolled 304 children in three age groups: 6 weeks–6 months (n=151), >6–12 months (n=76), and >12–24 months (n=77). Participants received two or three doses. Safety was evaluated through immediate reactions, adverse events (AEs), serious adverse events (SAEs), and withdrawals. Immunogenicity was measured 28 days after the final dose using serotype-specific IgG geometric mean concentrations (GMCs), opsonophagocytic activity (OPA) titers, and seroresponse rates. The trial was approved by the IRB of the National Ethics Council (code: No. 75/CN-HĐĐĐ on date June 4th, 2021) and was registered with ClinicalTrials.gov, NCT05140720. Results: Of 304 enrolled participants, 294 (96.7%) completed follow-up. No immediate adverse events or serious adverse events occurred. Unsolicited adverse events were reported in 17%, mainly respiratory, while serious adverse events occurred in 4%. Mild local/systemic reactions (e.g., injection site pain, crying) resolved without sequelae. Immunogenicity was strong, with GMCs 1.8–9.11 μg/mL, GMTs 277.8–22,342, and >90% achieving seroresponse for all 10 serotypes. Conclusions: PNEUMOSIL® demonstrated favorable safety and robust immunogenicity, supporting its inclusion in national immunization programs as an affordable option for pneumococcal disease prevention.

**Keywords:** PNEUMOSIL®; pneumococcal conjugate vaccines; Vietnam; vaccine safety; immunogenicity

## 1. Introduction

*Streptococcus pneumoniae* (pneumococcus) is a major cause of disease worldwide, ranging from conditions such as otitis media, sinusitis, and bronchitis—which may vary from mild to severe—to life-threatening illnesses including pneumonia, bacteremia, and meningitis, particularly in children under one year of age [1]. *S. pneumoniae* is one of the leading causes of morbidity and mortality globally, is particularly dangerous for children in low- and middle-income countries [2–4]. As of now,

 doi:10.20944/preprints202603.0834.v1



vaccination remains an effective strategy in reducing both morbidity and mortality caused by pneumococcus [5].

The first Pneumococcal Vaccines, which included antibodies to 14 capsular antigenic serotypes, was approved for use in 1977, followed by the 23-valent vaccine (PPSV23) in 1983. PPSV23 remains widely used in adults, but its poor immunogenicity in infants under 2 years of age necessitated the development of pneumococcal conjugate vaccines (PCVs). PCVs such as PCV7, have been developed to address the requirement of protection against pneumococcal diseases, particularly in infants and children [6].

Currently, three PCVs are widely used worldwide The 13-valent PCV (PCV13, Prevenar 13®, Pfizer) includes the ten serotypes in PCV10, along with serotypes 3, 6A and 19A. The 10-valent PCV (PCV10, Synflorix®, GSK Vaccines) provides protection against serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F. In addition, PCV10-SII (PNEUMOSIL), developed by the Serum Institute of India, covers serotypes 1, 5, 6B, 7F, 9V, 14, 19F, and 23F as in Synflorix, but also includes serotypes 6A and 19A, similar to Prevenar 13. It is now registered in over 64 countries worldwide. More recently, PCV15 [7], PCV20 [8] and PCV 21 have been introduced, futher expanding serotype coverage and offering broader protection.

In low-income and middle-income countries, PCV10 and PCV13 are gradually being introduced into routine vaccination programmes with support from Gavi.

However, a domestic vaccine for preventing pneumococcal diseases has not yet been produced in Vietnam, and the PCVs have not been incorporated into the national expanded programme on immunization. The vaccines currently available for preventing pneumococcal disease in Vietnam are PCV10 (Synflorix, GlaxoSmithKline), PCV13 (Prevenar13, Pfizer), PCV20 (Prevnar 20, Pfizer), and PPSV23 (Pneumo 23). Researching and developing an affordable PCV10 vaccine will contribute to increasing prevention options for individuals at a heightened risk of disease, particularly among children under 2 years old.

PNEUMOSIL® (PCV10-SII) developed by the Serum Institute of India, is a WHO-prequalified, cost-effective vaccine that includes serotypes 6A and 19A in addition to the ten serotypes covered by Synflorix. This makes it comparable to PCV13 in coverage while remaining affordable for low- and middle-income countries[9]. Despite the availability of PCVs in Vietnam, they have not yet been incorporated into the national immunization program, and no domestically produced pneumococcal vaccine exists. Therefore, evaluating the safety and immunogenicity of PNEUMOSIL® in Vietnamese children is essential to support its potential inclusion in national immunization strategies.

## 2. Materials and Methods

### *2.1. Study Design*

This was an open-label, single-arm bridging study conducted from June 2021 to June 2023 at Dong Hung ward, Hung Yen province - a rural site located in the North of Vietnam.

The study complied with the Declaration of Helsinki, the protocol, good clinical practices and ethical guidelines for biomedical research on human participants (Viet Nam Council of Medical Research, 2013). The trial was registered with Clinical Trials (NCT05140720). And the trial was approved by Institutional Ethics Committees within Vietnam's Ministry of Health (code: No. 75/CN-HĐĐĐ on date June 4th, 2021). Each participant's legal representative provided written informed consent before study participation.

### *2.2. Participants*

Eligible subjects included Vietnamese healthy children aged of either gender from 6 weeks to 24 months. Exclusion criteria comprised prior receipt of any pneumococcal vaccine, culture-confirmed pneumococcal disease, immunodeficiency, or a documented history of hypersensitivity to any investigational vaccine component. Participants were also excluded if they had received another vaccine, serum, or blood product within the preceding 30 days; presented with a body temperature

 doi:10.20944/preprints202603.0834.v1



≥37.0 °C or any acute infection; had received immunomodulating agents within the past six months; or were undergoing concomitant treatment with antimalarial drugs. For administration of the second and third doses, exclusion criteria additionally included the occurrence of any serious adverse event related to the study vaccination protocol or the emergence of any new condition meeting the initial exclusion criteria.

### *2.3. Vaccination Process*

In this study, a 0.5 mL dose of the SIIPL-PCV (PNEUMOSIL®) vaccine, lot numbers 2082Y001A and 2092Y001C, was administered. The vaccination regimen followed the dosing schedule approved by the World Health Organization (WHO) as part of the prequalification process. Prior to implementation, the dose and regimen were reviewed and approved by the Ministry of Health of Vietnam. All vaccinations were conducted under the supervision of trained healthcare professionals in a controlled clinical setting.

### *2.4. Clinical Trial Objectives and Endpoints*

The primary objective of the study was to characterize the safety profile of PNEUMOSIL® in enrolled participants. Safety endpoints included: (i) the proportion and severity of immediate adverse events occurring within 30 minutes after vaccine administration; (ii) the proportion and severity of solicited local and systemic adverse reactions during the first 7 days post-vaccination; and (iii) the proportion and severity of unsolicited adverse events and serious adverse events (SAEs) throughout the study period. Participant compliance with study procedures was also monitored.

Immunogenicity was assessed by pneumococcal serotype-specific immune response 28 days after the last dose of PNEUMOSIL®. The first endpoints were the proportion of participants with seroresponse (serotype-specific IgG concentrations ≥ 0.35 μg/mL or OPA titer ≥ 1:8). The second endpoints were geometric mean concentrations and titres (GMC and GMT) measured 28 days after the last vaccination.

### *2.5. Follow-Up and Data Collection*

Participants meeting the inclusion criteria and without any exclusion criteria were enrolled and randomized by investigators to receive PNEUMOSIL®. Following enrolment, baseline demographic characteristics—including date of birth, sex, weight, and height—were collected using a standardized questionnaire completed by the study physician. Prior to vaccination, each child's medical history was reviewed and a physical examination was performed to exclude contraindications to immunization.

Participants were stratified into three age groups. Infants aged 6 weeks to 6 months received three doses of PNEUMOSIL®. Children aged >6 to 12 months received two doses administered at a 1-month interval. Children aged >12 to 24 months received two doses administered at a 2-month interval.

Blood samples were collected prior to vaccination and 28 days after the final dose. Samples were stored and transported at 2–8 °C. Serum concentrations of anticapsular immunoglobulin G (IgG) against the 10 pneumococcal serotypes included in PNEUMOSIL® were quantified using enzyme-linked immunosorbent assay (ELISA) at the Murdoch Children's Research Institute, Australia. Functional immune responses were assessed using a four-fold multiplexed opsonophagocytic assay (OPA) [10,11]. Seroresponse was defined as an IgG concentration ≥0.35 μg/mL, a threshold associated with protection against invasive pneumococcal disease (IPD) in infants; functional seroresponse was defined as a reciprocal OPA titer ≥8 [12,13]. Clinical data management and statistical analyses were performed by VietStar Biomedical Research.

 doi:10.20944/preprints202603.0834.v1



*2.6. Safety Assessment*

All participants were monitored for safety from the administration of the first dose until 28 days after the final vaccination. Adverse events (AEs) were documented throughout this period. Immediately following each vaccination, participants were observed for 30 minutes to identify any acute reactions. Participants aged >6 months to ≤24 months attended three scheduled clinic visits, whereas those aged 6 weeks to 6 months attended four visits. A visit window of ±2 weeks was permitted. At each visit, participants underwent a physical examination, and parents or guardians were interviewed regarding adverse events and concomitant medication. Parents or guardians were instructed to report any serious adverse event (SAE) to the investigator without delay.

Injection-site and systemic reactogenicity was solicited in clinic at 30 minutes post-vaccination and daily for 7 days thereafter, with severity graded on a four-point scale according to protocol definitions. Any reactogenicity persisting beyond the follow-up period was documented as an unsolicited adverse event (AE) and monitored accordingly. Unsolicited AEs were recorded from the time of consent until 28 days after vaccination. All adverse events were categorized using MedDRA version 25.1 and graded for severity (mild, moderate, severe, or life-threatening) based on pre-specified definitions. All solicited local and systemic adverse events were presumed to be vaccine-related. Causality assessment of unsolicited AEs was performed by investigators using clinical judgment, with classification as very likely/certain, probable, possible, unlikely, unrelated, or unclassifiable.

Health staff received training in the documentation of solicited adverse events, unsolicited adverse events, and serious adverse events (SAEs). Measuring scales were provided within a structured diary to facilitate standardized recording. Detailed safety information for each AE was collected through subject diary cards and supplemented by telephone contact with study staff. All safety data were reviewed at each scheduled visit.

Serious adverse events (SAEs) were reported to the Institutional Ethics Committees and reviewed by an independent Data and Safety Monitoring Board within the stipulated timelines. All medical expenses and hospital visits related to SAEs were covered by the study sponsor.

*2.7. Immunogenicity Assessment*

The evaluable immunogenicity population comprised eligible participants who received all assigned vaccinations, provided blood samples within the required time frames, had at least one valid and determinate assay result for the planned analyses, did not receive prohibited vaccines, and had no major protocol violations. Pneumococcal serotype-specific IgG geometric mean concentrations (GMCs) were calculated for each age group, together with associated 95% confidence intervals (CIs). For each serotype, exact unconditional two-sided 95% CIs were determined. The proportions of participants achieving prespecified IgG concentrations 28 days after the final dose were also evaluated with 95% CIs; these thresholds were defined according to serotype-specific values previously established by ELISA. Opsonophagocytic assay (OPA) geometric mean titers (GMTs) were summarized in a manner analogous to IgG GMCs.

*2.8. Statistical Analysis*

Descriptive statistics were applied to summarize demographic characteristics, seroconversion rates, and adverse events. Geometric mean concentrations (GMCs) and geometric mean titers (GMTs) were reported together with standard deviations (SDs) and 95% CIs. Statistical significance of changes in GMCs and GMTs from baseline was assessed using paired t-tests, with p-values $<0.05$ considered significant. All analyses were performed using SAS® software, version 9.4.

 doi:10.20944/preprints202603.0834.v1



## 3. Results

### *3.1. Study Participants*

Overall, 312 participants were screened, of whom 304 were eligible and enrolled; all 304 (100%) received at least one dose of vaccine. Across age groups, completion of all planned doses was achieved by 95.3% of participants aged 6 weeks to 6 months (three-dose schedule) and 98.0% of participants aged >6 to 24 months (two-dose schedule). In total, 294 participants (96.7%) were included in the follow-up analysis conducted 28 days after the final vaccination. The common reasons for exclusion are presented in Figure 1. Baseline demographic characteristics were comparable across age groups (Table 1), with additional demographic breakdowns also provided in Table 1.

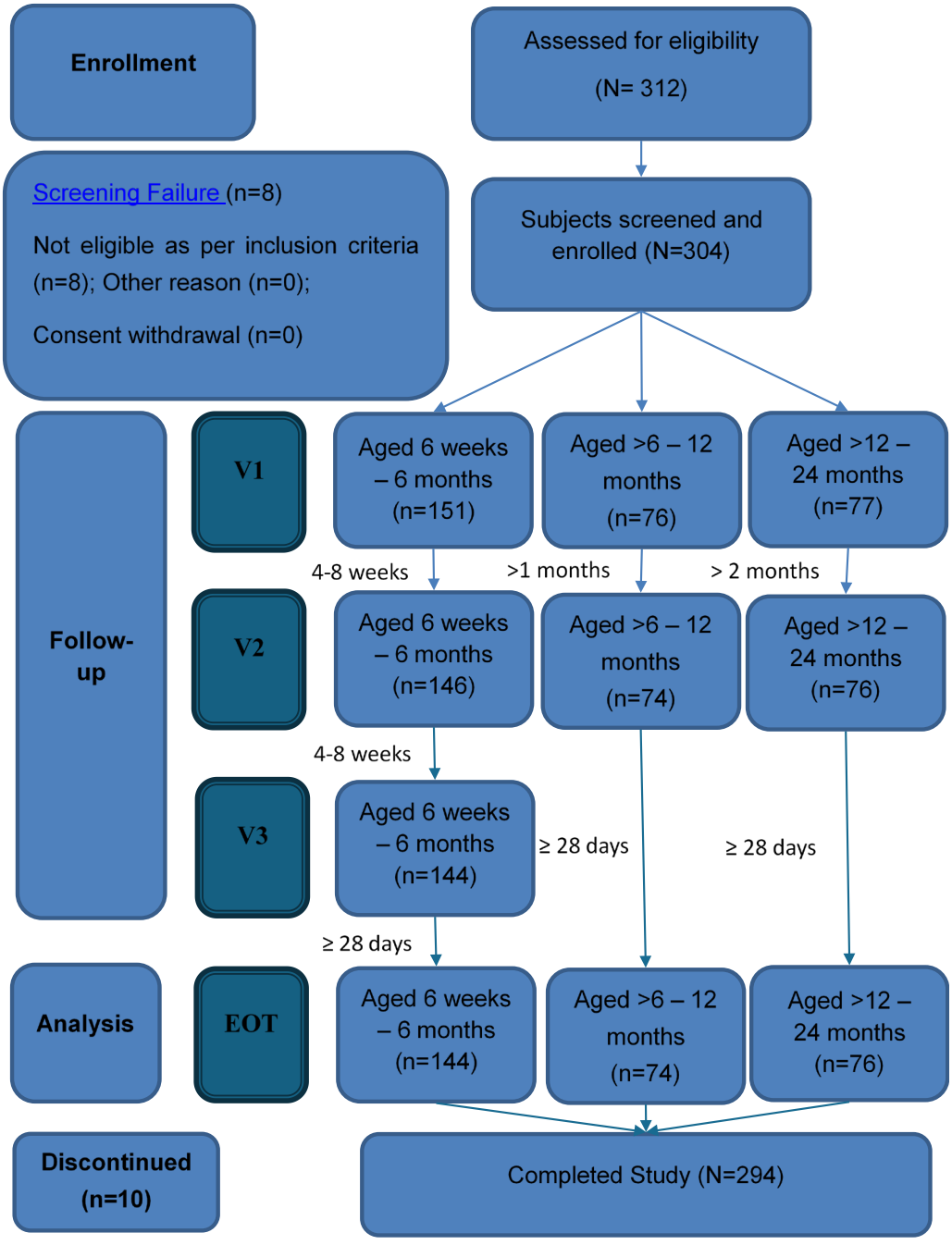



**Figure 1.** Enrollment flow chart.

 doi:10.20944/preprints202603.0834.v1



No significant differences in demographic characteristics were observed among the three study groups. Increases in height and weight were consistent with expected developmental progress. By study completion, 10 of 304 participants (3.3%) had discontinued participation, primarily due to personal circumstances or loss to follow-up. Notably, no participant withdrew because of safety concerns related to the investigational product. At enrollment, all participants underwent clinical examination by the investigator, and no significant abnormal findings were detected.

**Table 1.** Demographic characteristics of Enrolled Participants (n=304).

| Characteristics | Group 66. | Group >6 to 12 months (n=76) | Group >12 to 24 months (n=77) |
|---|---|---|---|
| **Age (days) (n=304)** | | | |
| Mean (SD) | 98.01 (42.92) | 291.39 (42.68) | 541.75 (102,00) |
| Median | 99.00 | 293.00 | 537.00 |
| Min- Max | 44.00 – 179.00 | 193.00 – 359.00 | 371.00 – 758.00 |
| **Gender (%)** | | | |
| Male | 84 (55.63%) | 32 (42.11%) | 38 (49.35%) |
| Female | 67 (44.37%) | 44 (57.89%) | 39 (50.65%) |
| **Weight, kg (n=304)** | | | |
| Mean (SD) | 6.29 (1.09) | 8.49 (0.97) | 10.28 (1.46) |
| **Height, cm (n=304)** | | | |
| Mean (SD) | 60.83 (4.08) | 70.92 (2.84) | 79.54 (4.35) |
| **Discontinued** (10/304) | | 3.3% | |

*3.2. Safety*

*Adverse events immediately during 30 minutes after taking the vaccine:*

No expected or unexpected adverse events, including serious adverse events (SAEs), were observed within 30 minutes of vaccine administration at any study visit.

*Adverse events during 7 days period after each of the three-dose visit:*

**Table 2.** Adverse events assessed to be probably possibly or remotely related to investigational product administration during the 7-day period following each of the three scheduled doses, stratified by age group.

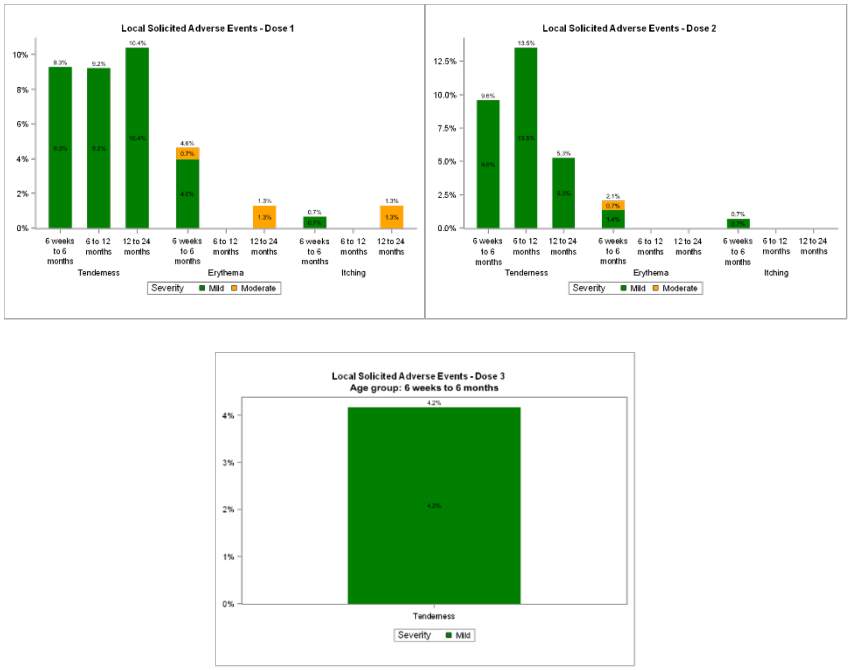
| | 6 weeks – 6 months group (n=151) | | | > 6 – 12 months group (n=76) | | > 12 – 24 months group (n=77) | |
|---|---|---|---|---|---|---|---|
| **Adverse event** | **After the first time visit (n=151)** | **After the second time visit (n=146)** | **After the third time visit (n=144)** | **After the first time visit (n=76)** | **After the second time visit (n=74)** | **After the third time visit (n=77)** | **After the second time visit (n=76)** |
| *Local ADEs* | | | | | | | |
| **Tenderness** | 14 (9.27) | 14 (9.59) | 6 (4.17) | 7 (9.21) | 10 (13.51) | 8 (10.39) | 4 (5.26) |
| **Erythema** | 7 (4.64) | 3 (2.05) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.29) | 0 (0.0) |
| **Itching** | 1 (0.66) | 1 (0.68) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.29) | (0.0) |
| *Systemic ADEs* | | | | | | | |
| **Fever** | 4 (2.64) | 1 (0.68) | 4 (2.78) | 3 (3.95) | 2 (2.7) | 1 (1.29) | 2 (2.64) |
| **Anorexia** | 1 (0.66) | 0 (0.0) | 2 (1.39) | 1 (1.32) | 2 (2.7) | 0 (0.0) | 0 (0.0) |
| **Crying** | 17 (11.26) | 9 (6.16) | 8 (5.6) | 4 (5.26) | 11 (14.86) | 6 (7.79) | 3 (3.95) |

 doi:10.20944/preprints202603.0834.v1



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Fussiness** | 0 (0.0) | 0 (0.0) | 1 (0.69) | 0 (0.0) | 1 (1.35) | 0 (0.0) | 0 (0.0) |
| **Fatigue** | 1 (0.66) | 0 (0.0) | 1 (0.69) | 0 (0.0) | 0 | 0 (0.0) | 0 (0.0) |
| **GI disorders** | 1 (0.66) | 0 (0.0) | 2 (1.39) | 0 (0.0) | 1 (1.36) | 0 (0.0) | 0 (0.0) |

**A**




**B**

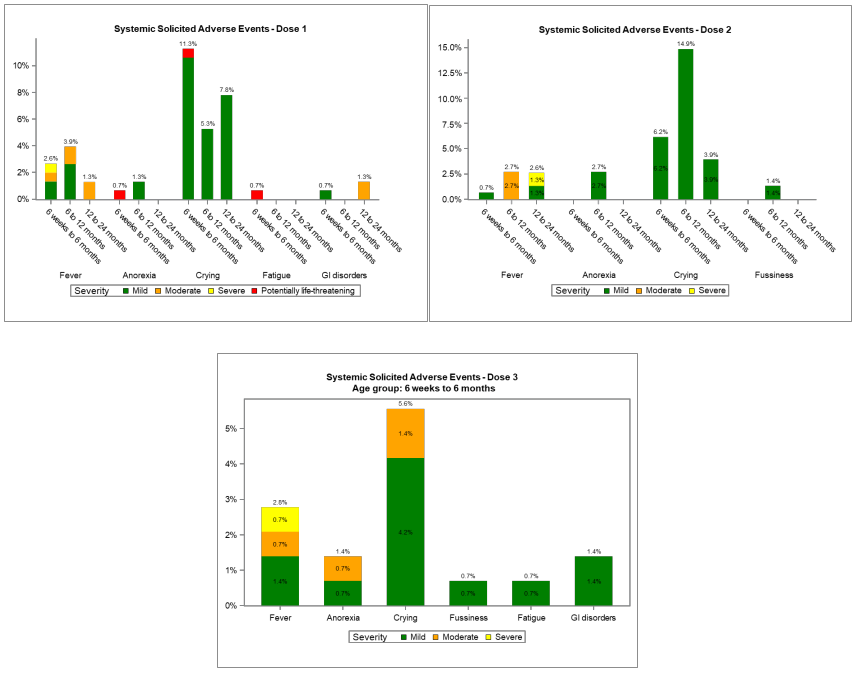



**Figure 2.** Percentages of participants with reported (A) local reactions and (B) systemic events following each vaccine dose.

 doi:10.20944/preprints202603.0834.v1



For dose 1, n = 304. For dose 2, n= 296. For dose 3, n = 144. The n values represent the number of participants with any diary data reported after the specified dose. Severity of adverse events was graded by parents or legal guardians according to instructions provided by the investigator staff: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and potentially life-threatening (Grade 4). For redness and swelling, grading was based on the description of the affected area. For pain and all systemic events, grading was determined by the extent to which the event interfered with daily activity. Fever severity was classified by temperature range: mild (38.0–38.4 °C), moderate (38.5–38.9 °C), severe (>39–40 °C), and potentially life-threatening (>40 °C)

Overall, the frequency and severity of local reactions demonstrated a slight decrease with subsequent doses. Local reactions persisted for a median duration of 1.0–2.0 days after each dose and were predominantly mild or moderate in intensity. Severe local reactions were uncommon, occurring in ≤1.3% of participants (n = 0–1 per age group) following each dose. The most frequently reported local adverse event within 7 days of vaccination was tenderness, which occurred at a low rate (<10%).

Similar proportions of participants across age groups reported systemic adverse events. The majority of systemic events were mild or moderate in severity, while severe systemic events occurred in ≤1.3% of participants after each dose. The most frequently reported systemic adverse event within 7 days of vaccination was crying, which was observed at a low rate (<10%). Fever >39 °C was reported in ≤0.7% of participants after each dose, and no cases of fever >40 °C were observed. Individual systemic events persisted for a median duration of 1.0–2.0 days.

A total of 75 unsolicited AEs were reported among the 52 participants. AEs were reported for 31 participants in the 6 weeks to 6 months age groups, 11 participants in the >6 to 12 months, and 10 participants in the >12 to 24 months. Most of AEs was belong to the infection and infestation. The majority of AEs were mild (n=26) or moderate (n=24) in severity; and all were resolved without any sequelae. There were only 2 unsolicited AEs (gastrointestinal disorders) considered to be unlikely related to PNEUMOSIL.

SAEs were reported in 12 participants. These included infection and infestations; bronchitis; gastrointestinal infection; influenza, and pneumonia. Most of SAEs were of moderate and severe intensity. The majority were unrelated to study vaccines. One SAE (influenza) was considered unlikely related to PNEUMOSIL. No death occurred during the study.

### *3.3. Immunogenicity*

**Serotype-Specific IgG Concentrations**

It can be seen that 28 days after the final dose of study vaccine, at least 90% of participants across all age group achieved a detectable IgG concentrations ≥ 0.35 µg/ mL for all vaccine pneumococcal serotypes, with the exception of serotype 6A (85.71%) and serotype 9V (88.57%) in > 6 – 12 months age group, and serotype 6B, which showed 80% seroprotection in the 6 weeks – 6 months group and 85.71%> 6 – 12 months age group (and respectively). However, the sero-response rate in the general population exceeded 90% of subjects achieving an IgG concentration ≥ 0.35 µg/mL for all serotypes, except for serotype 6B, which had a slightly lower rate of 88.57% (Table 3).

**Table 3.** Sero-response rate within IgG by ELISA 28 days after last vaccination.

| Serotype | 6 weeks – 6 months (n=35) n (%) [95% CI] | Aged group > 6 – 12 months (n=35) n (%) [95% CI] | > 12 – 24 moths (n=35) n (%) [95% CI] | Total (n= 105) n (%) [95% CI] |
|---|---|---|---|---|
| **1** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **5** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **6A** | 33 (94.29%) [78.65 % - 99.30%] | 30 (85.71%) [68.77% - 95.19%] | 35 (100.0%) | 98 (93.33%) [86.37% - 97.28%] |
| **6B** | 28 (80.00%) [62.39 % - 91.56%] | 30 (85.71%) [68.77% - 95.19%] | 35 (100.0%) | 93 (88.57%) [80.64% - 93.95%] |

 doi:10.20944/preprints202603.0834.v1



| Serotype | 6 weeks – 6 months (n=35) n (%) [95% CI] | Aged group > 6 – 12 months (n=35) n (%) [95% CI] | > 12 – 24 moths (n=35) n (%) [95% CI] | Total (n= 105) n (%) [95% CI] |
|---|---|---|---|---|
| **7F** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105(100.0%) |
| **9V** | 32 (91.43%) [75.38 % - 98.20%] | 31 (88.57%) [72.06% - 96.80%] | 34 (97.14%) [81.35% - 99.93%] | 97 (92.38%) [85.20% - 96.65%] |
| **14** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **19A** | 33 (94.29%) [78.65% - 99.30%] | 35 (100.0%) | 35 (100.0%) | 103 (98.10%) [92.34% - 99.77%] |
| **19F** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **23F** | 33 (94.29%) [78.65% - 99.30%] | 34 (97.14%) [81.35% - 99.93%] | 35 (100.0%) | 102 (97.14%) [91.17% - 99.41%] |

At 28 days after the last vaccination, over 97% of participants in each serotypes across all age groups achieved seroresponse with evaluation of OPA titers (reciprocal OPA titer ≥ 8) except serotype 6B in the 6 weeks – 6 months age group (94,29%) (Table 4).

**Table 4.** Response rate within OPA titers 28 days after last vaccination.

| Serotype | 6 weeks – 6 months (n=35) n (%) [95% CI] | Aged group > 6 – 12 months (n=35) n (%) [95% CI] | > 12 – 24 moths (n=35) n (%) [95% CI] | Total (n= 105) n (%) [95% CI] |
|---|---|---|---|---|
| **1** | 34 (97.14%) [81.35 % - 99.93%] | 35 (100.0%) | 34 (97.14%) [81.35 % - 99.93%] | 103 (98.10%) [92.34% - 99.77%] |
| **5** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **6A** | 35 (100.0%) | 34 (97.14%) [81.35% - 99.93%] | 35 (100.0%) | 104 (99.05%) [93.27% - 99.98%] |
| **6B** | 33 (94.29%) [78.65 % - 99.30%] | 34 (97.14%) [81.35% - 99.93%] | 34 (97.14%) [81.35 % - 99.93%] | 101 (96.19%) [89.96% - 98.95%] |
| **7F** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **9V** | 35 (100.0%) | 34 (97.14%) [81.35% - 99.93%] | 35 (100.0%) | 104 (99.05%) [93.27% - 99.98%] |
| **14** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **19A** | 35 (100.0%) | 35 (100.0%) | 35 (100.0%) | 105 (100.0%) |
| **19F** | 34 (97.14%) [81.35% - 99.93%] | 35 (100.0%) | 34 (97.14%) [81.35% - 99.93%] | 103 (98.10%) [92.34% - 99.77%] |
| **23F** | 35 (100.0%) | 34 (97.14%) [81.35% - 99.93%] | 35 (100.0%) | 104 (99.05%) [93.27% - 99.98%] |

For all 10 serotypes, IgG GMCs measured 28 days after the last vaccination were generally similar across age groups and exeeded 1 μg/mL, with highest levels observed for serotype 14. GMCs range from 1.41 to 8.67 μg/mL for participants in 6 weeks - 6 months age group, from 1.3 to 7.97 μg/mL for participants in > 6 - 12 months age group and from 2.52 to 12.8 μg/mL for participants in > 12 - 24 months age group (Table 5).

**Table 5.** Pneumococcal IgG GMCs (μg/mL) 28 days after last vaccination.

| Serotype | 6 weeks – 6 months (n=35) GMC (95% CI) | Aged group > 6 – 12 months (n=35) GMC (95% CI) | > 12 – 24 moths (n=35) GMC (95% CI) | Total (n=103) GMC (95% CI) |
|---|---|---|---|---|
| **1** | 6.81 (5.14 – 9.01) | 5.28 (4.07 – 6.86) | 4.03 (2.95 – 5.51) | 5.25 (4.45 - 6.19) |

 doi:10.20944/preprints202603.0834.v1



| Serotype | 6 weeks – 6 months (n=35) GMC (95% CI) | Aged group > 6 – 12 months (n=35) GMC (95% CI) | > 12 – 24 moths (n=35) GMC (95% CI) | Total (n=103) GMC (95% CI) |
|---|---|---|---|---|
| **5** | 2.39 (1.86 – 3.06) | 2.69 (2.16 – 3.36) | 2.52 (2.00 – 3.18) | 2.53 (2.22 - 2.89) |
| **6A** | 2.99 (1.97 – 4.55) | 1.58 (1.04 - 2.38) | 5.90 (3.98 – 8.73) | 3.03 (2.36 - 3.89) |
| **6B** | 1.41 (0.87 – 2.29) | 1.74 (1.17 – 2.58) | 6.00 (4.15 – 8.66) | 2.45 (1.88 - 3.19) |
| **7F** | 4.45 (3.29 – 6.03) | 5.02 (4.14 – 6.10) | 4.6 (3.31 – 6.40) | 4.69 (4.00 - 5.49) |
| **9V** | 1.75 (1.23 – 2.49) | 1.3 (0.88 – 1.91) | 2.56 (1.91 – 3.44) | 1.80 (1.47 - 2.20) |
| **14** | 8.67 (5.86 – 12.82) | 6.82 (5.03 – 9.25) | 12.8 (9.03 – 18.14) | 9.11 (7.45 - 11.15) |
| **19A** | 1.97 (1.42 – 2.73) | 3.29 (2.49 – 4.36) | 6.27 (4.61 – 8.54) | 3.44 (2.83 - 4.17) |
| **19F** | 7.58 (5.32 – 10.80) | 7.97 (5.98 – 10.63) | 10.83 (7.14 – 16.42) | 8.68 (7.10 - 10.62) |
| **23F** | 2.65 (1.8 – 3.91) | 2.87 (2.00 – 4.14) | 5.52 (4.06 – 7.51) | 3.48 (2.83 - 4.28) |

Opsonophagocytic assay (OPA) titers were determined in a subset of participants for each pneumococcal serotype to confirm the functional activity of PCV10-elicited immune responses. At 28 days after the final vaccination, OPA geometric mean titers (GMTs) for the 10 serotypes were largely comparable between participants aged 6 weeks to 6 months and those aged >6 to 12 months (Table 4). In contrast, GMTs across all 10 serotypes were higher in the >12 to 24 months age group following the last dose (Table 6).

**Table 6.** Pneumococcal OPA GMTs 28 days after last vaccination.

| Serotype | 6 weeks – 6 months (n=35) GMT (95% CI) | Aged group > 6 – 12 months (n=35) GMT (95% CI) | > 12 – 24 moths (n=35) GMT (95% CI) | Total (n=105) GMT (95% CI) |
|---|---|---|---|---|
| **1** | 209.4 (137.1 – 319.9) | 306.2 (208.9 – 449.0) | 334.2 (201.0 – 555.6) | 277.8 (216.5 - 356.4) |
| **5** | 656.5 (470.7 – 915.8) | 716.5 (528.0 – 972.4) | 1119 (830.9 – 1507) | 807.4 (674.4 - 966.7) |
| **6A** | 3219 (2277 –4551) | 2707 (1526 – 4802) | 8527 (6177 – 11771) | 4204 (3245 - 5446) |
| **6B** | 2272 (1112 – 4641) | 2267 (1299 – 3953) | 4913 (2723 - 8864) | 2935 (2058 - 4188) |
| **7F** | 22979 (17089 – 30901) | 12618 (9161 – 17381) | 38463 (27822 – 53174) | 22342 (18363 - 27184) |
| **9V** | 1077 (778.6 – 1489) | 1935 (1094 – 3424) | 5503 (4202 – 7207) | 2255 (1733 - 2935) |
| **14** | 9485 (6321 – 14231) | 7706 (5230 – 11356) | 21745 (16134 – 29307) | 11670 (9342 - 14579) |
| **19A** | 587.3 (435.1 – 792.6) | 1229 (858.7 – 1759) | 1535 (1164 – 2025) | 1035 (853.7 - 1254) |
| **19F** | 5277 (2959 – 9408) | 2645 (1719 – 4068) | 6898 (3536 – 13456) | 4583 (3307 - 6351) |

 doi:10.20944/preprints202603.0834.v1



| Serotype | Aged group<br>6 weeks – 6 months<br>(n=35)<br>GMT (95% CI) | > 6 – 12 months<br>(n=35)<br>GMT (95% CI) | > 12 – 24 moths<br>(n=35)<br>GMT (95% CI) | Total<br>(n=105)<br>GMT (95% CI) |
|---|---|---|---|---|
| **23F** | 8825<br>(6548 – 11894) | 4210<br>(2293 – 7728) | 16247<br>(11878 – 22222) | 8451<br>(6496 - 10995) |

## 4. Discussion

This study provides safety and immunogenicity data on SIIPL-PCV, a 10-valent pneumococcal conjugate vaccine formulated with serotypes selected to maximize coverage against pneumococcal disease in Vietnam. In addition, the findings offer preliminary evidence to support the co-administration of SIIPL-PCV within the vaccine registration process in Vietnam.

PNEUMOSIL® was well tolerated in all study participants. Local reaction and systemic events were mostly mild or moderate, transient in nature, and did not increase in frequency with subsequent doses. Within age groups, tenderness was the most common solicited local symptom, with crying as the most common solicited system symptom; these were mild to moderate in severity, self-limited, and considered related to PNEUMOSIL®. Reports of severe in severity solicited symptoms were infrequent. AEs occurred at similar frequencies across groups and reflected common medical events or conditions for this age range. The incidence of local and systemic AEs was notable lower compared with findings from other studies of the same vaccine [14].

12 participants reported SAEs, only 1 of which was considered unlikely related to the vaccine (influenza). During this study period, which coincided with seasonal transitions in Vietnam, most participants hospitalization were diagnosed with pneumonia. This trend can be attributed to the vulnerability of children aged 6 to 24 months, who are particularly susceptible to progressing from rhinopharyngitis to pneumonia during this time. There were no study withdrawals; no protocol violations were reported.

A small proportion of study participants experienced unexpected adverse events (AEs); however, the majority of unsolicited AEs were considered unrelated to PNEUMOSIL®. Notably, only two unsolicited AEs—both gastrointestinal disorders—were assessed as unlikely to be related to PNEUMOSIL®, primarily due to their onset occurring 7 days post-vaccination. The occurrence of unexpected AEs in clinical trials is generally anticipated. Evaluation of the causal relationship between AEs and the investigational product was conducted according to established principles of causality assessment by trained investigators, ensuring accuracy and objectivity.

Unsolicited adverse events and serious adverse events occurring within seven days post-vaccination were considered to be plausibly related to the investigational vaccine; however, the temporal association may reflect minimal causal relevance.

PCV10 catch-up regiments in Vietnam in vaccine-naive older infants and young children resulted in a robust immune response to all vaccine serotypes.

Robust immune responses to all 10 vaccine serotypes were elicited following the PCV10 regimen, as evidenced by serotype-specific IgG geometric mean concentrations (GMCs) and the proportion of participants achieving prespecified IgG thresholds 28 days after the final vaccination. In the general population, seroresponse rates exceeded 90% for all serotypes, with the exception of serotype 6B, which demonstrated a slightly lower rate of 88.6%. These findings are consistent with phase I/II and phase III trial data for this vaccine, in which seroresponse rates were above 90% for all serotypes except 6A and 6B [15,16]. Lower responses were observed for serotypes 6B and 6A. These findings should be interpreted in light of local epidemiology, as their prevalence in Vietnam is lower compared to other serotypes, suggesting limited impact on overall vaccine effectiveness. Antibody concentrations were generally higher among the oldest children at 28 days after the final vaccination. Functional immune responses, as measured by opsonophagocytic assay (OPA), demonstrated patterns consistent with IgG responses. Moreover, the proportion of participants with functional

 doi:10.20944/preprints202603.0834.v1



OPA antibodies (titers ≥8) exceeded 94%, which was comparable to findings from phase I/II and phase III trials of this vaccine [15,16].

While IgG geometric mean concentrations (GMCs) were higher for eight serotypes in the 12–24-month age group, IgG GMCs for serotypes 1 and 7F remained lower compared with younger age groups. The more robust immunologic responses observed in older children are consistent with the natural maturation of the immune system, which becomes more efficient with age, leading to stronger vaccine-induced responses. Overall, post-vaccination IgG antibody levels were generally higher in the older age group, which may be suggestive of prior exposure to *S. pneumoniae [17]*.

In this study, older children who received a 2-dose PCV10 regimen achieved immune responses comparable to those observed in younger infants receiving a 3-dose regimen. Overall, the majority of participants attained IgG geometric mean concentrations (GMCs) ≥0.35 μg/mL for each of the 10 serotypes at 28 days post-vaccination.

A key limitation of this study is the short-term follow-up, with immunogenicity assessed only 28 days after the final dose. Long-term persistence of immunity was not evaluated and warrants further investigation.

## 5. Conclusions

This study provides sufficient evidence supporting the safety and immunogenicity of PNEUMOSIL® in Vietnamese children. The data generated herein form a critical basis for evaluation by the national vaccine regulatory authority and will support approval and marketing authorization of the vaccine in Vietnam.

**Author Contributions:** Conceptualization, P.V.H, V.T.S; methodology, P.V.H, D.T.D; software, V.T.S, B.D.T.A, B.K.L, N.T.M; validation, P.V.H, L.T.H.G, V.T.S; visualization, H.X.C; formal analysis, V.T.S, L.T.H.G, D.T.D; investigation, V.T.S, V.N.H, B.D.T.A, H.V.T, L.T.H.G, N.T.M, B.K.L, D.T.G ;resources, P.V.H., L.T.H.G, D.T.D ; data curation, P.V.H, V.T.S, B.D.T.A, L.T.T.T, H.X.C, D.T.G; Writing-original draft preparation P.V.H, L.T.H.G, D.T.D ;writing-review and editing, V.T.S, B.D.T.A, B.K.L, N.T.M ,P.V.H, D.T.D, L.T.H.G, H.V.T, V.N.H, L.T.T.T ;project administration, L.T.H.G ;funding acquisition, P.V.H, D.T.D. All authors approved the final manuscript for submission.

**Funding:** This research was supported by The Company for Vaccine and Biological Production No.1 (VABIOTECH), Ministry of Health.

**Institutional Review Board Statement:** The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board/ Ethics Committee of the National Ethics Council (Protocol code No. 28/CN-HĐĐĐ, approval date: June 4th, 2021).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Data is available at corresponding authors upon reasonable request.

**Acknowledgments:** All listed authors meet the criteria for authorship set forth by the International Committee for Medical Editors. The authors wish to thank the infants and their families who participated in this trial, all investigators, study coordinators and nurses, and other staff members for contributing in many ways to this study.

**Conflicts of Interest:** P.V.H, D.T.D, and L.T.H.G are employees of the VABIOTECH.

## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| PCVs | Pneumococcal conjugate vaccines |
| WHO | World Health Organization |
| AEs | adverse events |
| SAEs | serious AEs |

 doi:10.20944/preprints202603.0834.v1



| | |
|---|---|
| GMCs | geometric mean concentrations |
| OPA | opsonophagocytic activity |
| SII | Serum Institute of India Pvt. Ltd. |
| GMT | geometric mean titres |
| IgG | immunoglobulin G |
| ELISA | enzyme-linked immunosorbent assay |
| IPD | invasive pneumococcal disease |
| SDs | standard deviations |
| CIs | confidence intervals |

## References


1. Centers for Disease Control and Prevention. *Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae*; 2021.
2. Troeger, C.; Blacker, B.; Khalil, I.A.; Rao, P.C.; Cao, J.; Zimsen, S.R.M.; Albertson, S.B.; Deshpande, A.; Farag, T.; Abebe, Z.; et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Infectious Diseases* **2018**, *18*, 1191-1210, doi:https://doi.org/10.1016/S1473-3099(18)30310-4.
3. World Health Organization. Bulletin of the World Health Organization. **2005**.
4. Black, R.E.; Cousens, S.; Johnson, H.L.; Lawn, J.E.; Rudan, I.; Bassani, D.G.; Jha, P.; Campbell, H.; Walker, C.F.; Cibulskis, R.; et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* **2010**, *375*, 1969-1987, doi:https://doi.org/10.1016/s0140-6736(10)60549-1.
5. Wahl, B.; O'Brien, K.L.; Greenbaum, A.; Majumder, A.; Liu, L.; Chu, Y.; Lukšić, I.; Nair, H.; McAllister, D.A.; Campbell, H.; et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. *The Lancet Globle Health* **2018**, *6*, e744-e757, doi:https://doi.org/10.1016/s2214-109x(18)30247-x.
6. American Academy of Pediatrics. Committee on Infectious Diseases. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics* **2000**, *106*, 362-366, doi:https://doi.org/10.1542/peds.106.2.362.
7. Kobayashi, M.; Farrar, J.L.; Gierke, R.; Britton, A.; Childs, L.; Leidner, A.J.; Campos-Outcalt, D.; Morgan, R.L.; Long, S.S.; Talbot, H.K.; et al. Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. *Morbidity and Mortality Weekly Report (MMWR )* **2022**, *71*, 109-117, doi:https://doi.org/10.15585/mmwr.mm7104a1.
8. Shirley, M. 20-Valent Pneumococcal Conjugate Vaccine: Pediatric First Approval. *Pediatric Drugs* **2023**, *25*, 613-619, doi:https://doi.org/10.1007/s40272-023-00584-9.
9. Koshal, S.S.; Ray, A.; Hora, R.; Kaur, A.; F Quadri, S.; Mehra, R.; Kumari, A.; Haldar, P.; Roy, A.D. Critical factors in the successful expansion of Pneumococcal Conjugate Vaccine in India during the COVID-19 pandemic. *Vaccine: X* **2023**, *14*, 100328, doi:https://doi.org/10.1016/j.jvacx.2023.100328.
10. Romero-Steiner, S.; Frasch, C.; Concepcion, N.; Goldblatt, D.; Käyhty, H.; Väkeväinen, M.; Laferriere, C.; Wauters, D.; Nahm, M.H.; Schinsky, M.F. Multilaboratory evaluation of a viability assay for measurement of opsonophagocytic antibodies specific to the capsular polysaccharides of Streptococcus pneumoniae. *Clinical and Vaccine Immunology* **2003**, *10*, 1019-1024, doi:https://doi.org/10.1128/CDLI.10.6.1019-1024.2003.
11. Goldblatt, D.; Plikaytis, B.; Akkoyunlu, M.; Antonello, J.; Ashton, L.; Blake, M.; Burton, R.; Care, R.; Durant, N.; Feavers, I. Establishment of a new human pneumococcal standard reference serum, 007sp. *Clinical and Vaccine Immunology* **2011**, *18*, 1728-1736, doi:https://doi.org/10.1128/CVI.05252-11.
12. Jódar, L.; Butler, J.; Carlone, G.; Dagan, R.; Goldblatt, D.; Käyhty, H.; Klugman, K.; Plikaytis, B.; Siber, G.; Kohberger, R. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. *Vaccine* **2003**, *21*, 3265-3272, doi:https://doi.org/10.1016/s0264-410x(03)00230-5.

 doi:10.20944/preprints202603.0834.v1



13. Rose, C.E.; Romero-Steiner, S.; Burton, R.L.; Carlone, G.M.; Goldblatt, D.; Nahm, M.H.; Ashton, L.; Haston, M.; Ekström, N.; Haikala, R. Multilaboratory comparison of Streptococcus pneumoniae opsonophagocytic killing assays and their level of agreement for the determination of functional antibody activity in human reference sera. *Clinical and Vaccine Immunology* **2011**, *18*, 135-142, doi:https://doi.org/10.1128/CVI.00370-10.
14. Adigweme, I.; Futa, A.; Saidy-Jah, E.; Edem, B.; Akpalu, E.; Dibbasey, T.; Sethna, V.; Dhere, R.; Kampmann, B.; Bengt, C. Immunogenicity and safety of a 10-valent pneumococcal conjugate vaccine administered as a 2+ 1 schedule to healthy infants in the Gambia: a single-centre, double-blind, active-controlled, randomised, phase 3 trial. *The Lancet Infectious Diseases* **2023**, *23*, 609-620, doi:https://doi.org/10.1016/S1473-3099(22)00734-4.
15. Clarke, E.; Bashorun, A.O.; Okoye, M.; Umesi, A.; Hydara, M.B.; Adigweme, I.; Dhere, R.; Sethna, V.; Kampmann, B.; Goldblatt, D. Safety and immunogenicity of a novel 10-valent pneumococcal conjugate vaccine candidate in adults, toddlers, and infants in The Gambia—results of a phase 1/2 randomized, double-blinded, controlled trial. *Vaccine: X* **2020**, *38*, 399-410, doi:https://doi.org/10.1016/j.vaccine.2019.08.072.
16. Clarke, E.; Bashorun, A.; Adigweme, I.; Hydara, M.B.; Umesi, A.; Futa, A.; Ochoge, M.; Obayemi, D.; Edem, B.; Saidy-Jah, E. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial. *The Lancet Infectious Diseases* **2021**, *21*, 834-846, doi:https://doi.org/10.1016/S1473-3099(20)30735-0.
17. Janapatla, R.P.; Hsu, M.-H.; Chen, C.-L.; Wei, S.-H.; Yu, M.-J.; Su, L.-H.; Lin, T.-Y.; Chiu, C.-H. Persistence of immunity in children immunised with 13-valent pneumococcal conjugate vaccine and impact on nasopharyngeal carriage: a cross-sectional study. *Thorax* **2020**, *75*, 689-692, doi:https://doi.org/10.1136/thoraxjnl-2019-213878.