# CVIA-074

# A Phase 3, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Serum Institute of India's 10-Valent Pneumococcal Conjugate Vaccine (PNEUMOSIL®) Administered in a 2+1 Schedule to Healthy Infants in The Gambia

**Trial Registration:** NCT03896477 (clinicaltrials.gov)

PACTR201907754270299 (Pan African Clinical Trials Registry)

**CONFIDENTIAL**

**April 18, 2020**

**Sponsored by:**

PATH
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USA

**Principal Investigator:**

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**Version 3.0**

## Confidentiality Statement

**This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable Independent Ethics Committees or Institutional Review Boards. The contents of this document shall not be disclosed to others without written authorization from PATH (or others, as applicable), unless it is necessary to obtain informed consent from parents of potential study participants.**

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## LIST OF ABBREVIATIONS AND ACRONYMS

| ABBREVIATION/ ACRONYM | DEFINITION |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| Alum | aluminum phosphate |
| AMC | Advance Market Commitment |
| AST | aspartate aminotransferase |
| BHDSS | Basse Health and Demographic Surveillance System |
| CDAP | 1-cyano-4-dimethylaminopyridinium tetrafluoroborate |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| COVID-19 | Disease caused by SARS-CoV-2 |
| CRF | case report form |
| $CRM_{197}$ | Cross Reactive Material 197 |
| CRO | contract research organization |
| CSR | Clinical Study Report |
| CV | coefficients of variation |
| DSMB | Data Safety Monitoring Board |
| DT | diphtheria toxoid |
| DTwP-HepB-Hib | Pentavalent – diphtheria, tetanus, whole-cell pertussis, hepatitis B, and *Haemophilus influenzae* type b combined vaccine |
| EC | ethics committee |
| ELISA | enzyme-linked immunosorbent assay |
| EOS | End of Study |
| EPI | Expanded Program on Immunization |
| FIP | Full Immunogenicity Population |
| Gambian | subjects enrolled from the MRC field sites in The Gambia |
| GCP | Good Clinical Practice |
| GMC | Geometric Mean Concentration |
| GMFR | Geometric Mean Fold Rise |
| GMP | Good Manufacturing Practice |
| GMT | geometric mean titer |
| GSK | GlaxoSmithKline |

| | |
|---|---|
| HepB | Hepatitis B virus |
| Hib | *Haemophilus influenzae* type b |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| ID | identification |
| IgG | immunoglobulin G |
| IM | intramuscular |
| IME | Important Medical Event |
| IP | investigational product |
| IPD | invasive pneumococcal disease |
| IPV | inactivated poliovirus vaccine |
| IRB | Institutional Review Board |
| IV | intravenous |
| IWC | Infant Welfare Card |
| LSLV | last subject last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOPA | multiplexed opsonophagocytic assay |
| MRCG at LSHTM | Medical Research Council Unit, The Gambia at the London School of Hygiene and Tropical Medicine |
| NMRA | National Medicines Regulatory Authority |
| NRA | national regulatory authority |
| NTF | Note To File |
| OPA | opsonophagocytic assay |
| OPV | oral poliovirus vaccine |
| PCV | pneumococcal conjugate vaccine |
| PE | physical examination |
| PFS | pre-filled syringe |
| PI | Principal Investigator (the term is used throughout to indicate PI or designee) |
| PSRT | Protocol Safety Review Team |
| PQ | pre-qualification |
| RC | research clinician |
| RCD | reverse cumulative distribution |

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|---|---|
| RDT | rapid diagnostic test for malaria |
| RE | reactogenicity event |
| REC | research ethics committee |
| RRF | reactogenicity record form |
| RV | rotavirus vaccine (Rotarix) |
| SAE | serious adverse event |
| SAPSARS-CoV-2 | Statistical Analysis PlanSevere acute respiratory syndrome coronavirus 2 |
| SC | Subcutaneous |
| SCC | Scientific Coordinating Committee |
| SIIPL | Serum Institute of India Pvt. Limited |
| SOP | standard operating procedure |
| SSP | study specific procedure |
| TEAE | treatment-emergent adverse event |
| TMF | Trial Master File |
| TPP | Target Product Profile |
| TRS | Technical Report Series |
| TT | tetanus toxoid |
| WBC | white blood cell |
| WHO | World Health Organization |
| WIRB | Western Institutional Review Board |

**STATEMENT OF COMPLIANCE**

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46)
- International Conference on Harmonisation (ICH) Guidance for GCP (E6)
- World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Research Involving Human Subjects (Oct 2013 or subsequent amendments)
- Local regulations in The Gambia

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training, Responsible Conduct of Research (RCR) and ICH-GCP training.

**PROTOCOL SIGNATURE PAGE**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH-GCP guidelines as outlined in the 'Statement of Compliance.'

Principal Investigator:

Signed: _____ Date: _____

Name:

Title:

Sponsor's Representative:

Signed: _____ Date: _____

Name:

Title:

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| **Contract Research Organization** | [redacted] |
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| **The Gambia National Medicines Regulatory Agency** | The Medicines Control Agency<br>54 Kairaba Avenue, Pipeline, The Gambia<br>Tel: +220 4380632 |

**PROTOCOL SUMMARY**

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|---|---|
| **TITLE** | A Phase 3, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Serum Institute of India's 10-Valent Pneumococcal Conjugate Vaccine (PNEUMOSIL®) Administered in a 2+1 Schedule to Healthy Infants in The Gambia |
| **STUDY NUMBER** | CVIA 074 |
| **SCC NUMBER** | SCC1642 |
| **PROJECT PHASE** | Phase 3 |
| **INVESTIGATIONAL PRODUCT(S)** | **Investigational Vaccine:**<br>Pneumococcal 10-valent conjugate vaccine (PNEUMOSIL) at a dosage of 2 μg for each serotype polysaccharide, except 4 μg for 6B serotype, conjugated to a carrier protein (recombinant $CRM_{197}$), with adjuvant (aluminum phosphate [alum]) and preservative (thiomersal) for intramuscular injection.<br>**Active Comparator Vaccines:**<br>1) Pneumococcal 13-valent conjugate vaccine ($CRM_{197}$) suspension for intramuscular injection (Prevenar 13; Pfizer)<br>2) Pneumococcal conjugate vaccine (Non-Typeable Haemophilus *influenzae* (NTHi) protein D, diphtheria or tetanus toxoid conjugates) adsorbed (Synflorix; GlaxoSmithKline) |
| **STUDY HYPOTHESES** | **Immunogenicity:**<br>• The immune responses to the 10 serotypes in PNEUMOSIL (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F) will be similar to the immune responses to these serotypes induced by Prevenar 13 and Synflorix at 4 weeks post booster dose.<br>**Safety:**<br>• PNEUMOSIL administered in a 2+1 schedule at 6 weeks, 14 weeks, and 9-18 months of age will have an acceptable safety and tolerability profile. |
| **STUDY OBJECTIVES** | **Primary Objectives:**<br>**Immunogenicity:**<br>1. To evaluate the serum immunoglobulin G (IgG) antibody responses (Geometric Mean Concentrations [GMCs]) to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody responses to these serotypes induced by Prevenar 13 |

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| | and Synflorix, at 4 weeks post booster dose (administered at 9-18 months of age)<br><br>**Safety, Tolerability:**<br><br>1. To assess the safety and tolerability of a 2-dose primary series and booster dose of PNEUMOSIL co-administered with routine pediatric vaccines, through 4 weeks post booster dose<br><br>**Secondary Objectives:**<br><br>**Immunogenicity:**<br><br>1. To evaluate the functional serum antibody responses (Geometric Mean Titers [GMTs]) to the 10 serotypes in PNEUMOSIL as measured by opsonophagocytic assay (OPA), alone and in comparison to the responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (subset of 50 subjects per group)<br><br>2. To assess seroresponse rates (IgG antibody levels and functional responses) to the 10 serotypes in PNEUMOSIL, alone and in comparison to seroresponse rates for these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (subset of 50 subjects per group for functional responses)<br><br>3. To evaluate the serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination (administered at 6 and 14 weeks of age)<br><br>4. To evaluate the functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL as measured by OPA, alone and in comparison to the functional antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination (subset of 50 subjects per group)<br><br>5. To evaluate the persistence of the post-primary serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 9-18 months of age (prior to a booster dose)<br><br>6. To evaluate the persistence of post-primary functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL as measured by OPA, alone and in comparison to the functional antibody responses to these |

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| | serotypes induced by Prevenar 13 and Synflorix, at 9-18 months of age (subset of 50 subjects per group prior to booster)<br>7. To evaluate the booster response [serum antibody concentrations (GMC) and functional responses (GMT)] to PNEUMOSIL, alone and in comparison to booster responses to Prevenar 13 and Synflorix, from 4 weeks after completion of primary vaccination to 4 weeks after a booster dose (subset of 50 subjects per group for functional responses) |
| **STUDY ENDPOINTS** | **Primary Endpoints:**<br>**Immunogenicity**:<br>• Serotype-specific serum IgG GMCs measured 4 weeks post booster dose<br>**Safety, Tolerability:**<br>• Number and severity of solicited local and systemic adverse events (AEs) through Day 6 post each vaccination<br>• Number, severity and relatedness of all unsolicited AEs until 9 months of age, and from booster vaccination through 4 week follow-up period.<br>• Number, severity and relatedness of all serious adverse events (SAEs) through the entire study period<br>**Secondary Endpoints:**<br>**Immunogenicity:**<br>For Secondary Objective 1 (post-booster OPA GMTs):<br>• Serotype-specific serum OPA GMTs measured 4 weeks post booster dose<br>For Secondary Objective 2 (post-booster seroresponse rates):<br>• Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured 4 weeks post booster dose<br>• Percentage of subjects with serotype-specific serum IgG concentrations ≥ 1.0 µg/mL measured 4 weeks post booster dose<br>• Percentage of subjects with serotype-specific serum OPA titers ≥ 1:8 measured 4 weeks post booster dose |

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| | For Secondary Objective 3 (post-primary IgG responses):<br>• Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured 4 weeks post completion of primary vaccination<br>• Serotype-specific serum IgG GMCs measured 4 weeks post completion of primary vaccination<br><br>For Secondary Objective 4 (post-primary OPA responses):<br>• Percentage of subjects with serotype-specific serum OPA titers ≥ 1:8 measured 4 weeks post completion of primary vaccination<br>• Serotype-specific serum OPA GMTs measured 4 weeks post completion of primary vaccination<br><br>For Secondary Objective 5 (persistence of post-primary IgG responses):<br>• Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured prior to booster dose<br>• Serotype-specific serum IgG GMCs measured prior to booster dose<br><br>For Secondary Objective 6 (persistence of post-primary OPA responses):<br>• Percentage of subjects with serotype-specific serum OPA titers ≥ 1:8 measured prior to booster dose<br>• Serotype-specific serum OPA GMTs measured prior to booster dose<br><br>For Secondary Objective 7 (booster effects):<br>• Ratio of serotype-specific serum IgG GMCs measured 4 weeks post booster dose to serotype-specific IgG GMCs measured 4 weeks post completion of primary vaccination<br>• Ratio of serotype-specific serum OPA GMTs measured 4 weeks post booster dose to serotype-specific serum OPA GMTs measured 4 weeks post completion of primary vaccination |
| **STUDY RATIONALE** | Based on supportive data from a number of immunogenicity, carriage and clinical effectiveness studies, the WHO issued a position paper in 2012 recommending that countries adopt either a 3+0 or alternatively a 2+1 schedule for routine PCV administration to infants, with the primary doses of each schedule administered by 6 months of age and the booster dose of the 2+1 |

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| | schedule administered at 9 months of age or later. The updated WHO position paper in 2019 specifies that the booster dose of a 2+1 schedule should be given at 9-18 months of age. Which of the two PCV schedules a country adopts should be based on factors such as the epidemiology of pneumococcal disease in the country and coverage rates for EPI vaccines at 9 months of age or later. Because of the longer duration of protection that a booster dose may provide – particularly against serotypes of concern such as types 1 and 5, an increasing number of countries have adopted a 2+1 schedule in their EPI programmes, including India in 2018.<br><br>The current Phase 3 descriptive study will provide data necessary to evaluate the safety and immunogenicity of PNEUMOSIL when administered in an alternative schedule to the 3 dose primary schedule (3+0) evaluated in the Phase 3 pivotal trial (VAC-056) – namely in a 2 dose primary and booster (2+1) schedule – and compare immunogenicity to that of both currently licensed second-generation PCVs administered in the same 2+1 schedule. A Phase 3 trial is also being planned to evaluate the safety and immunogenicity of PNEUMOSIL administered in a 2+1 schedule in Indian infants. These studies will support regulatory approval of PNEUMOSIL in countries that have adopted a 2+1 schedule for routine PCV immunization in their EPI programme.<br>The study design has necessarily been modified due to the interruption of field activities related to the Covid-19 pandemic. The planned booster vaccination at 9 months of age has been extended to an age range of 9-18 months. This is consistent with the 2019 WHO position paper. Standard EPI vaccines will be given with the booster dose if not already administered within the routine EPI schedule at the time field activities restart. |
| **STUDY DESIGN** | In this prospective, single center, randomized, active-controlled, observer-blind, Phase 3 descriptive study, 660 healthy Gambian pneumococcal conjugate vaccine (PCV)-naïve infants will be randomized 1:1:1 to receive 3 doses of either PNEUMOSIL, Synflorix or Prevenar 13 at 6 weeks, 14 weeks and 9-18 months of age. Standard EPI vaccinations in The Gambia, except Prevenar 13, will be given concomitantly with all 3 doses of study vaccine (except for subjects who receive the 9-month EPI vaccines earlier than the study booster dose due to impact of the COVID-19 pandemic). |

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| | After a parent signs an informed consent form (ICF), prospective subjects will be assessed for eligibility to participate in the study, including assessment of medical history, vital signs and physical examination. Consented and eligible subjects will be randomized and receive the first vaccination (V1) at 6 (+2) weeks of age, along with standard EPI vaccines except Prevenar 13. Subjects will return to the clinic at 10 (+2) weeks of age (V2) for relevant EPI vaccines only (except Prevenar 13), and at 14 (+2) weeks of age (V3) to receive the 2nd primary dose of study vaccine along with EPI vaccines. Blood will be collected in clinic 4 (+2) weeks later (V4) for immunogenicity assessments. Subjects will return for a booster vaccination (V5) at 9-18 (+1) months of age, followed 4 (+2) weeks later by an end of study (EOS) visit (V6). Blood for immunogenicity assessments will be collected prior to the booster dose at V5 and at V6. The EOS CRF completed at V6 will indicate completion of the study for the subject.<br><br>After the last subject completes V4, an interim analysis of immunogenicity objectives through end of V4 will be performed. Only the CRO statistical personnel will be unblinded for analysis of these data. |

**STUDY SCHEMA**

| Groups | N | Visits / Age (wks) | | | | | |
|---|---|---|---|---|---|---|---|
| | | V1 | V2 | V3 | V4 | V5 | V6 |
| | | 6 (+2) | 10 (+2) | 14 (+2) | V3+4 (+2) | 9-18 (+1) mo | V5+4 wks (+2) |
| PNEUMOSIL | 220 | X, E | E | X, E | B | B, X, E | B |
| Synflorix | 220 | X, E | E | X, E | B | B, X, E | B |
| Prevenar 13 | 220 | X, E | E | X, E | B | B, X, E | B |

wks = weeks, mo = months

X = study vaccination, E= EPI vaccines (except Prevenar 13), B = blood sample for immunogenicity testing

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| **STUDY POPULATION** | 660 healthy, male and female PCV-naïve infants residing in The Gambia who are from 6 to 8 weeks of age at enrollment (V1). |
| **STUDY DURATION** | All subjects will be followed for a minimum of approximately 37[1] weeks after randomization (4 weeks after the booster dose) and a maximum of 73 weeks[1], depending on age of booster vaccination<br>[1]Excluding any additional time due to visit windows |

# 1. BACKGROUND AND RATIONALE

## 1.1. Burden of Disease

The bacterium *Streptococcus pneumoniae* kills half a million children before their fifth birthday annually, mostly in low-resource areas of the world.[1] The most common cause of childhood morbidity and mortality due to the bacterium is pneumonia, which in 2013 was estimated to be the cause of roughly 900,000 (or 15% of all) under-five deaths worldwide, making it the most deadly infectious disease of young children today.[2] Although pneumonia has multiple bacterial and viral etiologies, *S. pneumoniae* is the leading cause of severe pneumonia. In addition to pneumonia, *S. pneumoniae* also causes a number of other serious invasive pneumococcal diseases (IPD), including sepsis and meningitis, which collectively result in tremendous morbidity and mortality. The highest incidence of IPD is seen at the extremes of age, in the elderly and children less than 2 years old.[3] Public health leaders agree that vaccines are the best way to address the enormous burden of pneumococcal disease, particularly in Africa and Asia, where 95% of all pneumococcal deaths occur.[4]

## 1.2. Pathogen and Clinical Disease

*S. pneumoniae* is a Gram-positive encapsulated bacterium that is commonly carried as a commensal in the human nasopharynx. More than 90 serotypes of the bacterium have been identified based on differences in the composition of its polysaccharide capsule, which is an essential virulence factor. Pneumococci are transmitted by direct contact with respiratory secretions from infected individuals and healthy carriers. Nearly all children harbor one or more strains, and become carriers during the first few years of life.[5] Carriage is typically asymptomatic; however, it is believed to be a precondition for invasive pneumococcal infection.[6]

The signs and symptoms of IPD depend on the type of pneumococcal infection, but may be nonspecific, especially in infants. The most common signs and symptoms of pneumococcal meningitis in infants include fever, lethargy, respiratory distress, jaundice, poor feeding, vomiting, diarrhea, seizures, restlessness, irritability, and bulging fontanel.[7] An infant with pneumococcal pneumonia may additionally have cough, fast breathing, hypoxemia, decreased breath sounds, crackles, chest retractions, and grunting.[8]

## 1.3. Pneumococcal Epidemiology in Africa and The Gambia

Although documentation of pneumococcal disease in children is limited in low-resource countries, several studies have estimated the extent of disease in Africa generally, and in The Gambia specifically. The studies conducted prior to the introduction of pneumococcal conjugate vaccine (PCV) have estimated rates of IPD to be as much as 10-fold higher in The Gambia and other African countries than in the developed world.[9,10,11] Based on 2 studies conducted during the period 1988 through 1994, the incidence of invasive pneumococcal disease in The Gambia was estimated to be at least 500 per 100,000 in children in their first year of life, and 250 per 100,000 in children less than 5 years of age.[12] The importance of IPD in The Gambia was also highlighted in a randomized, placebo-controlled, double-blind trial of a 9-valent PCV conducted in the Upper and Central River Divisions of the country between 2000 and 2004: the incidence of IPD due to all serotypes in the placebo arm of the study was 380 per 100,000, versus 190 per 100,000 in the vaccine arm.[13] A recently published population-based surveillance study conducted in the Upper River Region of The Gambia between May 2008 and December 2014 found that, after the introduction of PCV, the incidence of IPD decreased from 253 to 113 cases per 100,000 population among children aged 2-23 months old.[14]

Though there are more than 90 serotypes of *S. pneumoniae*, a small percentage are responsible for the large majority of cases of IPD. There are important regional differences in the dominant disease-causing serotypes (or serogroups); in particular, serotypes 1 and 5 account for a much larger percentage of IPD in the developing world. Serogroups 14, 6, 19, 18, 9, 23, and 7 are responsible for roughly 85% of IPD in the developed world, whereas the dominant serotypes causing IPD in Africa, Asia, and Latin America are 1, 2, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (Table 1).[15]

**Table 1. Proportion (Percent) of Invasive Pneumococcal Disease in Children Less Than 5 Years of Age due to Serotype by Region**

| Region | 1 | 2 | 4 | 5 | 6A | 6B | 7F | 9V | 14 | 18C | 19A | 19F | 23F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Africa | 11.7 | 1.9 | 2.3 | 10.7 | 9.4 | 8.5 | 0.8 | 2.2 | 13.0 | 1.4 | 3.9 | 5.4 | 6.5 |
| Asia | 9.5 | 2.6 | 1.6 | 6.7 | 3.5 | 11.5 | 2.0 | 3.1 | 11.6 | 2.4 | 2.6 | 8.1 | 9.7 |
| LAC | 8.4 | 0.3 | 1.6 | 8.5 | 4.5 | 9.4 | 2.5 | 2.7 | 26.5 | 4.3 | 2.9 | 3.6 | 5.3 |

Abbreviation: LAC = Latin America and the Caribbean

### 1.4. Licensed Pneumococcal Conjugate Vaccines

In 1983, Pneumovax® 23, a pneumococcal polysaccharide vaccine covering 23 serotypes developed by Merck, was first approved for use in older adults and the elderly to prevent pneumococcal disease. This vaccine contains capsular polysaccharide from serotypes 1, 2, 3, 4, 5, 6b, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. While Pneumovax 23 has been shown to be effective against IPD in immunocompetent adults,[16] it is poorly immunogenic in children less than 2 years old.[17]

The first effective pneumococcal vaccine for children less than 2 years old and infants was developed based on the success of the *Haemophilus influenzae* type b (Hib) conjugate vaccine, which elicits an enhanced immune response when the polysaccharide is conjugated to a carrier protein. Prevenar®, a 7-valent pneumococcal conjugate vaccine, contains the capsular antigens from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to Cross Reactive Material 197 ($CRM_{197}$, a non-toxic diphtheria toxoid protein). Developed by Wyeth (now Pfizer), Prevenar was first approved and introduced in the US for use in infants and young children in the year 2000. By the end of the decade, overall and serotype-specific IPD in the US were reduced by 45% and 94% respectively.[18] However, given the limited coverage offered by Prevenar, two second-generation PCVs, Synflorix® (GlaxoSmithKline [GSK] Biologicals) and Prevenar 13® (Wyeth, now Pfizer) were subsequently developed and approved for infants and young children, both expanding on Prevenar's 7 serotypes to offer protection against 10 and 13 serotypes, respectively. By adding serotypes 1, 5, and 7F in the case of Synflorix, and serotypes 1, 3, 5, 6A, 7F, and 19A in the case of Prevenar 13, the second-generation PCVs offer additional protection against common serotypes in Africa and Asia, most notably against serotypes 1 and 5.

### 1.5. Rationale for PNEUMOSIL® Development

Nearly 20 years after their introduction, the most significant barriers to global access to PCVs remain their cost and complex manufacturing process. The price of the vaccine is the critical factor that determines whether PCV introduction is considered cost-effective in a low resource setting. This reality

has underscored the importance of developing an affordable PCV tailored against the specific serotypes causing pneumococcal disease in low and middle-income countries.

Because of the high cost of PCV, introduction of the vaccine into low resource countries has been dependent on considerable external financial assistance. In 2009, Rwanda and The Gambia became the first low resource countries to introduce Prevenar, with assistance from Gavi and other international partners.[19] Since 2010 a global roll-out of Synflorix and Prevenar 13 has been underway in Gavi-eligible countries with the help of the pneumococcal Advance Market Commitment (AMC), a financing mechanism whereby donors commit funds to guarantee the price of future vaccines, creating incentives for producers and catalyzing competition to supply vaccines at long-term lower prices.[20] Fifty-four low-resource countries have now introduced PCV into their routine immunization programs with Gavi assistance.[21] In April 2011, Prevenar 13 replaced Prevenar in the Gambian EPI schedule. As these lifesaving vaccines continue to make their way into the developing world with external assistance, the rapid development of less expensive PCVs is also needed if countries in the developing world will be able to independently afford them over the long term. To this end, enhancing the participation of emerging-market manufacturers in PCV production is a critical factor in achieving a sustainable, affordable, and accessible supply of vaccine for countries with limited resources. Development of effective and more affordable PCVs is aligned with the Sustainable Development Goal of ending preventable deaths of newborns and children under 5 years of age by 2030.[22]

### 1.6. Introduction to PNEUMOSIL

The Serum Institute of India (SIIPL), a manufacturer of multiple WHO-prequalified vaccines, in collaboration with PATH, has been working since 2006 to develop a multivalent PCV designed to prevent pneumococcal disease and to be affordable for use in low resource countries. PNEUMOSIL[*], SIIPL's 10-valent candidate pneumococcal conjugate vaccine incorporates prevalent serotypes in Africa, Asia, and Latin America (serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F), thus offering comparable coverage to currently licensed PCVs in these settings.

In addition to selecting serotypes based on prevalence in low resource countries, SIIPL has optimized 3 critical components of the manufacturing practice – carrier protein production, polysaccharide production, and conjugation efficiency – that together substantially lower the cost of manufacturing a high-quality multivalent PCV. As a result, it will be possible to provide PNEUMOSIL at a price that is significantly lower than that of the currently licensed PCVs. If it becomes available under the AMC, PNEUMOSIL would provide significant cost savings to Gavi and to the Gavi-supported countries that have introduced pneumococcal vaccines procured through the AMC. This cost savings would result not only from a price substantially below the $3.05-$3.10 per dose contributed by Gavi and Gavi-supported countries to the manufacturers of the 2 existing AMC-eligible PCVs (GlaxoSmithKline's Synflorix and Pfizer's Prevenar 13), but also from price pressure that PNEUMOSIL's AMC eligibility would place on these vaccines. Finally, availability of PNEUMOSIL would address any potential long-term supply constraints for pneumococcal vaccine.

### 1.7. Summary of Nonclinical Studies

PNEUMOSIL has been made in compliance with Good Manufacturing Practice (GMP), and this candidate vaccine has been tested in multiple preclinical pharmacology and Good Laboratory Practice (GLP) studies to assess immunogenicity, toxicity and local tolerance, in compliance with Schedule Y

[*] Prior to trademark registration, SIIPL's candidate PCV was referred to as "SIILPCV10".

of the Drugs and Cosmetics Rules of India, ICH Harmonized Tripartite Guideline S6, and WHO recommendations.[23,24,25]

### 1.7.1. Pharmacology

A pharmacology study was conducted in New Zealand White rabbits using the GMP lot of PNEUMOSIL (#4193001) used in the Phase 1/2 clinical trial in The Gambia (VAC-017). Eight (8) animals (4 per sex) were immunized intramuscularly (IM) with a human dose-volume of PNEUMOSIL on study Day 1, 15, and 29. Serum was collected at baseline, at Day 29 (pre-dose, 2 weeks post second dose), and at Day 43 (2 weeks post the third and last dose). A second group of 8 animals was treated with Prevenar13 (human dose-volume), and served as a comparator. Serum samples were assessed individually for their humoral, serotype-specific immune response using 2 test methods: 1) a direct enzyme-linked immunosorbent assay (ELISA) to quantitate serotype-specific IgG; and 2) a multiplexed opsonophagocytic assay (MOPA) to estimate the amount of functional antibody (able to induce phagocytosis and killing) elicited in the blood of the rabbits by the vaccination. The assay results indicated that the total IgG and the functional antibody responses elicited by intramuscular (IM) immunization with GMP lot #4193001 and measured in the blood of the animals 2 weeks post 2nd and 3rd dose were comparable to those elicited by the Prevenar13 comparator, across all vaccine serotypes. It should also be noted that the same analyses were performed after a 3-dose schedule of immunization on multiple lots of PNEUMOSIL after 1 year of manufacture, and the IgG and OPA antibody titers achieved were comparable to the titers achieved on the lots at the time of manufacture.

### 1.7.2. Toxicology

A total of 7 preclinical toxicology studies of PNEUMOSIL have been conducted either in Sprague-Dawley rats or New Zealand white rabbits, 4 of which have been single-dose and 3 repeat-dose studies (Table 2).

**Table 2. Summary of PNEUMOSIL Nonclinical Studies**

| Study No. | Animal | Route | Treatment Groups* | Doses | Sacrifice Day(s) | Recovery (Days) | Additional Assessments‡ |
|---|---|---|---|---|---|---|---|
| G7628 | Rat | IM | G1, G2, G3, G4, G5, G6 | 1 | D15 | 14 | A1, A2 |
| G7629 | Rat | SC | G1, G2, G3, G4, G5, G6 | 1 | D15 | 14 | A1, A2 |
| G7630 | Rabbit | IM | G1, G2, G3, G4, G5, G6 | 1 | D15 | 14 | A1, A2 |
| G7631 | Rabbit | SC | G1, G2, G3, G4, G5, G6 | 1 | D15 | 14 | A1, A2 |
| G7557 | Rat | IM | G1, G2, G3, G4, G5, G6 | 5 | D58, D86 | 28 | A1, A2, A3, A5 |
| G7558 | Rabbit | IM | G1, G2, G3, G4, G5, G6 | 5 | D58, D86 | 28 | A1, A2, A3, A5 |
| 12976 | Rabbit | IM | G2, G3, G4 | 4 | D44, D72 | 28 | A1, A2, A3, A4, A5 |

Abbreviations: IM, intramuscular; SC, subcutaneous

*G1: negative control (saline), G2: vehicle control (alum), G3: Prevenar 13 (1x), G4: PNEUMOSIL (1x), G5: PNEUMOSIL (10x), G6: PNEUMOSIL (20x).

‡A1: safety labs, A2: histopathology of injection sites, A3: histopathology of select organs/tissues; A4: limited male fertility, A5: immunogenicity (IgG and OPA).

In 6 of these studies, groups of animals were administered PNEUMOSIL at doses of 1, 10, and 20 times the expected human dose; in addition, concurrent control groups were administered Prevenar 13, saline, and aluminum phosphate (alum) adjuvant. In Study 12976, groups of animals (rabbits) were administered alum, Prevenar 13, and PNEUMOSIL with or without preservative (thiomersal) at the expected human dose. In the case of all studies, the test and control articles were administered via the intended clinical route (intramuscularly) or subcutaneously. In the repeat-dose studies, the animals were administered either 5 doses of vaccine or control at 2-week intervals, or 4 doses at 2-week intervals in the case of Study 12976, and were followed by a 28-day recovery period. Blood was collected from all animals prior to vaccination and at termination. Blood was analyzed for standard safety laboratory parameters in all studies, and for immunogenicity (IgG and OPA) against the vaccine serotypes in the repeat-dose studies. These latter analyses demonstrated a significant increase from baseline in both total IgG and functional antibody titers in the vaccinated animal sera against all the pneumococcal serotypes included in PNEUMOSIL. The immunizations with buffer and vehicle control did not give rise to any major changes in the antibody titers against any of the vaccine serotypes.

In the single-dose rat studies (G7628, G7629), visual (edema) and microscopic evidence of local inflammation was seen in all treatment groups at a similar magnitude – indicating that the alum adjuvant was most likely the cause of these changes. Recovery was noted 14 days after administration, and therefore the effects were considered transient in nature. Increases in gamma- glutamyl transpeptidase (GGT) were observed in all treatment groups in the single intramuscular (IM)-dose study (G7628) but were not seen in the single subcutaneous (SC)-dose study (G7629) or the multi-dose study (G7557). Liver enzymes (alanine aminotransferase [ALT]/ aspartate aminotransferase [AST]) were not altered and liver weights were normal at time of sacrifice.

In the multi-dose rat study (G7557), the albumin/globulin (A:G) ratio was decreased (as a result of an increase in globulin level) and the white blood cell (WBC) count increased in the Prevenar 13 and SIILPCV10 treatment groups. These effects are commonly observed in vaccine animal testing, as they are expected pharmacological effects of stimulating the immune system. Coagulation parameters, prothrombin time (PT) and activated partial thromboplastin time (APTT), were within normal limits. Transient increases in serum fibrinogen, likely indicative of immune activation, were observed in Prevenar 13 and PNEUMOSIL treatment groups in the rat studies. Significant increases in serum creatinine were observed in all treatment groups of the multi-dose rat study (G7557), including the negative and vehicle control groups; while its cause is unclear, the consistency of the creatinine increase across groups suggests that it is unlikely to be an adverse effect of PNEUMOSIL and Prevenar 13. Microscopic examination of the kidneys at sacrifice showed that the organs were healthy.

In the rabbit, erythema was seen at the injection site in all treatment groups in the single SC-dose study (G7631) but not with IM administration. Microscopic evidence of local inflammation of a similar magnitude was seen at the injection site in all treatment groups in the 4 rabbit studies.

Subsequently it was concluded that these alterations were due to alum administration. Substantial recovery was noted at the end of the recovery period, suggesting a transient local inflammatory phenomenon. Based on assessment in the third repeat-dose study (12976), there was no effect of treatment on sperm motility and morphology.

In summary, single- and repeat-dose administration of PNEUMOSIL to rats and rabbits was well tolerated, and resulted in observed changes that were not adverse but rather a consequence of the pharmacological activity of PNEUMOSIL and the comparator Prevenar 13, or were seen across all treatment groups and not associated with the test product only.

### 1.8. Summary of Clinical Studies

Four clinical trials of PNEUMOSIL have been conducted:

1) A Phase 1, randomized, active-controlled, double-blind trial (PCV10-001) evaluating the safety and tolerability of PNEUMOSIL in healthy young Indian adults (n=34) has been completed. Eligible subjects were randomized 1:1 to receive a single dose of PNEUMOSIL or Pneumovax 23 and were followed through 28 days post vaccination.
2) A Phase 1/2, randomized, active-controlled, double-blind, age de-escalation trial (VAC-017) evaluating the safety, tolerability and immunogenicity of PNEUMOSIL in 34 PCV-naïve adults, 112 PCV (Prevenar 13)-primed toddlers (12-15 months of age), and 200 PCV-naïve infants in The Gambia has been completed. Eligible subjects were randomized 1:1 to receive a single dose of PNEUMOSIL or either Pneumovax 23 in adults or Prevenar 13 in toddlers, and a 3-dose primary series of PNEUMOSIL or Prevenar 13 (at 6, 10, and 14 weeks of age) in the infant cohort. EPI vaccines were concomitantly administered to infants, including pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, and *Haemophilus influenzae* type b [DTwP-HepB-Hib]). Adults and toddlers were followed for 28 days post vaccination, and infants for 84 days post final vaccination. A Data Safety Monitoring Board (DSMB) granted approval to advance to the toddler and infant cohorts following the adult and toddler cohorts respectively. Following database lock and unblinded data review, the decision was made to extend the study to evaluate a matched booster dose of PNEUMOSIL or Prevenar 13 in infants.
3) A Phase 2, randomized, active-controlled, double-blind trial (PCV10-002) evaluating the safety, tolerability and immunogenicity of a 2-dose regimen of PNEUMOSIL in 114 PCV-naïve Indian toddlers (12-15 months of age) has been completed. Eligible subjects were randomized 1:1 to receive a 2-dose regimen of PNEUMOSIL or Prevenar 13 at an 8 week interval, and were followed through 28 days post final vaccination.
4) A Phase 3, randomized, active-controlled, double-blind trial (VAC-056) evaluating the safety, tolerability, lot-to-lot consistency, immunogenicity and non-interference with concomitant vaccinations of PNEUMOSIL in 2,250 PCV-naïve infants in The Gambia has been completed. Analysis of safety and immunogenicity data for primary and secondary endpoints of the trial has been completed. A subset of subjects remained in the trial for long-term safety monitoring and evaluation of immune persistence 1 year post booster dose. Follow-up for the immune persistence phase has been completed and the analysis is ongoing. Eligible subjects were randomized (2:2:2:3) to receive 3 doses of either PNEUMOSIL (3 groups receiving vaccine from different lots) or Synflorix (1 group) at 6, 10, and 14 weeks of age. In the booster phase, the first 675 randomized subjects continued in the study to receive a booster dose of either PNEUMOSIL or Synflorix at 9 months of age that matched the treatment assignment for the priming phase. Other standard EPI vaccinations in The Gambia were given concomitantly with all 4 doses of the study vaccines. Overall, 2,182 and 634 infant subjects were evaluated for immunogenicity at 4 weeks post final primary series vaccination, and post booster dose, respectively.

PNEUMOSIL was well tolerated in all 4 trials, and no safety concerns were identified in any trial. PNEUMOSIL was also shown in the VAC-017 and PCV-10-002 studies to be immunogenic for all 10 serotypes contained in the vaccine, and in the VAC-056 study to be immunologically non-inferior to Synflorix for all 10 serotypes contained in PNEUMOSIL. A summary of safety and immunogenicity results follows. Please refer to the Investigator's Brochure (IB) for additional details on the methodology and results of the PCV10-001, PCV10-002, VAC-017, and VAC-056 trials.

### 1.8.1. Safety

**Laboratory Assessments**:

In the PCV10-001, VAC-017, and PCV10-002 trials, blood samples were collected for safety hematology, clinical chemistry, and organ function tests; a coagulation panel was also evaluated in adult subjects. Laboratory assessments were only performed at baseline for infants in the VAC-017 study. There were no notable trends from baseline to post vaccination in any laboratory parameter in the adult subjects in the PCV10-001 and VAC-017 studies, or in the toddler subjects in the PCV10-002 study.

**Reactogenicity**:

Solicited local and systemic reactogenicity was assessed daily for the first 7 days post vaccination in all 4 clinical studies by means of a subject diary (PCV10-001 and PCV10-002) or daily home visits by field workers (VAC-017 and VAC-056). Reactogenicity was assessed in all subjects in all 4 trials, except in the case of the primary series vaccinations in the VAC-056 study, in which half of the subjects in each treatment group (n = 1,125 total) were randomly selected to be included in the primary reactogenicity cohort.

When observed, reactogenicity after vaccination with PNEUMOSIL in all studies and age cohorts was generally mild or moderate and of limited duration.

In adults, the most common local reactogenicity event (RE) after a single dose of PNEUMOSIL was pain, reported in 70.6% and 58.8% of adults in the PCV10-001 and VAC-017 studies respectively. Only 1 Grade ≥ 2 local RE was reported in the PNEUMOSIL group in either trial (Grade 3 tenderness). Headache was the most common systemic RE after vaccination and was reported for 17.6% of adults who received PNEUMOSIL in both trials. No Grade ≥ 2 systemic RE was reported in adults who received PNEUMOSIL.

In the VAC-017 toddler cohort, the most common local RE post vaccination was tenderness (21.5% PNEUMOSIL, 21.4% Prevenar 13). A higher proportion of toddlers in the PNEUMOSIL group vs. the Prevenar 13 group had Grade 1 or 2 induration/swelling at the injection site (10.7% PNEUMOSIL; 1.8% Prevenar 13). No severe (Grade ≥ 3) tenderness or other local RE was reported, and no RE led to discontinuation in either the PNEUMOSIL or Prevenar 13 treatment group. Fever (axillary temperature ≥ 37.5°C) was the most common systemic RE (16.1% PNEUMOSIL, 19.6% Prevenar 13). Grade 3 fever was reported in 2 toddlers who received the PNEUMOSIL booster and 1 toddler who received the Prevenar 13 booster. A higher proportion of toddlers in the PNEUMOSIL group vs. the Prevenar 13 group had Grade 1 or 2 drowsiness (10.7% PNEUMOSIL; 0% Prevenar 13).

In the PCV10-002 PCV-naïve toddler study, the most common local RE post vaccination was tenderness (8.8% PNEUMOSIL, 21.1% Prevenar 13). Fever was the most common systemic RE (21.1% PNEUMOSIL, 15.8% Prevenar 13). There was no local or systemic RE that was severe, or that led to discontinuation in either the PNEUMOSIL or Prevenar 13 treatment group. There were no significant differences in RE frequency or severity between treatment groups.

Table 3 presents the highest grade (Grade ≥ 1) of selected REs occurring over the first 7 days following primary vaccination of infants in the VAC-017 study.

**Table 3. Highest Grade ≥ 1 of Selected Reactogenicity Events in Infants – Primary Series (VAC-017)**

| Reactogenicity Event Grade | Vaccination 1 | | Vaccination 2 | | Vaccination 3 | |
|---|---|---|---|---|---|---|
| | PNEUMOSIL N = 100 n (%) | Prevenar 13 N = 100 n (%) | PNEUMOSIL N = 100 n (%) | Prevenar 13 N = 100 n (%) | PNEUMOSIL N = 100 n (%) | Prevenar 13 N = 100 n (%) |
| Temperature | | | | | | |
| Grade 1: ≥ 37.5 to ≤ 38.0 | 29 (29.0) | 34 (34.0) | 11 (11.0) | 13 (13.0) | 15 (15.0) | 16 (16.0) |
| Grade 2: > 38.0 to ≤ 39.0 | 11 (11.0) | 7 (7.0) | 7 (7.0) | 6 (6.0) | 4 (4.0) | 4 (4.0) |
| Grade 3: > 39.0 to ≤ 40.0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 1 (1.0) | 0 (0.0) |
| Irritability | | | | | | |
| Grade 1: Crying more than usual/no effect on normal activity | 33 (33.0) | 29 (29.0) | 35 (35.0) | 30 (30.0) | 33 (33.0) | 37 (37.0) |
| Grade 2: Crying more than usual/interferes with normal activity | 4 (4.0) | 2 (2.0) | 5 (5.0) | 3 (3.0) | 3 (3.0) | 4 (4.0) |
| Grade 3: Crying that cannot be comforted/prevents normal activity | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 0 (0.0) |
| Drowsiness | | | | | | |
| Grade 1: Drowsiness easily tolerated | 8 (8.0) | 1 (1.0) | 6 (6.0) | 1 (1.0) | 2 (2.0) | 3 (3.0) |
| Grade 2: Drowsiness that interferes with normal activity | 0 (0.0) | 1 (1.0) | 0 (0.0) | 1 (1.0) | 0 (0.0) | 0 (0.0) |
| Decreased appetite | | | | | | |
| Grade 1: Eating less than usual/no effect on normal activity | 10 (10.0) | 1 (1.0) | 9 (9.0) | 8 (8.0) | 6 (6.0) | 9 (9.0) |
| Grade 2: Eating less than usual/interferes on normal activity | 0 (0.0) | 0 (0.0) | 1 (1.0) | 0 (0.0) | 1 (1.0) | 2 (2.0) |
| Tenderness at injection site | | | | | | |
| Grade 1: Mild reaction to touch | 15 (15.0) | 12 (12.0) | 18 (18.0) | 26 (26.0) | 21 (21.0) | 19 (19.0) |
| Grade 2: Cries/protests on touch | 4 (4.0) | 5 (5.0) | 2 (2.0) | 1 (1.0) | 0 (0.0) | 2 (2.0) |
| Erythema/redness at injection site | | | | | | |
| Grade 1: Erythema present but ≤ 2.5 cm diameter | 1 (1.0) | 8 (8.0) | 0 (0.0) | 4 (4.0) | 3 (3.0) | 3 (3.0) |
| Grade 2: Erythema > 2.5 cm diameter but < 50% surface area of the extremity segment | 0 (0.0) | 1 (1.0) | 1 (1.0) | 1 (1.0) | 0 (0.0) | 0 (0.0) |
| Induration/Swelling at Injection Site | | | | | | |
| Grade 1: Induration/Edema present but ≤ 2.5 cm diameter | 4 (4.0) | 8 (8.0) | 7 (7.0) | 16 (16.0) | 11 (11.0) | 13 (13.0) |
| Grade 2: Induration/Edema > 2.5 cm diameter but < 50% surface area of the extremity segment | 0 (0.0) | 2 (2.0) | 1 (1.0) | 2 (2.0) | 2 (2.0) | 1 (1.0) |

Source: VAC-017 CSR Table IS7A.

In the VAC-017 infant cohort, the most common local RE after a primary dose of study vaccine was tenderness (19-21% PNEUMOSIL, 17-27% Prevenar 13). No Grade ≥ 3 local RE was reported. A lower proportion of infants in the PNEUMOSIL group had Grade 1 or 2 erythema/redness (1.0%

PNEUMOSIL; 5.0-9.0% Prevenar 13) and induration/swelling (4.0-8.0% PNEUMOSIL; 10.0-18.0% Prevenar 13) after vaccinations 1 and 2. Fever (axillary temperature ≥ 37.5°C) was the most common systemic RE after the first vaccination (40.0% PNEUMOSIL, 41% Prevenar 13). The proportion of cases of fever was lower after vaccinations 2 and 3 (18.0-20.0% PNEUMOSIL; 20% Prevenar 13). One event of Grade 3 fever was reported in both treatment groups, and 1 episode each of Grade 3 irritability and cutaneous rash in the PNEUMOSIL group. A higher proportion of infants in the PNEUMOSIL group compared with infants in the Prevenar 13 group had Grade 1 or 2 vaccine-related drowsiness (6.0 - 8.0% PNEUMOSIL; 2.0% Prevenar 13) and decreased appetite (10.0% PNEUMOSIL; 1.0 - 8.0% Prevenar 13) after vaccinations 1 and 2. Most REs were transient and resolved within 24 to 48 hours.

When observed, reactogenicity in VAC-017 infants after a booster dose was generally mild or moderate. Overall, there were no notable differences in RE frequency or severity between infants receiving PNEUMOSIL and infants receiving Prevenar 13. Two (4.1%) infants in the PNEUMOSIL group and 1 (2.1%) infant in the Prevenar 13 group had Grade 3 fever. All other REs were mild or moderate in severity. Fever and irritability were the most common systemic REs, both occurring in a total of 12% of subjects (fever: 12.2% PNEUMOSIL, 12.7% Prevenar 13, irritability: 10.2% PNEUMOSIL, 14.9% Prevenar 13). Tenderness at the injection site was the most common local RE (18.3% PNEUMOSIL, 23.4% Prevenar 13). Most REs were transient and resolved within 24 to 48 hours.

In the VAC-056 study, the most frequently reported local reaction in the primary reactogenicity cohort was tenderness, experienced by 369 (49.1%) subjects in the PNEUMOSIL group and by 193 (53.0%) subjects in the Synflorix group. Erythema/redness and induration/swelling were experienced by less than 10% of the subjects in both vaccine groups. There was no significant difference in the local reactions reported between the vaccine groups, except for induration/swelling which was significantly more frequently reported in the Synflorix group than in the PNEUMOSIL group (p=0.0032) (significant difference only after Dose 1, p=0.0264). No Grade 3 local reaction was reported through Day 6 after any vaccination in the primary reactogenicity cohort. Most of the local reactions were of Grade 1 intensity. The proportion of subjects experiencing at least 1 solicited local reaction decreased after each round of vaccination.

The most frequently reported systemic reaction in the primary reactogenicity cohort was fever (axillary temperature of ≥ 37.5°C), experienced by 391 (52.1%) subjects in the PNEUMOSIL group and by 187 (51.4%) subjects in the Synflorix group, followed by irritability, experienced by 240 (32.0%) subjects in the PNEUMOSIL group and by 109 (29.9%) subjects in the Synflorix group. Cutaneous rash, drowsiness and decreased appetite were experienced by less than 8% of the subjects in both vaccine groups. Overall, there was no significant difference in the systemic reactions reported between the vaccine groups in the primary reactogenicity cohort. After Dose 3, fever was significantly more frequently reported in the PNEUMOSIL group than in the Synflorix group (p=0.0310). Most of the REs were of Grade 1 or Grade 2 intensity. The proportion of subjects experiencing at least 1 systemic RE tended to decrease after each round of vaccination.

There were no significant differences between vaccine groups in rates of severity of any solicited reaction after the booster dose in the VAC-056 study. When observed post booster dose, reactogenicity in infants was generally mild or moderate. All other REs were mild or moderate in severity. Fever was the most common systemic RE, experienced by 24 (5.6%) subjects in the PNEUMOSIL group and by 17 (7.5%) subjects in the Synflorix group. Tenderness at the injection site was the most common local

RE, experienced by 33 (7.7%) subjects in the PNEUMOSIL group and by 13 (6.1%) subjects in the Synflorix group. Most REs were transient and resolved within 24 to 48 hours.

**Adverse Events**:

In all 4 clinical studies, subjects were monitored for AEs from enrollment to final clinic visit, and an AE was assessed by the investigator with regard to severity, relatedness, and duration. There were no related SAEs in any of the 4 studies. There were also no significant differences or concerning trends in the frequency of treatment-emergent AEs (TEAEs), serious TEAEs or vaccine-related TEAEs in any of the 4 studies, or in deaths (0.1% PNEUMOSIL; 0.3% Synflorix) or TEAEs leading to subject withdrawal (0.3% in both groups) in the VAC-056 study.

In the VAC-017 toddler cohort, 3 (5.4%) toddlers in the PNEUMOSIL group and 1 (1.8%) toddler in the Prevenar 13 group had severe TEAEs, and all had resolved. None of the severe TEAEs was considered related to study vaccine. The only severe TEAE reported for > 1 toddler was microcytic anemia, which was reported for 2 (3.6%) toddlers in the PNEUMOSIL group. There were 2 related TEAEs reported in the PNEUMOSIL group (Grade 1 diarrhea, Grade 2 morbilliform/papular rash) and 1 related TEAE in the Prevenar 13 group (Grade 1 pruritus). Two (2) treatment-emergent SAEs were reported, one in each treatment group and neither deemed related to study vaccine.

In the PCV10-002 study, only 1 (1.8%) toddler in the PNEUMOSIL group and 2 (3.5%) toddlers in Prevenar 13 group experienced severe TEAEs. None of the severe TEAEs was considered related to study vaccine. The only severe TEAE reported for > 1 toddler was anemia, which was reported for 2 (3.6%) toddlers in the Prevenar 13 group. There were 4 related TEAEs reported in the PNEUMOSIL group (Grade 1 diarrhea [2 events], Grade 1 AST increased, Grade 2 WBC count increased) and 3 related TEAEs in the Prevenar 13 group (Grade 1 AST increased, Grade 1 WBC count increased, Grade 2 WBC count increased). One subject in the PNEUMOSIL group and 2 subjects in the Prevenar 13 group had treatment-emergent SAEs during the study, none of which was deemed related to study vaccine.

In the VAC-017 infant cohort, the most common TEAEs reported in both treatment groups through 12 weeks post final primary vaccination included upper respiratory tract infection (64.0% PNEUMOSIL, 48.0% Prevenar 13), tinea infection (31.0% PNEUMOSIL; 21.0% Prevenar 13), diarrhea (29.0% PNEUMOSIL; 19.0% Prevenar 13), and conjunctivitis (27.0% PNEUMOSIL; 19.0% Prevenar 13). The most common TEAE after the booster vaccination through 4 weeks of follow up was upper respiratory tract infection (28.6% PNEUMOSIL, 12.8% Prevenar 13), dermatitis (8.2% PNEUMOSIL, 6.4% Prevenar 13), and diarrhea (4.1% PNEUMOSIL, 10.6% Prevenar 13). The differences in the frequency of these TEAEs between the treatment groups were within the expected range for this early-stage clinical study. The only vaccine-related TEAE for more than 1 infant was Grade 1 vaccination site swelling (2.0% PNEUMOSIL, 6% Prevenar 13), and the only severe TEAE reported for > 1 infant was bronchiolitis (2% PNEUMOSIL, 0% Prevenar 13).

Six (6.0%) infants in the PNEUMOSIL group and 2 (2.0%) infants in the Prevenar 13 group had a treatment-emergent SAE through 12 weeks post primary vaccination, and one (2.0%) infant in the PNEUMOSIL group had a treatment-emergent SAE after the booster vaccination through 4 weeks of follow up. There was a numerical imbalance in serious cases of bronchiolitis (4 in the PNEUMOSIL group, 1 in the Prevenar 13 group) but no imbalance in overall TEAEs of bronchiolitis. No treatment-emergent SAE was considered to be related to study vaccine, and there was no temporal relationship to any vaccination.

In the VAC-56 study, the most common TEAEs reported in both treatment groups through 28 days post booster dose were upper respiratory tract infection (48.6% PNEUMOSIL, 50.7% Synflorix), diarrhea (18.7% PNEUMOSIL, 17.7% Synflorix), gastroenteritis (10.2% in both groups), and furuncle (10.0% PNEUMOSIL, 8.7% Synflorix) (Table 4). Most of the TEAEs were of mild or moderate severity. The most common vaccine-related TEAE was vaccination-site swelling (0.3% PNEUMOSIL, 0.7% Synflorix).

**Table 4. Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects – Safety Set (VAC-056)**

| | PNEUMOSIL (N=1,503) | | | Synflorix (N=747) | | |
|---|---|---|---|---|---|---|
| **PT*** | **Number of Events** | **Number of Subjects** | **% of Group** | **Number of Events** | **Number of Subjects** | **% of Group** |
| Upper respiratory tract infection | 1,041 | 730 | (48.6) | 552 | 379 | (50.7) |
| Diarrhoea | 317 | 281 | (18.7) | 139 | 132 | (17.7) |
| Furuncle | 183 | 150 | (10.0) | 77 | 65 | (8.7) |
| Gastroenteritis | 169 | 154 | (10.2) | 80 | 76 | (10.2) |
| Conjunctivitis | 116 | 110 | (7.3) | 67 | 64 | (8.6) |
| Cough | 103 | 95 | (6.3) | 39 | 39 | (5.2) |
| Bronchiolitis | 65 | 59 | (3.9) | 47 | 42 | (5.6) |
| Tinea infection | 62 | 62 | (4.1) | 22 | 22 | (2.9) |
| Febrile infection | 54 | 52 | (3.5) | 28 | 25 | (3.3) |
| Dermatitis diaper | 37 | 36 | (2.4) | 31 | 28 | (3.7) |
| Pneumonia | 44 | 41 | (2.7) | 21 | 21 | (2.8) |
| Rash maculo-papular | 37 | 37 | (2.5) | 17 | 16 | (2.1) |
| Tinea capitis | 30 | 29 | (1.9) | 23 | 22 | (2.9) |
| Oral candidiasis | 37 | 33 | (2.2) | 15 | 15 | (2.0) |
| Body tinea | 29 | 29 | (1.9) | 18 | 18 | (2.4) |
| Pyrexia | 31 | 31 | (2.1) | 16 | 16 | (2.1) |
| Impetigo | 27 | 27 | (1.8) | 19 | 19 | (2.5) |
| Rash pustular | 26 | 25 | (1.7) | 16 | 16 | (2.1) |
| Vomiting | 25 | 25 | (1.7) | 13 | 13 | (1.7) |
| Rash papular | 22 | 20 | (1.3) | 13 | 11 | (1.5) |
| Dermatitis contact | 18 | 17 | (1.1) | 7 | 7 | (0.9) |
| Skin candida | 14 | 14 | (0.9) | 11 | 11 | (1.5) |
| Dermatitis atopic | 12 | 12 | (0.8) | 11 | 11 | (1.5) |
| Seborrhoeic dermatitis | 17 | 17 | (1.1) | 5 | 5 | (0.7) |

Abbreviation: PT=preferred term
* Based on MedDRA dictionary version 20.0
Source: VAC-056 Final Statistical Report Table 14.3.1-5 and Listings 16.2.7-1.1.1 and 16.2.7-1.1.2.

A total of 2.4% of subjects in each vaccine group experienced at least one SAE through 28 days post booster. The most frequently reported SAEs were bronchiolitis, gastroenteritis and pneumonia in both vaccine groups. No SAE was considered related to study vaccine. Three deaths occurred in the VAC-

056 study through 28 days post booster, as a result of the following SAEs: pneumococcal meningitis (serotype 10A), pneumonia secondary to perinatal HIV infection, and pneumonia. None of the deaths was considered vaccine-related by the Investigator.

### 1.8.2. Immunogenicity

In the VAC-017 study, serum samples were collected 28 days after vaccination in the adult and toddler cohorts, and 28 days after completion of the primary vaccination series and prior to and 28 days post booster vaccination in the infant cohort, for evaluation by ELISA to determine the IgG concentration to each of the 10 serotypes contained in PNEUMOSIL. In the case of VAC-017 toddlers, a random subset was selected for this analysis (n=34), and this subset of toddlers also had serotype-specific IgGs determined from sera collected at baseline. In the infant cohort of VAC-017, the IgG concentration was also determined for each component of the co-administered pentavalent vaccine (DTwP-HepB-Hib). The functional activity of the antibody response to the 10 serotypes contained in PNEUMOSIL was also measured by OPA in randomly selected subsets of infants (n=20 per group) and toddlers (n=17 per group), and in all adults using the same serum samples collected 28 days after vaccination (only after primary vaccination in the case of infants). In the PCV10-002 study, serum samples were collected 28 days after the second vaccination to determine serotype-specific IgG concentrations; and the functional activity of the antibody response was measured by OPA in a randomly selected subset of toddlers (n=25 per group). In the VAC-056 study, serum samples were collected at 28 days after completion of the primary vaccination series and, for the first 675 randomized subjects, also at 28 days post booster dose, for evaluation of both serotype-specific IgG responses and functional activity as measured by OPA (subsets of n=250 per group post primary, and n=100 per group post booster for OPA). IgG antibody levels and neutralization titers were also measured, as indicated, to determine seroresponse rates or GMCs to antigenic components of EPI vaccines co-administered with primary (DTwP-HeB-Hib, polio, rotavirus) or booster (measles-rubella, yellow fever) doses of study vaccine.

PNEUMOSIL was shown to be immunogenic for all 10 serotypes contained in the vaccine in all cohorts evaluated in the VAC-017 and PCV10-002 studies, and the level of responses to each serotype in infants and toddlers was comparable to the responses observed in the Prevenar 13 control group. The percentage of infants achieving an IgG concentration of 0.35 µg/mL (the reference concentration for assessment of vaccine efficacy against IPD defined by the WHO[26]) at 28 days post final primary series vaccination was substantial across all serotypes in both treatment groups, with seroresponse rates of 91% or higher achieved in all cases except for serotypes 6A (79.0%) and 6B (89.0%) in the PNEUMOSIL group (Table 5). While they were generally higher in the Prevenar 13 group, IgG GMCs were > 1 µg/mL for all 10 serotypes in both treatment groups.

**Table 5. Percentage of IgG Seroresponders in the Infant Cohort – Primary Series (VAC-017)**

| | PNEUMOSIL (N = 100) | | Prevenar 13 (N = 100) | | PNEUMOSIL vs Prevenar 13 |
|---|---|---|---|---|---|
| Serotype | n (%)[a] | 90% CI[b] | n (%)[a] | 90% CI[b] | Difference (90% CI)[c] |
| IgG ELISA type 1 | 99 (99.0) | 95.34 - 99.95 | 100 (100) | 97.05 - 100.00 | -1.0 (-5.13- 2.66) |
| IgG ELISA type 5 | 100 (100) | 97.05 - 100.00 | 97 (97.0) | 92.43 - 99.18 | 3.0 (-1.10- 7.95) |
| IgG ELISA type 6A | 79 (79.0) | 71.19 - 85.48 | 91 (91.0) | 84.82 - 95.22 | -12.0 (-20.94- -2.97) |
| IgG ELISA type 6B | 89 (89.0) | 82.45 - 93.71 | 93 (96.9) | 92.12 - 99.14 | -7.9 (-15.00- -1.01) |
| IgG ELISA type 7F | 97 (97.0) | 92.43 - 99.18 | 100 (100) | 97.05 - 100.00 | -3.0 (-7.95- 1.10) |
| IgG ELISA type 9V | 94 (94.0) | 88.50 - 97.36 | 97 (97.0) | 92.43 - 99.18 | -3.0 (-9.17- 2.90) |
| IgG ELISA type 14 | 98 (98.0) | 93.84 - 99.64 | 96 (97.0) | 92.35 - 99.17 | 1.0 (-4.00- 6.27) |
| IgG ELISA type 19A | 92 (92.0) | 86.03 - 95.96 | 94 (97.9) | 93.59 - 99.63 | -5.9 (-12.38- 0.17) |
| IgG ELISA type 19F | 99 (99.0) | 95.34 - 99.95 | 97 (99.0) | 95.25 - 99.95 | 0.0 (-4.22- 4.33) |
| IgG ELISA type 23F | 91 (91.0) | 84.82 - 95.22 | 97 (97.0) | 92.43 - 99.18 | -6.0 (-12.77- 0.40) |

Abbreviations: CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, IgG = immunoglobulin G.
[a] Number of responders (IgG ≥ 0.35 µg/mL).
[b] Exact CIs based on Clopper-Pearson method.
c Exact CIs around treatment group differences were calculated based on Newcombe score.
Source: VAC-017 CSR Table I12.

Similarly, while the functional immune response to multiple serotypes (types 6A, 7F, 9V, and 19A) was superior for the Prevenar 13 group as measured by OPA GMTS (and as illustrated in divergent reverse cumulative distribution [RCD] curves), the percentage of infants with a functional antibody response (OPA titer ≥ 1:8) was substantial across all serotypes for both treatment groups – and was numerically higher for the PNEUMOSIL group for more serotypes (4 vs. 1) (Table 6). The small number of subjects with OPA data in all 3 cohorts limits what can be meaningfully concluded from these analyses.

IgG GMCs decreased substantially from 4 weeks post Vaccination 3 to just prior to the booster vaccination in both the PNEUMOSIL and Prevenar 13 groups. While GMCs were generally higher in the Prevenar 13 group at 4 weeks post Vaccination 3, pre-booster vaccination GMCs were generally comparable between groups due to the more substantial reduction in IgG concentrations in the Prevenar 13 group for serotypes that were significantly higher in the Prevenar 13 group post primary series. Both PNEUMOSIL and Prevenar 13 demonstrated a substantial booster effect across serotypes, indicating that the initial 3-dose series of both vaccines effectively 'primed' infants for boosting of immune responses.

**Table 6. Percentage of OPA Seroresponders in the VAC-017 Infant Cohort – Primary Series (VAC-017)**

| Seroresponders on OPA Titers | PNEUMOSIL (N = 20) | | Prevenar 13 (N = 20) | | PNEUMOSIL vs Prevenar 13 |
|---|---|---|---|---|---|
| | n (%)[a] | 90% CI[b] | n (%)[a] | 90% CI[b] | Difference (90% CI)[c] |
| OPA - Pn 1 | 15 (93.8) | 73.60 - 99.68 | 11 (84.6) | 58.99 - 97.19 | 9.1 (-15.55 - 36.11) |
| OPA - Pn 5 | 19 (95.0) | 78.39 - 99.74 | 19 (95.0) | 78.39 - 99.74 | 0.0 (-18.56 - 18.56) |
| OPA - Pn 6A | 20 (100) | 86.09 - 100.00 | 19 (100) | 85.41 - 100.00 | |
| OPA - 6B | 19 (100) | 85.41 - 100.00 | 19 (95.0) | 78.39 - 99.74 | 5.0 (-12.35 - 22.97) |
| OPA - 7F | 20 (100) | 86.09 - 100.00 | 20 (100) | 86.09 - 100.00 | |
| OPA - 9V | 20 (100) | 86.09 - 100.00 | 20 (100) | 86.09 - 100.00 | |
| OPA - 14 | 19 (100) | 85.41 - 100.00 | 18 (94.7) | 77.36 - 99.73 | 5.3 (-12.15 - 24.01) |
| OPA - 19A | 16 (94.1) | 74.99 - 99.70 | 20 (100) | 86.09 - 100.00 | -5.9 (-26.41 - 11.01) |
| OPA - 19F | 20 (100) | 86.09 - 100.00 | 19 (95.0) | 78.39 - 99.74 | 5.0 (-11.64 - 22.97) |
| OPA - 23F | 20 (100) | 86.09 - 100.00 | 20 (100) | 86.09 - 100.00 | |

Abbreviations: CI = confidence interval, OPA = opsonophagocytic assay.
[a] Number of responders (OPA titers ≥ 1:8).
[b] Exact CIs based on Clopper-Pearson method.
c Exact CIs around treatment group differences were calculated based on Newcombe score. Calculation of difference and CI around the difference was not possible when all subjects in both groups were responders.
Source: VAC-017 CSR Table II5.

In the VAC-017 toddler cohort, there was a substantial booster response for all serotypes in both treatment groups. No meaningful conclusions can be drawn from the generally higher Geometric Mean Fold Rise (GMFR) response after boosting with Prevenar 13 given the small number of boosted subjects, higher baseline GMCs in the PNEUMOSIL group, and the potential immunologic advantage of boosting with the homologous vaccine (Prevenar 13) that was used for priming. Additionally, OPA GMTs were similar in toddlers boosted with Prevenar 13, and there was no divergence in RCD curves of OPA titers in favor of Prevenar 13.

In the PCV10-002 naïve-toddler study, the percentage of seroresponders (IgG ≥ 0.35 µg/mL) was over 90.0% in both treatment groups, except for serotype 9V (89.0%) in the PNEUMOSIL group. While they were generally higher in the Prevenar 13 group, GMC point estimates (as well as lower bound of the 95% CI) were >1 µg/mL for all the serotypes in both treatment groups. Similarly, while the functional immune response to serotype 6A was superior for the Prevenar 13 group as measured by OPA GMTS, the percentage of infants with a functional response (OPA titer ≥ 1:8) was again substantial across all serotypes for both treatment groups, with OPA seroresponse rates of 92% to 100% in the PNEUMOSIL group and 96% to 100% in the Prevenar 13 group.

In the VAC-056 study, non-inferiority of the post-primary series immune responses was demonstrated for all 10 serotypes in PNEUMOSIL in comparison to the immune responses induced by the matched serotypes (1, 5, 6B, 7F, 9V, 14, 19F, 23F) or the lowest responder (6A, 19A) in Synflorix, based on both the proportion of IgG seroresponders (IgG ≥ 0.35 µg/mL) and GMCs. The lower bound of the 97.5% CI for the difference in seroresponse rates exceeded -10% (Table 7), and the lower bound of the 97.5% CI for the GMC ratio exceeded 0.5 (Table 8), for all 10 serotypes.

**Table 7. Non-Inferiority of IgG Antibody Response Post Primary Series: Treatment Group Proportions and Treatment-Group Difference in Proportions of IgG Responders (VAC-056)**

| | PNEUMOSIL (N=1458) | | | | Synflorix (N=724) | | | | Treatment group comparison: PNEUMOSIL - Synflorix | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Serotype** | **N†** | **n‡** | **(%)** | **(95% CI)** | **N** | **n** | **(%)** | **(95% CI)** | **Difference (%)** | **(97.5% CI)§** |
| **Type 1** | 1458 | 1454 | (99.7) | (99.3 – 99.9) | 724 | 717 | (99.0) | (98.0 – 99.6) | 0.7 | (-0.0 – 1.9)* |
| **Type 5** | 1458 | 1435 | (98.4) | (97.6 – 99.0) | 724 | 692 | (95.6) | (93.8 – 97.0) | 2.8 | (1.2 – 5.0)* |
| **Type 6A•** | 1458 | 1193 | (81.8) | (79.8 – 83.8) | 724 | 555 | (76.7) | (73.4 – 79.7) | 5.2 | (1.1 – 9.5)* |
| **Type 6B** | 1452 | 1142 | (78.7) | (76.5 – 80.7) | 724 | 555 | (76.7) | (73.4 – 79.7) | 2.0 | (-2.2 – 6.4)* |
| **Type 7F** | 1458 | 1443 | (99.0) | (98.3 – 99.4) | 724 | 709 | (97.9) | (96.6 – 98.8) | 1.0 | (-0.1 – 2.7)* |
| **Type 9V** | 1458 | 1391 | (95.4) | (94.2 – 96.4) | 724 | 690 | (95.3) | (93.5 – 96.7) | 0.1 | (-1.9 – 2.5)* |
| **Type 14** | 1456 | 1437 | (98.7) | (98.0 – 99.2) | 722 | 715 | (99.0) | (98.0 – 99.6) | -0.3 | (-1.4 – 1.0)* |
| **Type 19A•** | 1454 | 1386 | (95.3) | (94.1 – 96.4) | 724 | 555 | (76.7) | (73.4 – 79.7) | 18.7 | (15.1 – 22.5)* |
| **Type 19F** | 1453 | 1427 | (98.2) | (97.4 – 98.8) | 720 | 713 | (99.0) | (98.0 – 99.6) | -0.8 | (-1.9 – 0.5)* |
| **Type 23F** | 1457 | 1372 | (94.2) | (92.8 – 95.3) | 724 | 557 | (76.9) | (73.7 – 80.0) | 17.2 | (13.6 – 21.1)* |

Abbreviation: CI=confidence interval
† Number of observations contributing to analysis
‡ Number of responders (IgG ≥ 0.35 µg/mL)
§ PNEUMOSIL was considered non-inferior to Synflorix if at least 7 serotypes were non-inferior based either on the lower bound for the difference > -10% or the GMC ratio > 0.5, using 97.5% CIs to account for multiple comparisons.
• Synflorix proportion of responders for serotypes 6A and 19A was operationally defined as the lowest observed proportion of responders among the 8 serotypes in common with PNEUMOSIL
* Indicates individual comparisons for which the difference in proportions criterion was met
Source: VAC-056 Final Statistical Report Table 14.2.1-2.1

The observed proportion of IgG responders in the PNEUMOSIL group exceeded 94% for all serotypes except for 6A (81.8%) and 6B (78.7%). In the Synflorix group, the lowest proportion of IgG responders among the 8 serotypes in common with PNEUMOSIL was observed for serotype 6B (76.7%). The observed proportion of IgG responders was higher in the PNEUMOSIL group for all but 2 serotypes (14 [-0.3% difference] and 19F [-0.8% difference]), and significantly higher in the PNEUMOSIL group (i.e. lower 97.5% confidence bound for difference in rates > 0) for 4 serotypes (5, 6A, 19A, 23F). The observed IgG GMCs were higher in the PNEUMOSIL group for all but 3 serotypes (6A, 9V, and 19F). IgG GMCs were significantly higher in the PNEUMOSIL group (i.e. lower 97.5% confidence bound for GMC ratio > 1) for 6 serotypes (1, 5, 7F, 14, 19A, 23F), and significantly higher (i.e. upper 97.5% confidence bound for GMC ratio < 1) in the Synflorix group for 1 serotype (19F).

**Table 8. Non-Inferiority of IgG Antibody Response Post Primary Series: Treatment Group IgG GMCs and Treatment-Group GMC Ratios (VAC-056)**

| | PNEUMOSIL (N=1458) | | | Synflorix (N=724) | | | Treatment group comparison: PNEUMOSIL/Synflorix | |
|---|---|---|---|---|---|---|---|---|
| **Serotype** | **n** | **GMC** | **(95% CI)** | **n** | **GMC** | **(95% CI)** | **GMC Ratio** | **(97.5% CI)†** |
| **Type 1** | 1458 | 4.29 | (4.14 – 4.45) | 724 | 1.99 | (1.88 – 2.11) | 2.15 | (2.00 – 2.32)* |
| **Type 5** | 1458 | 1.65 | (1.59 – 1.71) | 724 | 1.20 | (1.14 – 1.26) | 1.37 | (1.28 – 1.47)* |
| **Type 6A‡** | 1458 | 1.00 | (0.95 – 1.06) | 724 | 1.13 | (1.02 – 1.25) | 0.89 | (0.78 – 1.01)* |
| **Type 6B** | 1452 | 1.21 | (1.13 – 1.30) | 724 | 1.13 | (1.02 – 1.25) | 1.07 | (0.93 – 1.24)* |
| **Type 7F** | 1458 | 2.97 | (2.85 – 3.10) | 724 | 2.29 | (2.16 – 2.43) | 1.30 | (1.19 – 1.41)* |
| **Type 9V** | 1458 | 1.31 | (1.26 – 1.36) | 724 | 1.42 | (1.34 – 1.50) | 0.92 | (0.85 – 1.00)* |
| **Type 14** | 1456 | 5.20 | (4.92 – 5.50) | 722 | 4.24 | (3.90 – 4.61) | 1.23 | (1.10 – 1.37)* |
| **Type 19A‡** | 1454 | 1.64 | (1.57 – 1.72) | 724 | 1.13 | (1.02 – 1.25) | 1.45 | (1.30 – 1.63)* |
| **Type 19F** | 1453 | 4.35 | (4.17 – 4.54) | 720 | 5.93 | (5.50 – 6.39) | 0.73 | (0.67 – 0.80)* |
| **Type 23F** | 1457 | 1.58 | (1.51 – 1.66) | 724 | 0.87 | (0.80 – 0.95) | 1.81 | (1.63 – 2.01)* |

Abbreviations: CI=confidence interval; GMC=geometric mean concentration
† PNEUMOSIL was considered non-inferior to Synflorix if at least 7 serotypes were non-inferior based either on the lower bound for the difference > -10% or the GMC ratio > 0.5, using 97.5% CIs to account for multiple comparisons.
‡ Synflorix GMC for serotypes 6A and 19A was operationally defined as the GMC for the serotype with the lowest observed proportion of responders (IgG ≥ 0.35 µg/mL) among the 8 serotypes in common with PNEUMOSIL
* Indicates individual comparisons for which the GMC ratio criterion was met
Source: VAC-056 Final Statistical Report Table 14.2.1-2.2

The observed proportion of OPA seroresponders (titer ≥ 1:8) post primary series was > 92% for all 10 serotypes in the PNEUMOSIL group (data not shown). The observed proportion of OPA responders was higher in the PNEUMOSIL group compared to the Synflorix group for all but 2 serotypes (14 [-0.8% difference] and 19F [-1.6% difference]), and was significantly higher (i.e. lower 95% confidence bound for difference in rates > 0) in the PNEUMOSIL group for 4 serotypes (1, 6A, 6B, 19A). Post-primary series OPA GMTs were significantly higher (i.e. lower 95% confidence bound for GMT ratio > 1) in the PNEUMOSIL group for 6 of the 10 serotypes (1, 5, 6A, 6B, 19A, 23F), and significantly higher (i.e. upper 95% confidence bound for GMT ratio < 1) in the Synflorix group for 2 serotypes (9V, 19F) (Table 9).

Immune responses to all EPI vaccines co-administered with the 3-dose primary series and the booster dose were shown to be equivalent between the PNEUMOSIL and Synflorix groups. The proportions of seroresponders exceeded 98% in both groups for diphtheria, tetanus, hepatitis B, and PRP. The proportion of subjects with anti-polio titers ≥ 1:8 exceeded 97% in both groups for type 1 and type 3; for polio type 2, the proportion of subjects with anti-polio titers ≥ 1:8 was 83.7% in the PNEUMOSIL group and 80.9% in the Synflorix group. The proportion of subjects with anti-rotavirus concentration ≥ 20 U/mL was low in both vaccine groups: 27.3% in the PNEUMOSIL group and 27.1% in the Synflorix group. For the pertussis antigens, the GMCs were slightly lower in the PNEUMOSIL group; GMC ratios were 0.82 (95% CI; 0.62-1.09) and 0.98 (95% CI; 0.77-1.25) for the anti-pertussis and anti-fimbriae 2/3 responses, respectively. The proportions of responders to EPI vaccines exceeded 96% in both groups for rubella and yellow fever. The proportion of subjects with anti-measles IgG ≥ 150 mIU/mL was 89.2% in the PNEUMOSIL group and 88.0% in the Synflorix group.

**Table 9. Functional Antibody Response Post Primary Series: Treatment Group OPA Geometric Mean Titers and Treatment-Group Geometric Mean Titer Ratios (VAC-056)**

| | PNEUMOSIL (N=247) | | | Synflorix (N=250) | | | Treatment group comparison: PNEUMOSIL/Synflorix | |
|---|---|---|---|---|---|---|---|---|
| **Serotype** | **n** | **GMT** | **(95% CI)** | **n** | **GMT** | **(95% CI)** | **GMT Ratio** | **(95% CI)** |
| **Type 1** | 247 | 85.17 | (71.34 – 101.69) | 249 | 27.55 | (22.96 – 33.06) | 3.09 | (2.40 – 3.98)* |
| **Type 5** | 247 | 161.34 | (139.94 – 186.02) | 249 | 115.93 | (98.85 – 135.97) | 1.39 | (1.12 – 1.72)* |
| **Type 6A** | 247 | 1317.16 | (1109.36 – 1563.88) | 241 | 7.06 | (5.83 – 8.56) | 186 | (144 – 241)* |
| **Type 6B** | 243 | 913.52 | (745.97 – 1118.70) | 245 | 467.65 | (365.27 – 598.73) | 1.95 | (1.42 – 2.69)* |
| **Type 7F** | 247 | 1833.71 | (1612.31 – 2085.51) | 250 | 1586.75 | (1392.62 – 1807.94) | 1.16 | (0.96 – 1.39) |
| **Type 9V** | 242 | 141.72 | (113.36 – 177.16) | 249 | 376.77 | (324.01 – 438.13) | 0.38 | (0.29 – 0.49)* |
| **Type 14** | 244 | 1019.34 | (816.53 – 1272.52) | 247 | 1102.64 | (878.56 – 1383.87) | 0.92 | (0.67 – 1.27) |
| **Type 19A** | 247 | 148.59 | (121.35 – 181.95) | 236 | 11.09 | (9.19 – 13.39) | 13.4 | (10.2 – 17.7)* |
| **Type 19F** | 247 | 594.27 | (509.98 – 692.49) | 250 | 895.39 | (784.96 – 1021.35) | 0.66 | (0.54 – 0.81)* |
| **Type 23F** | 246 | 767.24 | (648.95 – 907.10) | 243 | 253.09 | (197.10 – 325.00) | 3.03 | (2.25 – 4.09)* |

Abbreviations: CI=confidence interval; GMT=geometric mean titer; OPA=opsonophagocytic activity
* Identifies statistically significant differences
Source: VAC-056 Final Statistical Report Table 14.2.2-2.2

Finally, a booster response was demonstrated for all 10 serotypes in both vaccine groups (data not shown). Post-booster IgG GMCs were significantly higher in the PNEUMOSIL group for 8 serotypes (1, 5, 6A, 6B, 7F, 14, 19A, 23F), and significantly higher in the Synflorix group for 2 serotypes (9V, 19F) (Table 10).

**Table 10. Booster Response: Treatment Group IgG GMCs and Treatment-Group GMC Ratios (VAC-056)**

| | PNEUMOSIL (N=425) | | | Synflorix (N=209) | | | Treatment group comparison: PNEUMOSIL/Synflorix | |
|---|---|---|---|---|---|---|---|---|
| **Serotype** | **n** | **GMC** | **(95% CI)** | **n** | **GMC** | **(95% CI)** | **GMC Ratio** | **(95% CI)** |
| **Type 1** | 425 | 5.73 | (5.27 – 6.22) | 209 | 2.45 | (2.16 – 2.78) | 2.34 | (2.02 – 2.71) |
| **Type 5** | 425 | 1.31 | (1.21 – 1.41) | 208 | 0.83 | (0.75 – 0.92) | 1.57 | (1.38 – 1.79) |
| **Type 6A** | 424 | 4.87 | (4.41 – 5.39) | 209 | 0.42 | (0.35 – 0.49) | 11.6 | (9.67 – 14.0) |
| **Type 6B** | 423 | 8.33 | (7.71 – 9.00) | 209 | 4.42 | (3.98 – 4.90) | 1.89 | (1.65 – 2.15) |
| **Type 7F** | 425 | 6.37 | (5.88 – 6.90) | 209 | 4.06 | (3.65 – 4.50) | 1.57 | (1.37 – 1.80) |
| **Type 9V** | 424 | 1.81 | (1.67 – 1.95) | 209 | 2.07 | (1.87 – 2.30) | 0.87 | (0.76 – 0.99) |
| **Type 14** | 420 | 6.85 | (6.09 – 7.70) | 204 | 4.62 | (3.88 – 5.50) | 1.48 | (1.21 – 1.82) |
| **Type 19A** | 423 | 3.97 | (3.64 – 4.34) | 205 | 0.94 | (0.78 – 1.14) | 4.22 | (3.52 – 5.06) |
| **Type 19F** | 416 | 6.16 | (5.68 – 6.68) | 204 | 9.70 | (8.68 – 10.83) | 0.63 | (0.55 – 0.73) |
| **Type 23F** | 425 | 4.08 | (3.72 – 4.47) | 209 | 2.13 | (1.88 – 2.42) | 1.91 | (1.63 – 2.24) |

Abbreviations: CI=confidence interval; GMC=geometric mean concentration; IgG=immunoglobulin G
Source: VAC-056 Final Statistical Report Table 14.2.2-3.3.2

**Table 11. Functional Antibody Response Post Booster: Treatment Group OPA Geometric Mean Titers and Treatment-Group Geometric Mean Titer Ratios (VAC-056)**

| | PNEUMOSIL (N=99) | | | Synflorix (N=100) | | | Treatment group comparison: PNEUMOSIL/Synflorix | |
|---|---|---|---|---|---|---|---|---|
| **Serotype** | **n** | **GMT** | **(95% CI)** | **n** | **GMT** | **(95% CI)** | **GMT Ratio** | **(95% CI)** |
| **Type 1** | 98 | 344.53 | (261.77 – 453.46) | 97 | 187.16 | (141.59 – 247.40) | 1.84 | (1.25 – 2.72) |
| **Type 5** | 99 | 409.87 | (312.35 – 537.84) | 100 | 360.59 | (281.89 – 461.25) | 1.14 | (0.79 – 1.64) |
| **Type 6A** | 98 | 3063.37 | (2328.56 – 4030.06) | 95 | 44.98 | (25.86 – 78.25) | 68.10 | (37.07 – 125.09) |
| **Type 6B** | 98 | 2824.56 | (2207.88 – 3613.50) | 100 | 1610.81 | (1276.29 – 2033.01) | 1.75 | (1.25 – 2.46) |
| **Type 7F** | 99 | 6977.27 | (5601.56 – 8690.85) | 100 | 4036.08 | (3270.20 – 4981.32) | 1.73 | (1.28 – 2.34) |
| **Type 9V** | 98 | 1137.28 | (862.30 – 1499.94) | 100 | 1229.05 | (979.30 – 1542.50) | 0.93 | (0.65 – 1.32) |
| **Type 14** | 97 | 3114.71 | (2331.38 – 4161.22) | 99 | 1411.94 | (978.24 – 2037.92) | 2.21 | (1.38 – 3.51) |
| **Type 19A** | 97 | 645.56 | (489.69 – 851.04) | 95 | 51.47 | (32.40 – 81.76) | 12.54 | (7.36 – 21.37) |
| **Type 19F** | 99 | 1592.40 | (1255.72 – 2019.35) | 98 | 1580.46 | (1189.81 – 2099.38) | 1.01 | (0.70 – 1.46) |
| **Type 23F** | 99 | 3846.82 | (2962.23 – 4995.58) | 100 | 1226.89 | (967.91 – 1555.18) | 3.14 | (2.21 – 4.45) |

Abbreviations: CI=confidence interval; GMT=geometric mean titer; OPA=opsonophagocytic activity
Source: VAC-056 Final Statistical Report Table 14.2.2-3.4.2

Post-booster OPA GMTs were significantly higher in the PNEUMOSIL group for 7 serotypes (1, 6A, 6B, 7F, 14, 19A, 23F). There was no serotype with significantly higher OPA GMT in the Synflorix group (Table 11).

### 1.9. Clinical Development Plan for PNEUMOSIL

The ultimate goal of PNEUMOSIL clinical development is to achieve licensure through a WHO-recognized national regulatory authority (NRA), followed by prequalification by WHO to support product acquisition by Gavi and UNICEF for its distribution to low- and middle-resource countries. The product specifications detailed in Part C of the WHO Technical Report Series (TRS) 977 Annex 3 (2013)[23] and the associated Target Product Profile (TPP) for the Advance Market Commitment (AMC) for Pneumococcal Conjugate Vaccines (2008)[27] – which establishes additional essential criteria for the AMC for PCVs – are a critical guide for the PNEUMOSIL clinical development plan, to ensure that planned trials serve to evaluate the vaccine on the basis of the essential attributes for a PCV deemed suitable for use in Gavi-eligible countries. As was the case for the second-generation PCVs, the path to WHO prequalification and Gavi eligibility for PNEUMOSIL is demonstration of the following in a Phase 3 pivotal trial in infants: 1) vaccine efficacy based on immunologic non-inferiority to a licensed and prequalified comparator vaccine post a 3-dose primary series, 2) manufacturing quality demonstrated by post-primary lot-to-lot consistency, 3) non-interference with co-administered EPI vaccines, 4) immunologic memory as indicated by a booster response, and 5) an adequate safety and tolerability profile after primary series and booster vaccination. An additional TPP requirement is that the first dose of the vaccine must be shown to be administrable at 6 weeks of life or earlier. The results of the VAC-056 study have demonstrated that PNEUMOSIL meets all of these requirements of a licensed and prequalified PCV. On the basis of these results, the Product Summary File for PNEUMOSIL was submitted to WHO for prequalification in January 2019, and was officially accepted for review in March 2019. In December 2019 PNEUMOSIL was awarded WHO prequalification.

As indicated in Section C.2.2.2 of the WHO TRS 977 Annex 3, an additional requirement for PCV licensure is that clinical data be relevant to the country in which licensure is being sought, taking into account country-specific factors such as the schedule for routine PCV immunization. The current descriptive Phase 3 trial will provide data necessary to evaluate the safety and immunogenicity of PNEUMOSIL when administered in an alternative schedule to the 3 dose primary schedule (3+0) being evaluated in the Phase 3 pivotal trial – namely in a 2 dose primary and booster (2+1) schedule – and compare immunogenicity to that of both currently licensed second-generation PCVs (Prevenar 13 and Synflorix) administered in the same 2+1 schedule. A Phase 3 trial is also being planned to evaluate the safety and immunogenicity of PNEUMOSIL administered in a 2+1 schedule in Indian infants. These studies will support regulatory approval of PNEUMOSIL in countries that have adopted a 2+1 schedule for routine PCV immunization in their EPI programme.

### 1.10. Study Rationale

Based on supportive data from a number of immunogenicity, carriage and clinical effectiveness studies, the WHO issued a position paper in 2012 recommending that countries adopt either a 3+0 or alternatively a 2+1 schedule for routine PCV administration to infants, with the primary doses of each schedule administered by 6 months of age and the booster dose of the 2+1 schedule administered at 9 months of age or later.[28] An updated WHO position paper issued in 2019 specifies that the booster dose of a 2+1 schedule should be administered at 9-18 months of age.[29] Which of the two PCV schedules a country adopts should be based on factors such as the epidemiology of pneumococcal disease in the country and coverage rates for EPI vaccines at 9 months of age or later. Because of the longer duration of protection that a booster dose may provide – particularly against serotypes of concern such as types 1 and 5 –, an increasing number of countries have adopted a 2+1 schedule in their EPI programmes, including India in 2018.

Given the TPP requirement regarding dosage schedule, and studies indicating higher seropositivity using an 8-week versus 4-week interval between primary doses,[30] study vaccine will be administered to infants enrolled in this Phase 3 trial at 6 weeks, 14 weeks, and 9-18 months of age. EPI vaccines will be co-administered with study vaccine during the primary dose visits, as well as during a study visit at 10 weeks of age (without co-administered study vaccine). This is an earlier schedule than the standard Gambian EPI schedule, as indicated in Table 12. Administering the infant EPI vaccines at this earlier schedule as part of the clinical trial ensures that all subjects are fully vaccinated, and avoids complications of missed vaccinations, and over-vaccination in the case of PCV.

**Table 12. Gambian EPI Schedule for Children 0 to 18 Months Old***

| Age at Immunization | Antigen |
|---|---|
| At birth | BCG, OPV, HepB |
| 2 months | OPV, DTwP-HepB-Hib, PCV, RV |
| 3 months | OPV, DTwP-HepB-Hib, PCV, RV |
| 4 months | OPV, DTwP-HepB-Hib, PCV, IPV |
| 9 months | OPV, measles-rubella, yellow fever |
| 18 months | OPV, measles-rubella, DTwP, Vitamin A |

Abbreviation: BCG, Bacillus Calmette–Guérin; OPV, Oral Polio Vaccine; RV, Rotavirus

*Should any changes to the EPI schedule in The Gambia occur before or during the study, the vaccines given alongside the

study vaccines will be modified accordingly to reflect the current programme.

The broadest possible age range consistent with WHO recommendations for timing of the booster dose in a 2+1 schedule (9-18 months of age) has been adopted in order to manage uncertainty in the study introduced as a result of the COVID-19 pandemic, which necessitated a suspension of study visits (to protect study subjects, their families and study staff from potential exposure to SARS-CoV-2). Given the uncertain date for resumption of study visits, the protocol allows the booster vaccination to be administered at 9-18 months of age, with the plan to complete the booster vaccinations in as expedited a manner as possible once the study is resumed in order to capture as many subjects at 9 months of age as possible. The rationale for prioritizing boosting at 9 months of age is that this age is aligned with the EPI schedule in The Gambia as well as many other low-to-middle income countries, and is commonly the age at which the booster dose of a 2+1 PCV schedule is given in such countries. EPI vaccines will be co-administered with the booster dose of study vaccine, except in the case of subjects who have reached 9 months of age prior to resumption of the study. In these subjects, 9-month EPI vaccines will continue to be administered at 9 months (+1 month window) to the degree it is considered to be reasonable by the PI in country, in discussion with the sponsor. Such decisions will take into account the operations of the routine governmental EPI clinics, the level of SARS-CoV-2 transmission in country and broader guidance on field operations provided by MRCG leadership in line with Government of The Gambia policies.

It is important to note that surveillance data from the Basse Health and Demographic Surveillance System (BHDSS) in the Upper River Region of The Gambia provide reassurance that this Phase 3 trial, in which some infants will receive PNEUMOSIL or Synflorix, instead of Prevenar 13, can be safely conducted in the country. Because of the early and successful introduction of 7-valent Prevenar and then Prevenar 13 in the national EPI schedule, the incidence of IPD due to serotypes included in Prevenar 13, and prevalence of nasopharyngeal carriage of vaccine-type pneumococci, have decreased significantly in Gambian children since PCV introduction.[11,29] In regard to IPD due to serotypes not included in PNEUMOSIL, the BHDSS has not detected a case of IPD in children aged 2-59 months due to serotype 4 since 2013, and has never detected a case due to serotype 18C since surveillance began in 2009. These data, together with BHDSS surveillance data showing numerical reduction in serotype-specific IPD in adults,[11] suggest robust indirect (herd) protection against Prevenar 13 vaccine-type disease in The Gambia. In regard to serotype 3 (not included in either PNEUMOSIL or Synflorix), it should be noted that this serotype was one of three that failed to meet the pre-specified non-inferiority criteria in the US pivotal trial of Prevenar 13 (Study 004).[31] There is therefore uncertainty whether Prevenar 13 offers protection against pneumococcal disease due to serotype 3.[32] Due to cross-reactivity from serotypes 6B and 19F, immune responses to 6A and 19A induced by Synflorix are not only measurable, but have been shown to provide statistically significant cross-protection in surveillance studies of vaccine effectiveness for individual serotypes against IPD (also, Synflorix is indicated for protection against serotype 19A disease in Europe, Canada and other countries).[33,34,35]

To ensure that all subjects in this Phase 3 trial ultimately gain maximal long-term protection against pneumococcal disease, infants who are enrolled in the PNEUMOSIL and Synflorix groups will be offered a dose of Prevenar 13 outside the study after Visit 6 has been completed for all study subjects and the study has been unblinded for the site team.

## 2. HYPOTHESES, OBJECTIVES AND ENDPOINTS

### 2.1. Study Hypotheses

**Immunogenicity:**

The immune responses to the 10 serotypes in PNEUMOSIL (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F) will be similar to the immune responses to these serotypes induced by Prevenar 13 and Synflorix at 4 weeks post booster dose.

**Safety:**

PNEUMOSIL administered in a 2+1 schedule at 6 weeks, 14 weeks, and 9-18 months of age will have an acceptable safety and tolerability profile.

### 2.2. Study Objectives

#### 2.2.1. Primary Objectives:

**Immunogenicity:**

1. To evaluate the serum IgG antibody responses (GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (administered at 9-18 months of age)

**Safety, Tolerability:**

1. To assess the safety and tolerability of a 2-dose primary series and booster dose of PNEUMOSIL co-administered with routine pediatric vaccines, through 4 weeks post booster dose

#### 2.2.2. Secondary Objectives:

**Immunogenicity:**

1. To evaluate the functional serum antibody responses (GMTs) to the 10 serotypes in PNEUMOSIL as measured by OPA, alone and in comparison to the responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (subset of 50 subjects per group)
2. To assess seroresponse rates (IgG antibody levels and functional responses) to the 10 serotypes in PNEUMOSIL, alone and in comparison to seroresponse rates for these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (subset of 50 subjects per group for functional responses).
3. To evaluate the serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination (administered at 6 and 14 weeks of age)
4. To evaluate the functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL as measured by OPA, alone and in comparison to the functional antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination (subset of 50 subjects per group)
5. To evaluate the persistence of the post-primary serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody

responses to these serotypes induced by Prevenar 13 and Synflorix, at 9-18 months of age (prior to a booster dose)

6. To evaluate the persistence of post-primary functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL as measured by OPA, alone and in comparison to the functional antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 9-18 months of age (subset of 50 subjects per group prior to booster)
7. To evaluate the booster responses [(serum antibody concentrations (GMC) and functional responses (GMT)] to PNEUMOSIL, alone and in comparison to booster responses to Prevenar 13 and Synflorix, from 4 weeks after completion of primary vaccination to 4 weeks after a booster dose (subset of 50 subjects per group for functional responses)

## 2.3. Study Endpoints

### 2.3.1. Primary Endpoints:

**Immunogenicity:**

- Serotype-specific serum IgG GMCs measured 4 weeks post booster dose

**Safety, Tolerability:**

- Number and severity of solicited local and systemic adverse events (AEs) through Day 6 post each vaccination
- Number, severity and relatedness of all unsolicited AEs until 9 months of age, and from booster vaccination through 4 week follow-up period.
- Number, severity and relatedness of all serious adverse events (SAEs) through the entire study period

### 2.3.2. Secondary Endpoints:

**For Secondary Objective 1 (post-booster OPA GMTs)**:

- Serotype-specific serum OPA GMTs measured 4 weeks post booster dose

**For Secondary Objective 2 (post-booster seroresponse rates)**:

- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured 4 weeks post booster dose
- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 1.0 µg/mL measured 4 weeks post booster dose
- Percentage of subjects with serotype-specific serum OPA titers ≥ 1:8 measured 4 weeks post booster dose

**For Secondary Objective 3 (post-primary IgG responses)**:

- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured 4 weeks post completion of primary vaccination

- Serotype-specific serum IgG GMCs measured 4 weeks post completion of primary vaccination

**For Secondary Objective 4 (post-primary OPA responses)**:

- Percentage of subjects with serotype-specific serum OPA titers ≥ 1:8 measured 4 weeks post completion of primary vaccination
- Serotype-specific serum OPA GMTs measured 4 weeks post completion of primary vaccination

**For Secondary Objective 5 (persistence of post-primary IgG responses)**:

- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 μg/mL measured prior to booster dose
- Serotype-specific serum IgG GMCs measured prior to booster dose

**For Secondary Objective 6 (persistence of post-primary OPA responses)**:

- Percentage of subjects with serotype-specific serum OPA titers ≥ 1:8 measured prior to booster dose
- Serotype-specific serum OPA GMTs measured prior to booster dose

**For Secondary Objective 7 (booster effects)**:

- Ratio of serotype-specific serum IgG GMCs measured 4 weeks post booster dose to serotype-specific IgG GMCs measured 4 weeks post completion of primary vaccination
- Ratio of serotype-specific serum OPA GMTs measured 4 weeks post booster dose to serotype-specific serum OPA GMTs measured 4 weeks post completion of primary vaccination

## 3. STUDY DESIGN

This is a prospective, single center, randomized, active-controlled, observer-blind, Phase 3 descriptive study in which 660 healthy Gambian pneumococcal conjugate vaccine (PCV)-naïve infants will be randomized 1:1:1 to receive 3 doses of either PNEUMOSIL, Synflorix or Prevenar 13 at 6 weeks, 14 weeks and 9-18 months of age. Standard EPI vaccinations in The Gambia, except Prevenar 13, will be given concomitantly with all 3 doses of study vaccine (except for subjects who receive the 9-month EPI vaccines earlier than the study booster dose due to impact of the COVID-19 pandemic). The study schema is presented in Table 13.

**Screening:** After parental informed consent is obtained, prospective subjects will be screened to determine eligibility. While informed consent may occur as early as 4 weeks of age, the screening window will be 6 to 8 weeks of age. Randomization will take place only after a subject has satisfied all eligibility criteria, including confirmation of 1) no acute illness that precludes vaccination; 2) a negative rapid diagnostic test (RDT)/blood film for malaria; and 3) normal vital signs. These same criteria will need to be satisfied prior to administration of any subsequent vaccination.

**Primary Series Vaccination and Follow up:** Subjects (n=660) deemed eligible to participate in the study by the Principal Investigator (PI) will be randomized in a 1:1:1 ratio based on a pre-established randomization scheme, to receive the first dose of either PNEUMOSIL, Synflorix or Prevenar 13 at 6 (+2) weeks of age (V1). Treatment assignment will be stratified by field site. Subjects will return to the clinic at 10 (+2) weeks of age (V2) for Gambian EPI vaccines (except for Prevenar 13), and at 14 (+2) weeks of age (V3) to receive the 2$^{nd}$ primary dose of study vaccine along with EPI vaccines.

**Table 13. Study Schema**

| Groups | N | Visits / Age (wks) | | | | | |
|---|---|---|---|---|---|---|---|
| | | V1 | V2 | V3 | V4 | V5 | V6 |
| | | 6 (+2) | 10 (+2) | 14 (+2) | V3+4 (+2) | 9-18 (+1) mo | V5+4 (+2) |
| PNEUMOSIL | 220 | X, E | E | X, E | B | B, X, E | B |
| Synflorix | 220 | X, E | E | X, E | B | B, X, E | B |
| Prevenar 13 | 220 | X, E | E | X, E | B | B, X, E | B |

wks = weeks, mo = months

X = study vaccination, E= EPI vaccines, B = blood sample for immunogenicity testing

A follow-up visit (V4) will take place at 4 (+2) weeks after the second study vaccine administration, during which blood will be collected for immunogenicity assessments.

**Booster Vaccination and Follow Up:** All subjects will return to clinic at 9-18 (+1) months of age for a booster vaccination of study vaccine that matches the original treatment assignment (V5). Standard EPI vaccinations based on the Gambian EPI schedule (measles-rubella vaccine, yellow fever vaccine, OPV) will be co-administered with the booster dose of study vaccine, except for subjects who receive the 9-month EPI vaccines earlier than the study booster dose due to impact of the COVID-19 pandemic.Prior to vaccination, a blood sample will be collected for immunogenicity assessments. Subjects will be evaluated at a follow-up visit 4 (+2) weeks later (V6), during which another blood sample will be collected for immunogenicity assessments. This visit will serve as the EOS visit for the subjects.

Unblinding of the CRO statistical personnel will occur after the last subject completes V4 to conduct an interim analysis of immunogenicity objectives through end of V4. The Sponsor, Principal Investigator, site team and rest of the contract research organization (CRO) personnel will continue to remain blinded to individual treatment assignments until all subjects complete Visit 6.

As previously noted, infants who are enrolled in the PNEUMOSIL and Synflorix groups will be offered a dose of Prevenar 13 outside the study after visit 6 for all study subjects have been completed and the study has been unblinded for the site team to ensure all recruited infants gain maximal long-term pneumococcal protection.

**Safety Monitoring**: Planned safety assessments will provide the data for active monitoring of vaccine safety during conduct of the trial through 4 weeks post the final (booster) vaccination.

Immediate solicited reactogenicity and vital signs will be assessed at 30 (+/- 10) minutes following study vaccine administration in all subjects. Severity of solicited reactions will be assessed by toxicity grading scale (see Section 9.2.2). The solicited local reactions assessed will include tenderness, erythema/redness, and induration/swelling at the study vaccine injection site. The solicited systemic reactions will include cutaneous rash, fever (based on axillary temperature), irritability, drowsiness, and decreased appetite.

The subjects will be monitored daily at home by field workers for assessment of local and systemic reactogenicity during the 6 days after each study vaccine administration. Reactogenicity scoring will be reviewed by a research clinician (RC) prior to being entered into the OpenClinica database system.

Subjects will be monitored for adverse events (AEs) at each clinic visit through 9 months of age, and from booster vaccination through 4 weeks of follow up. For subjects who receive the booster vaccination at 9 (+1) months of age, monitoring for all unsolicited AEs will occur through the entire study period. For subjects who receive the booster vaccination at > 10 months of age, only monitoring for serious adverse events (SAEs) will occur from 10 months of age until booster vaccination. Monitoring for all unsolicited AEs will resume from when the booster vaccination is administered through the 4-week follow-up period.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 21.0 or later) and assessed by the PI with regard to severity, relatedness, and duration. Any SAE ongoing at the time of the subject's EOS visit will be attempted to be followed until it is resolved, assessed as resolved with sequelae by the PI, or until last subject last visit (LSLV) in the trial (i.e. last subject completes V6). Any SAE deemed related to study vaccine that is ongoing at the time of LSLV will continue to be followed until it is resolved, assessed to be resolved with sequelae, or assessed to be stable/chronic. SAEs deemed not related to study vaccine that are unresolved at the time of LSLV will be classified as ongoing for the purposes of data lock but will continue to be followed by the investigator team or referred on, if appropriate, according to good practice in The Gambia.

To facilitate rigorous safety monitoring, data captured on CRFs at each visit will be entered into the OpenClinica database system within 3 business days from the date of the clinic visit. Home visit data (Day 1-6 following vaccination) will be entered in the OpenClinica database system within 3 days of the Day 6 home visit.

The Protocol Safety Review Team (PSRT), including the PI, RCs, PATH Clinical Lead, and CRO staff, will conduct a weekly review of aggregated safety data and of clinical trial conduct during the active vaccination periods of the trial. These reviews will be blinded for all members of the PSRT. After the last subject completes V4, the CRO lead biostatistician will not participate in PSRT reviews. The PSRT has the authority to implement a study pause based on review of safety findings, or if alerted to unexpected clinical findings by the PI. If the PSRT elects to implement a study pause, the study team will pause the study for randomization and vaccination purposes, until an independent DSMB approves lifting the pause. The PSRT, PI or PATH Clinical Lead may also seek additional guidance from the DSMB as dictated by the occurrence of certain events that do not warrant a study pause.

**Immunogenicity Testing:** Serum samples collected 4 weeks after completion of the 2-dose primary series (V4), prior to the booster dose (V5) and 4 weeks after the booster dose (V6) will be analyzed by ELISA to determine serum IgG concentrations to each of the 10 serotypes included in PNEUMOSIL. Analysis of primary immunogenicity objective 1 (post-booster IgG GMCs), and secondary immunogenicity objectives 2 (post-booster IgG seroresponse rates), 3 (post-primary IgG responses), 5 (persistence of post-primary IgG responses), and 7 (booster effects) will be based on these data. Serum samples collected at Visits 4, 5 and 6 will also be analyzed by OPA to determine the functional immune responses (serotype-specific OPA titers) to the 10 serotypes included in PNEUMOSIL. Analysis of secondary objectives 1 (post-booster OPA GMTs), 2 (post-booster OPA seroresponse rates), 4 (post-primary OPA responses), 6 (persistence of post-primary OPA responses), and 7 (booster effects) will be based on these data.

# 4. STUDY POPULATION

## 4.1. Description of Study Population

The study population will consist of healthy, Gambian male and female, PCV-naïve infants from 6 to 8 weeks of age, to be recruited, screened, and determined to be eligible or otherwise by the site staff (under the direction of the PI) at the Medical Research Council Unit, The Gambia at the London School of Hygiene and Tropical Medicine (MRCG at LSHTM).

Since 1947, the MRCG at LSHTM has been conducting medical research focused on infectious diseases of significance to people of The Gambia and other African countries, with the goal of reducing the burden of illness and death in the country and throughout the developing world. The MRCG at LSHTM has conducted seminal vaccine trials, in particular against *H. influenzae* type b and *S. pneumoniae* that have resulted in important benefits to The Gambia as a result of early vaccine introduction and disease surveillance. The VAC-017 and VAC-056 studies were also conducted at the MRCG at LSHTM.

Clinical vaccine trials at the MRCG at LSHTM are conducted at field sites based within the compounds of government urban health centers or at other facilities within the vicinity of the respective health centers if space at the health center itself is insufficient. These field sites are within a short distance of the main MRCG at LSHTM administrative and laboratory site in Fajara, which includes a ward and clinical unit for subject inpatient treatment, as well as clinical laboratories. The present trial will be conducted at multiple field sites.

In order to be eligible for randomization and vaccination, prospective subjects must meet all of the inclusion criteria and none of the exclusion criteria as follows:

### 4.2. Inclusion Criteria

1. They are healthy infants. Subjects are deemed healthy if, based on medical history and clinical assessment, they are determined to be without acute or chronic, clinically significant pulmonary, cardiovascular, hepatobiliary, gastrointestinal, renal, neurological, or hematological functional abnormality or illness that requires medical therapy.
2. They are between 6 and 8 weeks (i.e. 42 to 56 days) old, inclusive. Subjects will be eligible from the day they reach 6 weeks until the day they reach 8 weeks only.
3. Subject's parent must provide voluntary written/thumb-printed informed consent for the subject to participate in the study. As local languages in The Gambia are non-written, informed consent may be obtained from an English-illiterate parent but will require an English-literate impartial witness who is also fluent in the relevant local language (and who is not an employee of MRCG at LSHTM) to be present for consenting and to co-sign the ICF to confirm that the information in the ICF has been provided in full and that the subject's parent is consenting for their infant to take part in the trial having had any questions answered to the parent's apparent satisfaction.
4. Subject's parent must be able to comprehend and comply with study requirements and procedures and must be willing and able to return for all scheduled follow-up visits.
5. Subjects must have been born full-term, have a weight-to-height Z score of ≥ -2 SD at the time of enrollment (WHO child growth standard), and be ≥ 3.5 kg at randomization.

   Note: Subjects with borderline z-score or weight at initial screening may be rescreened if within the age window.
6. Subject's parents must have a readily identifiable place of residence in the study area, be available for the duration of trial participation, and have a consistent means of telephone contact.

   Note: A telephone and/or telephone credit will be provided to subjects enrolled in the trial to ensure they are always able to contact a member of the field team in the case of illness/adverse event.

### 4.3. Exclusion Criteria

1. Use of any investigational medicinal product prior to randomization or planned use of such a product during the period of study participation.
2. Previous vaccination against *S. pneumoniae*.
3. History of *S. pneumoniae* infection confirmed by culture from a normally sterile site.
4. History of allergic disease or history of a serious reaction to any prior vaccination or known hypersensitivity to any component of the study vaccines. This includes such reactions in older siblings.
5. History of anaphylactic shock.
6. Any abnormal (Grade ≥ 1) vital sign.
   Note: An abnormal vital sign, including fever (axillary temperature of ≥ 37.5°C), may be repeated to determine whether a subject is eligible for randomization. A minimum of 48 hours following a documented fever must pass before the subject can be reassessed for eligibility. The last vital sign measurement must be used as the baseline value for the study.
7. Any moderate or severe (Grade ≥ 2) acute illness.
   Note: Infants with a Grade 1 acute illness may be enrolled at the discretion of the PI.
   Note: Subjects with moderate or severe acute illness may return for clinical re-assessment; if the illness has sufficiently resolved, they may still qualify for randomization.
8. A positive RDT/blood film for malaria.
   Note: Subjects with a positive RDT may be retested post treatment. A RDT for malaria will be undertaken on the day of each vaccination to ensure a subject is not vaccinated with a concurrent malaria infection. As an RDT may remain persistently positive for a period despite successful malaria treatment, a blood film may be obtained in infants who have recently been treated for malaria and if negative the infant may be enrolled even if the RDT at this point remains positive, assuming they are otherwise clinically well.
9. History of administration of a non-study vaccine within 30 days prior to administration of study vaccine or during the course of study participation, other than EPI vaccinations, and any catch up campaigns administered through The Gambian health authority.
   Note: BCG administered to subjects who did not receive BCG at birth must be given at least 7 days prior to study vaccine.
10. Chronic administration (defined as more than 14 consecutive days) of immunosuppressant or other immune modifying drugs prior to the administration of the study vaccine, including the use of glucocorticoids. The use of topical and inhaled glucocorticoids will be permitted.
11. Administration of immunoglobulins and/or any blood products or anticipation of such administration during the study period.
12. History of known disturbance of coagulation or blood disorder that could cause anemia or excess bleeding (e.g., thalassemia, coagulation factor deficiencies, severe anemia at birth). Any clearly documented history in a first-degree relative (e.g., parent, sibling) of the same is also exclusionary.
13. Family history of suspected primary immunodeficiency in a first-degree relative.
14. Subject had a sibling die of likely sudden infant death syndrome (SIDS) or die suddenly and without apparent other cause or preceding illness in the first year of life.
15. Evidence of a clinically significant congenital abnormality as judged by the PI or designee.
16. History of meningitis, seizures or any neurological disorder.
17. Evidence by history taking alone of exposure to an HIV-positive individual through maternal fetal transmission, breast milk, or other blood-borne mechanisms.

18. Subject is a direct descendant (child or grandchild) of any person employed by the Sponsor, the CRO, the PI, study site personnel, or site.
19. Any medical or social condition that in the opinion of the PI may interfere with the study objectives, pose a risk to the subject, or prevent the subject from completing the study follow-up.

Note that specific exclusion criteria (e.g., abnormal vital sign, acute illness, positive RDT/blood film) will be reassessed at all study vaccination visits. Any subject who cannot be vaccinated due to an acute abnormality assessed at the V2 (EPI vaccines alone), V3 or V5 may return once the acute issue has resolved. A minimum of 48 hours must have passed after a documented fever, before a subject can be vaccinated. This safety requirement will not be deemed a protocol deviation should the visit fall outside the vaccination window; however, it will be encouraged to maintain the vaccination window whenever possible in these situations.

Note that there is no further screening once initial randomization has taken place.

# 5. STUDY PRODUCTS

## 5.1. PNEUMOSIL

### 5.1.1. Product Description

PNEUMOSIL consists of 10 individually fermented and purified pneumococcal polysaccharides that have been subsequently conjugated to recombinant $CRM_{197}$, a detoxified diphtheria toxin, using 1-cyano-4-dimethylaminopyridinium tetrafluoroborate (CDAP) conjugation chemistry.

One single 0.5 mL dose of PNEUMOSIL contains 2µg of polysaccharide for serotypes 1, 5, 9V, 14, 19A, 19F, 23F, 7F and 6A, and 4µg for serotype 6B. It is formulated with aluminum phosphate (0.125 mg $Al^{3+}$ per dose) as an adjuvant in an appropriate buffer, and the multi-dose presentation used in this trial contains thiomersal (25 µg per dose) as a preservative. The vaccine is a turbid white suspension.

### 5.1.2. Manufacturer

PNEUMOSIL is manufactured and supplied by SIIPL.

### 5.1.3. Presentation and Formulation

PNEUMOSIL will be supplied in a 5-dose (multi-dose) vial, in cartons containing 50 labeled vials and 1 product leaflet. Each vial label will include the following information: name of the medicinal product, composition, dose and fill volume, route of administration, lot number, manufacturing date, retest dates (if applicable), storage condition, and a cautionary statement ("For Clinical Trial Use Only").

### 5.1.4. Storage

PNEUMOSIL should be stored between 2°C and 8°C. It must not be frozen.

### 5.1.5. Potential Safety Risks

As with any vaccine, severe allergic reaction is a potential rare event. Known hypersensitivity to any component of the vaccine (including diphtheria toxoid and $CRM_{197}$) is a contraindication to vaccination.

In the VAC-017 study, the most commonly reported solicited adverse reactions in infants (n=100) after any of the 3 primary doses of PNEUMOSIL administered at 6, 10, and 14 weeks of age, and co-administered with DTwP-HepB-Hib vaccine, were irritability (69%), fever (53%), injection site tenderness (45%), injection site induration/swelling (21%), and decreased appetite (20%). Reported Grade 3 solicited adverse reactions in infants after any of the 3 primary doses of PNEUMOSIL were fever (1%), rash (1%) and irritability (1%).

In the VAC-056 study, the most frequently reported local reaction in infants (n=751) after any of the 3 primary doses of PNEUMOSIL were fever (52.1%), tenderness (49.1%), and irritability (32.0%).

The most commonly reported solicited adverse reactions in subjects from the infant cohort of the VAC-017 study (n = 49) after a booster dose of PNEUMOSIL administered at 10-13 months of age were injection site tenderness (18.3%), injection site induration/swelling (12.3%), fever (12.2%) and irritability (10.2%). The only reported Grade 3 solicited adverse reaction in these subjects was fever (4.1%; >39.0 – ≤40.0°C).

The most commonly reported solicited adverse reactions in subjects from the toddler cohort (n = 56) in the VAC-017 study after a booster dose of PNEUMOSIL at 12-15 months of age were injection site tenderness (21.5%), fever (16.1%), decreased appetite (12.5%), drowsiness (10.7%), and injection site induration/swelling (10.7%). The only reported Grade 3 solicited adverse reaction in toddlers was fever (3.6%). Refer to Section 1.8.1 and to the Investigator's Brochure (IB) for additional details on adverse reactions reported in clinical trials of PNEUMOSIL.

## 5.2. Synflorix

### 5.2.1. Product Description

Synflorix consists of 10 individually fermented and purified pneumococcal polysaccharides that have been subsequently conjugated to non-typeable *Haemophilus influenzae* protein D (serotypes 1, 4, 5, 6B, 7F, 9V, and 14), tetanus toxoid (serotype 18C), or diphtheria toxoid (serotype 19F) using CDAP conjugation chemistry.

One single 0.5 mL dose of Synflorix contains 1µg of polysaccharide for serotypes 1, 5, 6B, 7F, 9V, 14, and 23F, and 3µg of serotypes 4, 18C, and 19F. It is formulated with aluminum phosphate (0.5 mg $Al^{3+}$ per dose) as an adjuvant. The vaccine is a turbid white suspension.

### 5.2.2. Manufacturer

Synflorix is manufactured and supplied by GSK Biologicals.

### 5.2.3. Presentation and Formulation

Synflorix will be supplied in a single-dose vial. Each vial will be labeled with the following minimum information: name of the medicinal product, route of administration, expiry date, lot number, dose volume, and a cautionary statement ("For Clinical Trial Use Only").

### 5.2.4. Storage

Synflorix should be stored between 2°C and 8°C. It must not be frozen.

### 5.2.5. Potential Safety Risks

As with any vaccine, severe allergic reaction is a potential rare event. Synflorix should not be administered to subjects with known hypersensitivity to any component of the vaccine.

In In the VAC-056 study, the most commonly reported solicited adverse reactions in infants (n=364) after any of the 3 primary doses of Synflorix administered at 6, 10, and 14 weeks of age, and co-administered with DTwP-HepB-Hib vaccine, were tenderness (53.0%), fever (51.4%), and irritability (29.9%).

The most relevant additional clinical data for identifying potential solicited adverse reactions in infants who receive Synflorix in the current trial are from a Phase 3 study evaluating the safety and tolerability of Synflorix administered to Filipino infants (n = 300) as a 3-dose primary series at 6, 10, and 14 weeks of age, and co-administered with DTwP-HepB-Hib vaccine.[36] The most commonly reported solicited adverse reactions after any of the 3 primary doses of Synflorix were injection site tenderness (67.2%), irritability (66.2%), fever (60.9%), injection site erythema (47.0%), drowsiness (38.8%), injection site swelling (36.4%), and decreased appetite (25.9%). Reported Grade 3 solicited adverse reactions after any of the 3 primary doses of Synflorix were injection site tenderness (9.4%), fever (6.1%; >39.0 – ≤40.0˚C), irritability (2.9%), drowsiness (1.0%), and decreased appetite (0.2%). Injection site swelling > 30mm was reported in 9.3% of infants, and injection site erythema > 30 mm was reported in 2.4%.

A Phase 3 trial evaluating the safety and tolerability of a booster dose of Synflorix administered to toddlers aged 12-18 months (n = 737), and co-administered with INFANRIX hexa® (combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B (recombinant), inactivated poliomyelitis and adsorbed conjugated *Haemophilus influenzae* type b vaccine), was conducted in Finland, France and Poland.[35] The most commonly reported solicited adverse reactions after the booster dose of Synflorix were injection site tenderness (61.5%), injection site erythema (61.4%), irritability (59.6%), injection site swelling (46.0%), drowsiness (41.2%), fever (33.3%) and decreased appetite (31.3%). Grade 3 solicited adverse reactions after the booster dose of Synflorix were injection site tenderness (6.4%), fever (3.3%; >39.0 – ≤40.0˚C), irritability (2.0%), drowsiness (0.7%), and decreased appetite (0.5%). Injection site swelling > 30 mm was reported in 9.1% of toddlers, and injection site erythema > 30 mm was reported in 13.1%. Grade 4 fever (>40.0˚C) was reported in 0.1% of toddlers.

In both Phase 3 trials the incidence of solicited reactions reported after each vaccination dose was within the same range as after vaccination with the comparator, 7-valent Prevenar. Refer to the Summary of Product Characteristics for Synflorix (2014)[37] for additional information on adverse reactions that have been reported in clinical trials and post-marketing surveillance.

## 5.3. Prevenar 13

### 5.3.1. Product Description

A single 0.5 mL dose of Prevenar 13 contains 2.2 µg of the following pneumococcal polysaccharides serotypes – 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F – and 4.4 µg of pneumococcal polysaccharide serotype 6B, all conjugated to $CRM_{197}$ and absorbed onto aluminum phosphate (0.125mg aluminum). The vaccine is a turbid white suspension.

### 5.3.2. Manufacturer

Prevenar 13 is supplied by Pfizer Limited.

### 5.3.3. Presentation and Formulation

Prevenar 13 is supplied in a single dose 0.5 mL pre-filled glass syringe (PFS) with a plunger stopper and protective tip cap. It will be labeled with the following minimum information: name of the medicinal product, route of administration, expiry date, lot number, dose volume, and a cautionary statement ("For Clinical Trial Use Only").

#### 5.3.4. Storage

Prevenar 13 should be stored between 2°C and 8°C. It must not be frozen.

#### 5.3.5. Potential Safety Risks

Hypersensitivity to any component of the vaccine (including diphtheria toxoid and $CRM_{197}$) is a contraindication.

In infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age in US clinical trials, the most commonly reported solicited adverse reactions were irritability (>70%), injection site tenderness (>50%), decreased appetite (>40%), decreased sleep (>40%), increased sleep (>40%), fever (>20%), injection site redness (>20%), and injection site swelling (>20%). Refer to the product insert for Prevenar 13 (2014)[38] for additional information on adverse reactions that have been reported in clinical trials and post-marketing surveillance.

### 5.4. Vaccine Storage, Transport, and Temperature Monitoring

The temperature of study vaccines will be monitored during shipment, storage and transportation to the field sites to ensure that temperature deviations do not occur.

The temperature of all vaccine shipments will be monitored throughout transit using a continuous temperature monitoring system. Vaccines will not be used until the temperature of the vaccines throughout transit has been confirmed to be within acceptable limits.

Upon receipt at MRCG at LSHTM, Fajara, all vaccines will be stored at 2°C to 8°C in dedicated refrigerators that are safe, locked, and not accessible to unauthorized personnel – including study team personnel blinded for study conduct purposes. The refrigerators will be under continuous temperature monitoring with maintenance of daily temperature logs, and connected to a power source with a reliable back-up system. Vaccine needed for a particular day will be transported from the main MRCG at LSHTM facility at Fajara to the field site in a cold box with continuous temperature monitoring. Any unused vaccines at the end of clinic will be returned to MRCG at LSHTM, Fajara for storage if found within acceptable temperature range or will be kept aside for accountability.

It is the responsibility of designated unblinded site personnel to ensure that vaccine has not been exposed to temperatures outside the allowed range during transport or storage at the facility prior to being dispensed for vaccination. Should there be a deviation outside the allowed temperature range, the affected vaccine(s) will be quarantined. The temperature deviation will be reported to the CRO who will advise the unblinded investigator team of the action to be taken based on the magnitude and duration of the temperature deviation. All vaccine accountability procedures, including cold chain monitoring will be documented and are the responsibility of the unblinded study personnel.

### 5.5. Dose Preparation and Administration

A limited number of appropriately trained, unblinded study personnel (herein referred to as unblinded personnel) will be responsible for preparing study vaccine doses in accordance with the randomly determined assignment, administering the study and other EPI vaccines, and handling all vaccine

accountability procedures. The number of unblinded personnel will remain limited, and these personnel will not participate in the other aspects of the clinical trial, to help ensure the integrity of the blind at the site. The unblinded personnel will not reveal subjects' randomization assignments to the subjects' parents, or staff associated with the Sponsor, CRO, or site. Unblinded personnel will retrieve a subject's randomization assignment after being informed by the PI that a subject is eligible for randomization. They will prepare the study vaccine based on the subject's randomization assignment in a setting distinct from the clinic staff, and then the unblinded study nurse will administer study vaccine to a subject in a separate clinic area. Vaccination will only ever take place in a clinical setting in which there is immediate access to the medical personnel (certified in pediatric life support), equipment and medications required for emergency resuscitation.

Since PNEUMOSIL, Synflorix and Prevenar 13 are suspensions containing an alum adjuvant, study vaccine must be shaken gently immediately prior to use, in order to obtain a uniform homogenous white suspension. Inspection of each vial/PFS will occur immediately prior to use. If a vial/PFS or its contents appear unusual in any way, the vial/PFS will not be used, and procedures detailed in the Study Specific Procedures (SSP) for documentation and disposal will be followed.

Synflorix and Prevenar 13 are single dose presentations. For PNEUMOSIL, a single dose will be drawn from each multi-dose vial and the remaining will be kept aside for accountability. PNEUMOSIL and Synflorix will be drawn up into a syringe which is not readily distinguishable in appearance from the syringe in which Prevenar 13 will be administered to ensure the parents of subjects in these cohorts also remain blinded. All three vaccines, i.e., PNEUMOSIL, Synflorix and Prevenar 13 are white suspensions and therefore are not readily distinguishable by appearance alone. The syringe barrels will be masked to not reveal the commercial label on the Prevenar 13 PFS. It is expected that all doses of PNEUMOSIL and Synflorix will be administered immediately after preparation; however in no circumstance will the dose be administered more than 6 hours after preparation (and the dose will stored between 2°C and 8°C during this interval).

EPI vaccines will be administered in an unblinded manner. Unblinded nursing staff will administer vaccines based on WHO best practices.[39] Vaccination of EPI and PCV will be documented on the subject's Infant Welfare Card (IWC). A detailed account of procedures related to preparation and administration of study vaccine will be included in the SSP.

- PNEUMOSIL, Synflorix or Prevenar 13 will be administered as an IM injection into the anterolateral aspect of the left thigh, using a 23G x 25mm needle.
- Injectable EPI vaccines (DTwP-HepB-Hib, IPV, measles-rubella, and yellow fever vaccines) will be administered as an IM injection into the anterolateral aspect of the right thigh.
- When more than one injectable vaccine is to be given into the same limb the injections will be separated by a minimum of 2.5 cm
- RV and OPV vaccines will be administered orally according to standard local procedures.

Injectable vaccines may be given at other sites if there is a good reason to do so (e.g., local infection, or pre-existing swelling). In exceptional circumstances this could mean administering up to three vaccines, including study vaccine, into the same leg. Such decisions will be made on a case by case basis by the PI, and the reasons documented clearly in the clinical notes. When more than one vaccine is administered into the same leg, the leg may be temporarily marked with a pen to ensure local reactogenicity is assessed accurately. The site at which study vaccine is administered will be documented in the CRF for all subjects.

### 5.6. Accountability and Disposal

Following vaccination, the vaccine vials/PFS will be labeled with the screening number of the subject to whom the vaccine has been administered using prepared stickers. The person who administered the vaccine and the time and date of vaccine administration will also be documented in an appropriate vaccine accountability log on the day of vaccination. All used vials/PFS without the needle will be stored in a dedicated space that is accessible only to the unblinded site personnel and the unblinded CRO monitor (and ultimately disposed of after completion of the study).

In case a vial/PFS of vaccine is broken or unusable, the unblinded site personnel will promptly inform the unblinded monitor and store the vial/PFS for accountability, following all safety precautions. In case a broken vial/PFS cannot be stored safely for accountability, appropriate discard and documentation will be followed after consultation with the unblinded monitor. Study product prepared but not administered to subjects, and all unused study product, will likewise be documented per drug accountability processes and discarded after the study is completed or terminated after notification by the CRO study drug monitor.

The designated unblinded site personnel will maintain a complete and accurate inventory of study vaccines received (including the quantity of vaccines received, date of receipt, condition at receipt, temperature noted during transit), those administered, and any broken or destroyed.

The unblinded CRO monitor will visit the site (including field sites) periodically throughout the trial to review and verify vaccine accountability records, as well as to ensure compliance with all trial procedures by the unblinded site personnel. After final vaccine accountability is completed by the unblinded CRO monitor, any used or unused vials/PFS of study vaccine will be destroyed at the site under the supervision of the unblinded site personnel after permission from the local regulatory authority has been obtained. Due to the need to maintain blinding, no vaccine accountability records will be sent to the Sponsor or included in the trial master file (TMF) until after database lock.

# 6. STUDY PROCEDURES

## 6.1. Recruitment and Informed Consent

This will be a single-center study to be conducted at the MRCG at LSHTM, with prospective subjects to be recruited and consented at multiple field sites.

### 6.1.1. Community and Individual Sensitization

Recruitment for the trial will take place at MRCG at LSHTM clinical trial facilities (field sites) based in or close to the compounds of a number of government health centers in the peri-urban coastal region of The Gambia. The health centers provide antenatal and obstetric services as well as inpatient care. They are also the sites through which the national EPI vaccine program is delivered to infants and children.

Prior to commencing any trial-related activities a process of 'community sensitization' will take place. A series of 'kola nut'[†] meetings with the Alkalo (community leader) and other senior members of the local community including representatives of women's and mother's groups will take place. During these meetings, the PI and other members of the clinical trial team will explain the purpose of the trial, as set out in the ICF, and a chance for the attendees at the meeting to ask any questions they may have will be given. Following these meetings, information regarding the trial will be disseminated

[†] Kola nuts (the seeds of *Cola nitida* and *Cola acuminata*) are given to members of the community at the end of the meeting as a sign of thanks and respect.

throughout the local community through well-established community networks. The aim here is that the community as a whole is aware of the trial and that any concerns or misunderstandings are avoided.

Information regarding the trial may also be provided to mothers attending antenatal clinics to raise awareness of the trial in advance and to give them further time to consider and discuss possible participation.

Potentially eligible infants will subsequently be identified by members of the clinical trial team in the early post-natal period at around the time that the newborn vaccines (BCG, OPV and hepatitis B) are administered and 'individual sensitization' of the parents will be undertaken. Sensitization at this age is necessary as the first set of primary EPI vaccines is recommended in The Gambia at 8 weeks of age, so recruitment at this visit is too late to catch infants in the 6 to 8 week eligibility window.

During individual sensitization, parents will be approached and, if interested, the details of the study, as outlined in the ICF, will be explained to them by the study staff. Having had a chance to ask initial questions, they will then be given a copy of the ICF and encouraged to discuss the study with other close family members. It will be important to ensure that the subject's father is also aware of the study. According to the mother's preference a field worker may visit the home to provide information to the father or may provide such information by telephone. Contact details are taken from any parent who remains potentially interested following individual sensitization. The family will then be given a minimum of an overnight period to consider the information in the ICF before informed consent/enrollment can take place – i.e., individual sensitization and consent cannot take place on the same day. However, in most cases the interval will be significantly longer than this, given most sensitization will occur in the post-natal period and consent will not take place before an infant reaches at least 4 weeks of age and will generally occur at 6 weeks of age. Of note, neither community nor individual sensitization alter the later process of consent during which the ICF is reviewed again line by line on a one-to-one basis.

### 6.1.2. Initial and Continuing Informed Consent

Informed consent is the process of ensuring that study subjects' parent(s) fully understand the purpose of the study and what will and may happen during participation in the research study and what the risks are. The informed consent process continues throughout the study. Key study concepts will be reviewed with the study subjects' parent(s) at designated times and as needed; this review process will be fully documented. Additionally, if any new information becomes available that, in the judgment of PATH and/or the PI, may affect parents' decision to have their infant continue in the trial, such information will be shared, and may be the basis for requiring a new consent form to be signed. Parent(s) of enrolled subjects whose booster vaccination (Visit 5) was delayed due to suspension of the study in response to the COVID-19 pandemic will be required to complete a consent addendum at the time that the study is resumed. A dose of Prevenar13 will be offered outside the study protocol to any subject whose parent does not consent to the delayed booster vaccination to ensure long term pneumococcal protection is not compromised.

If interested following individual sensitization, a subject's parent(s) will be invited to one of the field sites, at which point documented informed consent can be obtained. Prior to initiation of this process at the site, parents must provide study staff with the IWC to confirm their infant's identity and age. Certified copies of IWCs will be retained as a part of the source documents for the trial.

A prospective subject may be as young as 4 weeks old on the day of consent. The parent providing consent must be 18 years or over on the day consent was provided. Consent from grandparents or guardians will not be accepted.

Parents who are literate in English will be provided with all the information in the ICF again by the PI or designee in English. English literacy will be confirmed in this case by asking the parent to read and explain a section of the consent form. Parents who are not literate in English (this is common in The Gambia) will have all the information in the ICF explained to them verbally in their local language by a member of the study team who is documented to be fluent in the language in question (all members of the team are English literate). The ICF is only written in English as local languages are spoken but not routinely written. However, the translation of the ICF into the local language will be agreed upon and recorded by the field team for consistency purposes prior to any consent taking place. These processes have been agreed upon by The Gambia Government/MRC Joint Ethics Committee. Of note, the tribe to which a parent belongs is not necessarily the same as the first language spoken. If consent is obtained in this way, an impartial witness, who is fluent in English and the local language, must be present throughout the process of informed consent and is required to attest that all the information in the ICF has been given to the parent. They must also confirm that the parent has had the chance to ask questions and that these have been answered to the parent's apparent satisfaction.

After understanding all aspects of the study and having all questions answered, the parent will be required to undertake an 'Assessment of Understanding' – a series of questions to check that key elements of the study have been fully understood. If understanding is confirmed (according to predefined criteria) the parent is required to sign or provide a thumb print confirming agreement to have the parent's infant participate in the study. Some parents may mark or sign the ICF rather than thumb-printing even though they are not English literate. This is acceptable according to the parent's preference. If the consent has been undertaken in a language other than English the impartial witness must also sign and date the ICF to confirm the information has been given (as above). The language of consent and the relationship of the person providing consent for their child (e.g., mother or father) will also be documented on the ICF. The PI or designee who has taken consent will also sign and date the form.

A copy of the ICF will be provided to the parent and the original ICF will be filed with other subject records by the site team.

The ICF will only be completed once at the time of enrollment and prior to screening (unless new information necessitating repeat consent is required).

Regardless of duration on study, ongoing willingness of subjects to participate will be documented in the source documents at each visit.

## 7. STUDY VISITS

### 7.1.1. Screening (Visit 1)

Once informed consent has been documented the subject will be considered to be enrolled in the trial, and may be screened to determine study eligibility. The screening period may encompass more than 1 day to allow for resolution of an exclusionary acute illness and/or abnormal vital sign. All inclusion/exclusion criteria must be assessed from data obtained within the screening period, unless otherwise specified in the eligibility criteria. After informed consent has been obtained, the following screening procedures will be performed:

1. Screening number will be assigned.
2. Demographic and contact information will be obtained including address (with adequate detail for another individual to identify the residence), telephone number(s), and email (if

applicable).

3. Complete medical history will be obtained from the subject's parent. The IWC will also be reviewed for this purpose.
4. A history of medications taken that are of specific relevance to study eligibility (e.g., immunosuppressant medications) will be obtained from the subject's parent. The IWC will also be reviewed for this purpose.
5. Vaccination history will be obtained from the IWC, which will represent the source document for this information.
6. Length and weight will be measured. The weight-for-length Z score will be calculated.
7. A physical examination (PE) will be performed, including vital signs (temperature, pulse rate, respiratory rate and peripheral oxygen saturation) and assessment of the major organ systems. Any subject with a ≥ Grade 1 vital sign based on the toxicity grading tables in Appendix 1 and 2 will not be eligible for randomization (note: toxicity scores for pulse rate and > Grade 1 respiratory rate are based on severity of clinical manifestations of bradycardia/tachycardia and respiratory distress, respectively). Infants may return for repeat assessments once during the screening period to be reassessed for eligibility. The last measurement will be taken as the baseline for purposes of analysis.

The PI will use good clinical judgment in considering an infant's overall eligibility. Infants who are not eligible will be recorded as screen failures, along with the basis for this determination, on the appropriate CRF. An infant deemed a screen failure may not be rescreened. Any infant who fails screening due to an abnormal clinical finding will receive counseling from the PI, may receive initial care from the clinical trial team, and will be referred for further medical management as indicated according to good clinical practice in The Gambia.

#### 7.1.2. Randomization and Vaccination Visits (Visit 1, 2, 3, and 5)

In most cases, eligibility will be determined in a single clinic visit, and no additional assessments will be needed prior to randomization and first study vaccination, when these are completed on the same day. If the screening period encompasses more than 1 day to allow for resolution of an acute illness, positive RDT/blood film, abnormal vital sign and / or borderline z-score or baseline weight <3.5 kg, or due to time or logistic constraints, the following procedures will need to be performed prior to randomization and first vaccination. These procedures will also be performed prior to subsequent vaccinations during the trial for all subjects.

1. Ongoing willingness to participate in the study will be documented.
2. Interval medical history will be obtained.
3. Eligibility for vaccination will be confirmed based on review of inclusion/exclusion criteria at the Visits. No moderate or severe acute illness may be noted, and no vital sign may be ≥ Grade 1 based on toxicity score (see Appendix 1 and 2). Randomized subjects may return to clinic at V2 to receive the EPI vaccines or at V3 or V5 to receive the 2$^{nd}$ or booster study vaccines after resolution of an acute illness (or other cause of abnormal vital signs), without this resulting in a protocol deviation. Ideally this vaccination visit will occur within the allowable visit window (+2 weeks). A minimum of 48 hours must be allowed after a documented fever (axillary temperature of ≥ 37.5°C) before a subject may receive a study vaccination. Note that, although no study vaccines are administered at V2 (10 (+2) weeks) the same criteria will apply in determining eligibility for vaccination at this visit.

4. If not already recorded, unsolicited AEs will be documented and graded for severity.
5. Concomitant medications will be recorded.
6. If not already recorded, the occurrence of any SAE will be documented – inclusive of location, duration, severity, relatedness and clinical summary – and will result in notification, based on guidelines set forth by the NRA and Investigational Review Boards (IRBs) pertaining to both reporting timelines and processing of related forms. Submission to the Sponsor will occur within a 24-hour time frame, from the time the event is first documented by the PI.
7. Negative malaria parasitemia will be confirmed by RDT/blood film for malaria (generally a capillary sample will be used for this purpose).
8. Targeted PE will be performed, to confirm absence of exclusionary acute illness or abnormality of the extremities (skin and lymph nodes) targeted for vaccination.
9. A blood sample will be obtained for immunogenicity testing at V5 prior to vaccine administration.
10. After assessment of items 1-6 above, any basis for determining that an infant is a screen failure, or for withholding re-vaccination in the case of subjects returning for follow-up vaccinations (V2, V3 and V5) will be documented. Any subject who is not randomized will be referred back to their normal clinic for routine EPI vaccination.

The PI must approve the randomization of the subject, based on confirmation that the subject meets all eligibility criteria. Randomization will occur at Visit 1 using a predefined randomization scheme, with allocations occurring in a 1:1:1 ratio to PNEUMOSIL, Synflorix or Prevenar 13 and with stratification by field site. A subject's allocation will be selected in numeric order from a set of sealed randomization envelopes. The assignment will be associated with a unique randomization ID. Following assignment, the unblinded study personnel will maintain a list documenting the vaccine assigned and administered to given randomization IDs in a secure location that is not accessible to blinded study personnel. The subject will be referred to by screening number for the remainder of the study. The randomization identification (ID) will be required on select CRFs.

Once eligibility has been confirmed and randomization has taken place -- or it has been determined that a subject returning for a vaccination at Visits 2, 3 or 5 may be re-vaccinated -- unblinded study personnel will perform the following procedures in an area of the clinic that is not readily accessible to blinded study personnel:

1. Subject randomization ID will be recorded.
2. The assigned study vaccine will be administered and documented on the CRF at Visits 3 and 5 as to timing and location of administration (see Section 5.5 for details).
3. The EPI vaccines due at the given vaccination visit will be administered and documented on the IWC and CRF (see Section 5.5 for details). It will also be noted on the IWC that a pneumococcal conjugate vaccine has been given.
4. All subjects will be provided with a study ID card documenting their screening number, the fact that they are enrolled in the clinical trial, and that they have received a study vaccine. It will also include telephone contact details for study personnel, and state that, should the subject become unwell, a member of the clinical trial team should be contacted immediately. This card will be attached to the IWC.
5. All subjects will also be provided with a photo ID card confirming their randomization in the

study.

After study vaccine administration is complete at Visits 1, 3 and 5, the subject will be observed by blinded study personnel for the remainder of that visit and for all subsequent non-vaccination-related trial conduct. Immediately following vaccination the following will occur:

1. Subjects will be monitored for vital signs and solicited reactogenicity with recording of all these events at 30 (+/-10) minutes post vaccination. See Appendices 1 and 2 for appropriate severity grading scales.
2. Parents of subjects will be reminded about daily home visits for the subsequent 6 days after vaccination, and place of residence and phone contact details will be reconfirmed.
3. The date of the subsequent clinic visit will be established.

Note: Study vaccination **must** occur on the day of randomization. Subjects who are discontinued from the study after vaccination will not be replaced. However, if a subject is discontinued after randomization but prior to vaccination, he or she will be replaced using a new randomization assignment for the replacement subject.

Note: As only routine EPI vaccines are given at V2, no reassessment of vital signs, local and systemic reactogenicity assessment or home visits occur after this vaccination although the subject should nonetheless remain at the trial site for at least 15 minutes after vaccine administration. The fact they are fit to go home will be documented in the clinical notes by a nurse or clinician at this visit.

**Home Visits – Days 1 through 6 Post Vaccination**

The subjects will be monitored daily at home by field workers for assessment of local and systemic reactogenicity during the 6 days after each study vaccine administration.

Field workers will be provided with a reactogenicity record form (RRF) for recording of reactogenicity events. The RRF will be retained as part of the source documents in the subject's file. The grading scales to be used for assessment of severity of local and systemic reactogenicity events are listed in Appendix 1 (Section 16.1). **Any Grade 3 or higher reactogenicity assessed by a field worker will result in immediate clinic contact, and the subject will be seen in the clinic within 24 hours of the event.** Field workers will contact the site to assist with scheduling if subjects are noted to be experiencing any medical condition (i.e., solicited or unsolicited AE) that needs to be evaluated by the PI at an unscheduled clinic visit.

Independent of a clinic visit, an RC will review the reactogenicity scoring with the field worker at the end of the 6-day assessment period, and sign off to confirm that this review has occurred. Following this review, an anonymized copy of the RRF will be submitted for data entry. If the condition of the RRF is such that data entry could be difficult, the source RRF could be transcribed to a new RRF for copying and submission. In this case the reason for this will be explained in the clinical notes. If more than 1 measurement of a particular parameter is taken and recorded, the value corresponding to the greatest magnitude of the RE will be used as the basis for categorizing and recording the event on the CRF during the given period of assessment. Any local or systemic reactogenicity or other AE ongoing at the day 6 home visit will prompt a day 7 follow-up visit in clinic. If a solicited AE is ongoing on day 6 post vaccination, or occurs after 6 days post vaccination, the event will be recorded on the AE CRF and continued to be followed as per AE monitoring requirements.

### 7.1.3. Post-Vaccination Visits (Visit 4, 6 and Unscheduled Visits)

All subjects will be seen in clinic at Visit 4 (4 weeks post completion of the primary vaccination) and at Visit 6 (4 weeks post booster vaccination). The following procedures will be completed at these visits, as well as at any required unscheduled visit before Visit 6:

1. Screening number, address and telephone number(s) will be confirmed.
2. Unsolicited AEs will be recorded, including assessment of relatedness to vaccination and severity grade
3. The occurrence of any SAE will be documented – inclusive of location, duration, severity, relatedness and clinical summary – and will result in notification as set forth by the NRA and IRBs pertaining to both reporting timelines and processing of related forms. Submission to the Sponsor will occur within a 24-hour time frame, from the time the event is first documented by the PI.
    a. Follow-up will be attempted on any SAE that is ongoing at the time of a subject's last visit, until the event is resolved, assessed to be resolved with sequelae by the PI, or until LSLV. Any SAE deemed related to study vaccine that is ongoing at the time of LSLV will continue to be followed until it is resolved, assessed to be resolved with sequelae, or assessed to be stable/chronic. SAEs deemed not related to study vaccine that are unresolved at the time of LSLV will be classified as ongoing.
4. Concomitant medications will be recorded.
5. Vital signs will be measured, recorded, and graded. See Appendix 1 and 2 for severity grading of abnormal vital signs.
6. A targeted PE will be performed, including local examination of the vaccination site and for any clinically significant finding.
7. Blood sample for immunologic testing will be obtained by venipuncture (Visits 4 and 6).
8. Any follow-up visits will be scheduled.
9. Exit from the study will occur after Visit 6 (following completion of the EOS CRF)

Evaluations to be performed at each study visit are shown in Table 14 as follows:

**Table 14. Study Visits**

| Step No. | Evaluation | V1* | V2# | V3 | V4 | V5 | V6 |
|---|---|---|---|---|---|---|---|
| | | 6-8 weeks | V1+4 (+2) | V2+4 (+2) | V3+4 (+2) | 9-18 (+1) mos | V5+4 (+2) |
| 1 | Signing of ICF and confirmation of ongoing informed consent (+) | ✓ | + | + | + | ✓ | + |
| 2 | Assign screening number and confirm (+) | ✓ | + | + | + | + | + |
| 3 | Demographics | ✓ | | | | | |
| 4 | Record contact information – address and telephone number(s) – and confirm (+) | ✓ | + | + | + | + | + |
| 5 | Full medical history (including concomitant medications) and vaccination history | ✓ | ~ | ~ | ~ | ~ | ~ |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6 | Vital signs and PE (targeted after screening)* | ✓^✓ | ✓ | ✓^✓ | ✓ | ✓^✓ | ✓ |
| 7 | Blood sample for immunogenicity testing | | | | ✓ | ✓@ | ✓ |
| 8 | Rapid malaria diagnostic test* | ✓ | ✓ | ✓ | | ✓ | |
| 9 | Eligibility check* | ✓ | ✓ | ✓ | | ✓ | |
| 10 | Assign randomization ID | ✓ | | | | | |
| 11 | Study vaccination | ✓ | | ✓ | | ✓ | |
| 12 | EPI vaccination | ✓ | ✓ | ✓ | | ✓α | |
| 13 | Record local/systemic solicited reactions | ✓ | | ✓ | | ✓ | |
| 14 | Record adverse events (including SAE)* | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 15 | Record concomitant medications* | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 16 | Schedule/confirm next visit | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 17 | Exit study‡ | | | | | | ✓ |

Age ranges indicated for V1/V5. Other vaccination/follow up visits to be scheduled at 4 weeks post prior visit + 2 week window.
* If screening extends beyond 1 clinic visit assessments (*) need to be repeated on the day of randomization/1st vaccination.
@Blood sample to be collected prior to administration of booster dose
#EPI vaccination visit; ~Confirmation of medical history; ^ Evaluations will be conducted twice – before and after vaccination
α Except for subjects who receive the EPI vaccines earlier than the study booster dose due to impact of the COVID-19 pandemic

### 7.1.4. Interim Contacts and Visits

Interim unscheduled contacts and visits (e.g., unscheduled visits) in between regularly scheduled follow-up visits may occur at any time at the request of the subject's parent or as deemed necessary by the PI. All unscheduled interim contacts and visits will be captured in the subject's study records and on applicable CRFs.

## 7.2. Refusing of Procedures, Missed Visits, Withdrawal, and Early Termination

Subjects' parents may refuse procedures on behalf of subjects at any time during enrollment in the study and can withdraw consent at any time. The PI may also, at his discretion, withdraw the subject from participating in the study at any time if he considers it in the best interest of the subject, with clear documentation as to the reason.

Minor protocol deviations (e.g., a missed visit window for a follow up visit, but the subject is seen for the visit within a reasonable time frame) do not constitute grounds for withdrawal of the subject *per se*, though these will be clearly documented on a protocol deviation CRF and in the clinical notes. If a subject fails to come to clinic for a study visit, extensive follow-up will be undertaken to locate and recall him/her. If the subject still fails to present to clinic within the allowed window for the visit, then he or she may still be permitted to complete the visit and related procedures at a suitable later date on a case-by-case basis. The PI will use discretion regarding the window allowed, or if the visit will be deemed a "Missed Visit." If a subject has exceeded the visit window for a vaccination visit, the PI, in consultation with the Sponsor, will have the discretion to determine whether the subject ought to be withdrawn from further study vaccinations and only be offered the routine EPI vaccines. For major protocol violations (e.g., a subject receives a non-trial investigational medical product) a notification to the appropriate regulatory authorities may be required, and the subject may be withdrawn from the study. Such decisions will be made by the PSRT on a case-by-case basis. However subjects will be withdrawn from the study if any of the following events occur after informed consent has been given:

- The subjects' parent requests that the subject be withdrawn.
- The PI determines that the subject is unable to comply with the protocol.
- The subject is lost to follow-up.

  Note: A subject will be considered lost to follow-up only after telephonic attempts to contact the subject's parent have failed, and a visit to the home to attempt a contact has occurred and the subject still cannot be located.
- The Sponsor decides to suspend or discontinue development of PNEUMOSIL.

If a subject is withdrawn for a major protocol violation, the subject may continue to be followed for safety monitoring if he/she has received a study vaccination.

In the event of a subject's withdrawal or early termination, the following activities will be attempted to be performed and information recorded in the database:

1. Contact information will be reviewed and updated.
2. Results from prior visits will be reviewed and any outstanding data queries completed.
3. Date of withdrawal will be recorded. The date of withdrawal will be designated as the date when the last contact with the subject's parent occurred (telephone or face-to-face).
4. The reason for withdrawal or early termination will be documented.
5. PE will be performed if possible.
6. New AEs requiring reporting since the last visit will be documented.
7. All previously documented AEs and SAEs will be updated in regard to classification (ongoing, resolved, etc.).
8. Concomitant medications requiring reporting since last visit will be documented.
9. The subject's final study visit will be documented and the EOS CRF completed. Efforts made to complete the EOS CRF in the event that the subject's parent cannot or is unwilling to be contacted will be documented.
10. If a subject is withdrawn from the study after 2$^{nd}$ dose of EPI vaccines for safety reasons, the subject will be offered the routine EPI vaccines, including Prevenar 13, (provided no contraindications to the EPI vaccines have been reported)

In the case of early subject withdrawal or early termination, samples already collected will be retained for appropriate immunogenicity measurements unless the parent asks that these samples not be tested or be destroyed. If immunogenicity testing has already been carried out the data will be retained within the final analysis set irrespectively.

### 7.3. Concomitant Medications and Treatments

All concomitant medications, therapies and procedures will be recorded in source documents during each clinic visit of the study as outlined above. Subjects may receive all medications and procedures deemed necessary based on good medical practice in The Gambia. To enable the PI to directly assess potential AEs, subjects' parents will be encouraged to obtain initial medical care for subjects at the field site during their enrollment in the trial except in the event of an emergency situation in which another health facility is more readily accessible. Any necessary medical care will follow what is considered to represent good medical practice in The Gambia, and access to such medical therapies will be made available to all subjects during enrollment in the trial. Essential treatments and medications will be

provided by the trial team free of charge within the scope of their clinical expertise, although referral to government facilities will be appropriate in some cases (e.g. surgical conditions or trauma).

That said, certain medications will not be allowed according to the protocol (unless for clinical need which will always take priority); if a subject uses the following medications, the PSRT will determine whether to discontinue the subject from the study or from receiving further study vaccinations:

- Use of any investigational drug or vaccine other than the study vaccines.
- Administration of a vaccine that is neither part of the EPI schedule nor administered as part of a national campaign.
- Chronic administration (defined as more than 14 days) of immunosuppressant or other immune modifying agents. For corticosteroids, this means prednisone or equivalent >10 mg per day; topical and inhaled steroids are allowed.
- Administration of immunoglobulins or any blood products during the study period.

### 7.4. Blinded and Unblinded Study Personnel

With the exception of the designated unblinded site personnel described below, all study site personnel, including the PI and the Sponsor, will remain blinded to subjects' treatment assignments. All CRO personnel, with the exception of the unblinded monitor, clinical supplies manager, an administrator and statistician for the DSMB (if required) will remain blinded to the treatment assignments. After the last subject completes V4, an independent CRO statisticican (whose responsibilities are otherwise limited to supporting the DSMB) will be unblinded to conduct an interim analysis of immunogenicity objectives through end of V4. Study unblinding will be conducted and documented in accordance with relevant CRO standard operating procedures (SOPs). The Sponsor, Principal Investigator, site team and rest of the CRO personnel will continue to remain blinded to individual treatment assignments until all subjects complete Visit 6.

During conduct of the study, a limited number of unblinded site personnel will be responsible for preparing and administering study vaccines, performing vaccine accountability, and maintaining the security of the treatment assignments. The unblinded site personnel will not be involved in the safety assessment of the subjects, or in any other aspect of the study. All other site personnel, including those who perform the clinical evaluations (such as but not limited to assessment of medical history, vital signs assessment, and PE), will be blinded with respect to the identity of the vaccine administered to the subjects.

The CRO will assign blinded monitor(s) to visit the site (including all field sites) during the study period, in order to assess and verify activities of the blinded study personnel, review appropriate documentation, and provide a report to the CRO and Sponsor of ongoing activities and issues requiring resolution. The blinded monitor(s) will be responsible for all aspects of the clinical trial related to subjects, the blinded site staff, and regulatory and audit readiness. Monitoring can occur both at the site and remotely with standard reports and escalation as needed to the PI or PSRT. The CRO will also assign an unblinded study monitor, who will visit the site (including all field sites) during the study period to assess and verify activities of the unblinded site personnel, review appropriate documentation, and provide a report to the CRO and Sponsor of ongoing activities and issues requiring resolution. The unblinded study monitor will be responsible for review of treatment assignments, vaccine storage and accountability, and dosing-related matters. The unblinded monitor will be responsible for escalating issues to the PI or PSRT in a blinded manner. Any unblinding of additional project team personnel required to resolve issues will be clearly documented in the TMF. Of note, all reports to blinded

personnel by the unblinded CRO monitor will be constructed in order to maintain the blind during the trial. No report that would break the blind will be released into the TMF until after database lock.

### 7.5. Unblinding Procedure

In the event of a medical emergency, the PI may require that the blind be broken for the subject experiencing the emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care.

An identical set of sealed randomization envelopes will be available at the site for this purpose, and should unblinding be necessary the PI will access these envelopes and obtain the envelope corresponding to the randomization ID of the subject in question.

Training surrounding such unblinding will be done during the site initiation visit. Documentation of the unblinding event (including the rationale and requestor) will be recorded and duly entered into the OpenClinica database system. Every effort will be made not to unblind the subject unless it is considered necessary for their welfare. Prior to unblinding, the PI must attempt (to the extent possible, without jeopardizing the subject's health) to contact the Sponsor (or designee) to discuss the decision to break the blind. The PI will be expected to provide a rationale for the necessity of unblinding based on the expectation that knowledge of the subject's treatment assignment will have a meaningful impact on the subject's medical care in the short term. If a subject's treatment assignment is unblinded, the subject will remain in the study and continue with protocol-defined study visits, but not receive further study vaccines. The decision to unblind will be communicated to The Gambia Government/MRC Joint Ethics Committee and all other regulatory bodies as required. At the end of the study, documentation of all unblinded subjects (and the rationale for unblinding) will be incorporated into the TMF.

## 8. LABORATORY EVALUATIONS

Blood samples will be collected from subjects for immunogenicity testing.

### 8.1. Sample Collection, Distribution, and Storage

Blood samples collected for the immunogenicity endpoints will be separated into aliquots by the MRCG at LSHTM research laboratories as per study SSP and stored at -70°C or lower in the MRCG at LSHTM biobank before being shipped to the central immunology laboratory (see Section 8.3). Continuous temperature monitoring and backup generators will be in place to ensure proper sample storage. Any blood samples obtained for clinical evaluations will be transported to the MRCG at LSHTM clinical laboratory for testing, although for efficiency a blood film for malaria parasites may be undertaken in the government laboratory at the health center when deemed necessary.

Volumes of blood required at different time points for immunogenicity testing are shown in Table 15.

**Table 15. Total Blood Volume Required**

| Immunogenicity Test | Visit 4 | Visit 5 | Visit 6 | Total |
|---|---|---|---|---|
| ELISA IgG for 10 serotypes in PNEUMOSIL | 3.0 mL | 3.0 mL | 3.0 mL | **9.0 mL** |
| OPA for 10 serotypes in PNEUMOSIL | | | | |

### 8.2. Clinical Laboratory Assays

Clinical laboratory tests obtained at the discretion of the PI and RCs will be performed at the Clinical Laboratories Services, MRCG at LSHTM in Fajara. The Clinical Laboratories Services subscribes to proficiency testing programs, and operates based on the principles of Good Clinical Laboratory Practice (GCLP) and ISO15189.

Additional investigations may also be undertaken on subjects for research and/or diagnostic purposes in order to more fully characterize particular AEs (e.g., to identify respiratory viruses in the nasopharynx, or investigate the cause of focal chest findings on PE with a chest x-ray). The circumstances in which such additional investigations may be undertaken, beyond those required as part of routine clinical care, will be specified in study specific procedures for the trial.

### 8.3. Immunological Assays

The following immunological assays are to be undertaken:

- ELISA IgG: The serum IgG concentration to each of the 10 serotypes contained in PNEUMOSIL will be measured by ELISA in serum samples collected at Visits 4, 5 and 6. This will be performed at the [redacted], using the WHO reference PCV ELISA protocol.
- OPA: The functional activity of the serum IgG response to the 10 serotypes contained in PNEUMOSIL will be determined in serum samples collected at Visits 4, 5 and 6 (subset of 50 subjects per group). This activity will be determined using the 4-fold MOPA assay developed at the University of Alabama at Birmingham, also to be performed at the [redacted].

After the completion of immune testing, all remaining samples at the central laboratory will be destroyed.

All study results will be shared with the central laboratory at the conclusion of the study. In addition, subjects' parents will be provided an overall summary of the findings of this study through a community meeting held at each recruitment site.

### 8.4. Assay Qualification, Standardization, and Validation

The ELISA IgG and MOPA assays that will be used to measure the magnitude and the functional activity of the polysaccharide antibody responses – constituting primary and secondary endpoints of the trial – are standardly used in the field to measure immunogenicity as a surrogate marker for efficacy of PCVs, and were validated at the WHO Pneumococcal Serology Reference Laboratory, at [redacted]. A detailed description of these two standard assays can be found at: http://www.vaccine.uab.edu/.

### 8.5. Biohazard Containment

As transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and processing of blood, and shipping and handling of all specimens for this study. The laboratory SOPs and SSPs will ensure appropriate coverage of the needs for this trial. All biological specimens will be transported using packaging mandated by the site and CRO SOPs, and aligned with

other applicable regulations. All dangerous materials, including diagnostic specimens and infectious substances, will be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

# 9. SAFETY ASSESSMENT AND REPORTING

The PI is responsible for the detection and documentation of:

- Events meeting the criteria and definition of an AE as provided in this protocol throughout the study period
- Events meeting the criteria and definition of an SAE throughout the study period

## 9.1. Collection of Safety Events

AEs, including SAEs, will be systematically collected at relevant clinic visits through Visit 6. Reactogenicity events will be assessed in all subjects immediately (30 minutes) after study vaccine administration and at the daily home visits for the first 6 days following each study vaccine administration.

In addition, subjects' parents will be instructed to contact the PI immediately should the subject manifest any signs or symptoms. Subjects' parents will be provided with contact details for the field site team and will be provided with telephone credit for this purpose. Site staff will be available 24 hours a day by telephone and in person for emergency needs and during clinic hours to assess subjects for the duration of the trial (First Subject First Visit [FSFV] to LSLV).

## 9.2. Definitions

### 9.2.1. Adverse Event or Medical Event

- An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or psychological/physiologic observations occurring in a subject enrolled in the clinical trial. This includes all subjects from whom consent has been obtained whether or not they have yet been randomized and received a study vaccine (PNEUMOSIL, Synflorix or Prevenar 13). The event does not need to be causally related to trial participation or receipt of a study vaccine. An AE is temporally related to participation in the study and will be documented as to whether or not it is considered to be related to vaccine. An AE includes, but is not limited to, the following:
  - An intercurrent illness or injury during the course of the study.
  - Any clinically significant worsening of a preexisting condition.
- A protocol-related AE is one that occurs from the time of enrollment until the EOS visit that is not considered to be related to receipt of the study vaccine, but is considered by the PI or the medical monitor (Sponsor or designee) to be related to the research conditions, i.e., related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during blood sampling or other protocol-specified activity.
- A treatment-emergent AE is defined as an event that is not present prior to administration of the study vaccination, or, if present prior to the administration of the study vaccination, increases in intensity after administration of the study medication during the course of the study.

- Reactogenicity events include local and systemic reactions noted immediately post vaccination, or during follow-up visits through day 6 after study vaccine administration by field workers and confirmed by the PI.
  - Any solicited AE that is ongoing on day 6 post study vaccine administration, or occurs after 6 days post study vaccine administration will be entered as an unsolicited AE and followed in line with the follow-up for other unsolicited AE.

### 9.2.2. Severity (Intensity) of Adverse Event

The severity of all solicited AEs will be graded from Mild (Grade 1) to Potentially Life Threatening (Grade 4), based on the criteria given in Appendix 1 (Section 16.1). All AEs leading to death are Grade 5 events. Adverse events are graded based on the worst severity grade during the illness/symptoms. The grading scales for solicited AEs in the Appendix have been derived from the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events* (Version 2.0, November 2014), from the US National Institutes of Health.

All other unsolicited AEs will be classified as an AE and graded based on the AE severity scale in Table 16 below.

**Table 16. Severity Grading**

| Grade | Description |
|---|---|
| 0 | No AE (or within normal limits). |
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 | Moderate; minimal, local, or noninvasive intervention indicated. |
| 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling. |
| 4 | Life-threatening consequences; urgent intervention indicated. |
| 5 | Death related to AE. |

Derived from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

### 9.2.3. Causal Relationship of an Adverse Event

A suspected adverse drug reaction (ADR) means any AE for which there is a reasonable possibility that the study vaccine caused the AE. A reasonable possibility means there is evidence to suggest a causal relationship between the vaccine and the AE. All cases judged by either the PI or the Sponsor as having a reasonable suspected causal relationship to the study vaccine will qualify as ADRs. Medical judgment will be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, confounding factors such as concomitant medication, concomitant diseases, and relevant history. Assessment of causal relationship will be recorded on the CRFs and on the SAE form (in case of SAEs).

The likelihood of the relationship of the AE to study vaccine is to be recorded as follows:

- Related: There is a reasonable causal relationship between the vaccine administered and the AE.
- Not Related: There is no reasonable causal relationship between the vaccine administered and the AE.

  Note: solicited reactogenicity events will not be judged for relatedness.

### 9.2.4. Assessment of Outcome of Adverse Event

The outcome of the AE will be assessed and recorded as per the following categories:

- Ongoing.
- Recovered/resolved.
- Recovered/resolved with sequelae.
- Stable/chronic.
- Fatal.
- Unknown.

### 9.2.5. Unexpected Adverse Event / Drug Reaction

An AE or suspected ADR is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) for PNEUMOSIL or if it is not listed at the severity that has been observed. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. If the classification of an unexpected AE/ADR is serious and is thought to be related to the study vaccine, then it is classified as a suspected unexpected serious adverse reaction (SUSAR).

### 9.2.6. Serious Adverse Event

An SAE is a specific AE that:

- Results in death.
- Is life-threatening.*
- Requires inpatient hospitalization or prolongation of an existing hospitalization.**
- Results in a persistent or significant disability or incapacity.***
- Results in a congenital anomaly or birth defect.

***Life-threatening** refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death but, as it actually occurred, did not create an immediate risk of death.

For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

****Hospitalization** is an admission to a health facility (e.g., government health center, MRCG at LSHTM clinical services department, Edward Francis Small Teaching Hospital) in the situation where there is an AE. A period of observation at a clinical trial site or government health facility is not

considered to represent hospitalization for the purposes of SAE reporting. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the PI on a SAE form. Such situations include, but are not limited to, the following:

- A hospitalization for a preexisting condition that has not worsened.
- Hospitalization for social reasons.

***Disability** is defined as a substantial disruption in a person's ability to conduct normal life functions. If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events (IME) that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias or convulsions that do not result in hospitalization.

### 9.2.7. Adverse Event Recording and Reporting

Recording and reporting of AEs, including SAEs, will occur from signing of the ICF (enrollment) through the EOS visit for each study subject enrolled in the study, with the exception that only SAEs will be recorded and reported from 10 months of age until booster vaccination for subjects who receive the booster at > 10 months of age.

The PI must completely and promptly record each AE in the source documentation and on the AE CRF, regardless of relationship to the vaccine administered/procedure as determined by the PI. The PI will attempt, if possible, to establish a diagnosis based on the signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the PI will report the diagnosis as the AE, not the signs and symptoms. Adverse events will be classified by MedDRA term and by severity/intensity, relatedness, and outcome.

Enrolled subjects who subsequently screen fail (i.e., who never underwent randomization) will have AEs recorded from enrollment until the time they are determined to be ineligible for randomization. These AEs will be listed in separate appendices from those subjects randomized and vaccinated. For the purposes of data capture they will be closed at the point the subject is deemed ineligible.

Reporting of AEs will follow the regulatory guidelines of the National Medicines Regulatory Authority (NMRA), the local ethics committee (EC) in The Gambia, LSHTM Research Ethics Committee, WIRB and the PATH Research Ethics Committee (REC) in the US, in regard to requirements, processes and forms.

### 9.2.8. Serious Adverse Event Reporting

If an AE is classified as serious or an IME, an SAE form will be completed and submitted within 24 hours of the PI becoming aware of the SAE, including information on the location, severity, relatedness, and clinical summary of the event to the Sponsor. In addition, the SAE submission will follow the regulatory guidelines of the NMRA, the local EC in The Gambia, LSHTM Research Ethics Committee and WIRB in the US, in regard to requirements, processes and forms. It is the

responsibility of the Sponsor to ensure that the manufacturer (SIIPL) is notified of SAEs. Any SAE deemed related to study vaccine that is ongoing at the time of LSLV will continue to be followed until it is resolved, assessed to be resolved with sequelae, or assessed to be stable/chronic. SAEs deemed not related to study vaccine that are unresolved at the time of LSLV will be classified as ongoing.

### 9.3. Unanticipated Problems

An Unanticipated Problem is any incident, experience, or outcome that meets all of the following criteria:

A. Unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in protocol-related documents, such as the institutional review board-approved research protocol and informed consent document, and the characteristics of the subject population being studied.
B. Related or possibly related to a subject's participation in the research.
C. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

All unanticipated problems will be reported in the continuing review report submitted to the NMRA, the local EC, LSHTM Research Ethics Committee and WIRB per reporting requirements of each regulatory body. All serious unanticipated problems involving risk to participants or others will be promptly (within 48 hours) reported by telephone, by email, or by facsimile to the Sponsor. Follow-up reports will be submitted as soon as additional information becomes available.

### 9.4. Medication Errors

A medication error is any preventable event that may cause or lead to inappropriate investigational use or subject harm while the investigational product (IP) is in control of the healthcare professional, subject, or consumer. Examples of medication error that will require reporting to the Sponsor include the following:

- Administration of unassigned treatment.
- Administration of expired investigational material.
- Injection by the wrong route.

All AEs and SAEs will be handled as specified in this protocol whether or not they are associated with a medication error.

## 10. SAFETY MONITORING

The PI will be responsible for continuous monitoring of all study subjects' safety through to their EOS visit. In case of urgent need, subjects' parents will have the means to get in contact with field site staff at any time (24 hours per day) – and the site will have the means to transport subjects to clinic (or another appropriate clinical setting) or will provide fares for this purpose – to allow for expeditious clinical evaluation of, and provision of medical care to subjects. The PI will also be available by cell phone 24-hours per day for medical emergencies.

### 10.1. Protocol Safety Review Team

Safety will be monitored routinely throughout the study by the PSRT, which will include the PI and clinical trial coordinator from the MRCG at LSHTM, the PATH Clinical Lead and Clinical Operations Lead, and CRO staff (including the Clinical Project Manager and data management personnel). The PATH Clinical Lead will serve as the PSRT Chairman. The PSRT will conduct a weekly review of aggregated safety data and of clinical trial conduct during the active vaccination periods of the trial. These reviews will be blinded for all members of the PSRT. After the last subject completes V4, the CRO lead biostatistician will not participate in PSRT reviews. Blinded safety reports will be prepared routinely by the CRO for the PSRT that will include at a minimum the following:

- Accrual data and subject status data with regard to completion of/discontinuation from the study, sorted by field site.
- Visit windows expected, deviations, and completions, sorted by field site.
- Summary of reactogenicity data by vaccination number (#1, #2, boost), classified by severity.
- AEs sorted by MedDRA term, severity, and relatedness to study vaccine.
- Any new or updated AEs that have occurred in the interval from the previous report.
- Data management summaries and status of missing data, missing CRFs and manual queries, sorted by field site.
- Quality review of any site findings by blinded or unblinded monitors that are critical to the integrity of the study. These findings will be provided in a manner that maintains the blind.
- All SAEs will be provided to the PSRT, with history and subsequent follow-up information as pertains to the SAE, within the first 24 hours following site awareness of the SAE (as per other SAE notification rules).
- Site-specific performance issues with source data verification, inclusion/exclusion criteria, documentation practices and audit readiness.
- Additional reports as required by ongoing conduct of the trial.

The PSRT has the authority to implement a study pause based on review of safety findings, or if alerted to unexpected clinical findings by the PI. If the PSRT elects to implement a study pause, the study team will pause the study for randomization and vaccination purposes, until an urgent DSMB meeting approves lifting the pause.

If a study pause is initiated, randomized subjects will continue with their scheduled follow-up visits (V4 and V6), but not vaccination visits. In that case, the visit will be on hold during the pause; if the study is resumed, the subject will still be considered to be within their vaccination window, and all future visits adjusted based on the date of resumed vaccination. Such a pause in the study would not constitute a protocol deviation in regard to subject visit windows, and the pause would be taken into consideration for restarting the assigned vaccination visit schedule. A Note to File (NTF) will be written to explain such an occurrence. If at any time a decision is made to permanently discontinue further vaccinations, the PI will notify The Gambia Government/MRC Joint Ethics Committee, LSHTM Research Ethics Committee and NMRA, and the Sponsor will notify WIRB expeditiously. In this case, those subjects already enrolled in the study who have received a study vaccine will complete the 4-week safety follow-up period. Such safety follow-up could be extended by the PSRT based, if necessary, on the advice of the DSMB if judged to be appropriate according to the reasons for study discontinuation.

### 10.2. Data Safety Monitoring Board

The DSMB will be composed of independent experts in vaccines, infectious diseases, pediatrics and biostatistics. There will be no formal meetings of the DSMB however, they would convene on an as-needed basis. If the PSRT elects to implement a study pause, the study team will pause the study for randomization and vaccination purposes, until the DSMB approves lifting the pause based on unblinded review of all safety data accrued during the trial. DSMB reviews will indicate whether or not safety concerns were identified, and whether the trial should continue without change, be modified, or be terminated. The Sponsor will carefully consider the DSMB recommendations. If the Sponsor does not agree with these recommendations, a meeting will be held between the Sponsor, PI and DSMB to reach consensus on the appropriate action(s) to take in regard to the trial. However, if attempts to reach consensus fail, the Sponsor's opinion will prevail. In such situations, the Sponsor will inform the regulatory authorities, The Gambia Government/MRC Joint ethics committee, LSHTM Research Ethics Committee and WIRB of the DSMB findings, the Sponsor's perspective, and any changes to the trial.

The PSRT, PI or PATH Clinical Lead may also seek additional guidance from the DSMB as dictated by the occurrence of certain events that do not warrant a study pause.

### 10.3. Protocol Deviation and Protocol Violation

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or site SOP/SSP requirements. The noncompliance may be either on the part of the subject or the site team/PI.

A protocol violation is a significant departure from processes or procedures required by the protocol. Violations often result in data that are not deemed evaluable for a *per-protocol* analysis, and may require that the subject(s) who violates the protocol be discontinued from the study.[40]

When appropriate, corrective actions and preventive actions (CAPAs) will be developed by the site to address protocol violations and deviations, and will be implemented promptly. These practices will be consistent with ICH E6 (R2) Guidelines.

## 11. DATA MANAGEMENT

The Sponsor-designated CRO's study monitors will visit the site at regular intervals (including field sites) as per the monitoring plan and perform pre-agreed source data verification of the data recorded in the paper CRF against the source documents available at the site. In addition, missing data forms and fields will be queried by daily electronic edit checks or through manual edits of the data by the data management team. Study monitors will closely evaluate pre-screening data, inclusion/exclusion criteria, informed consents, data entry timeliness, and visit dates and windows at each field site to ensure integrity of the study is maintained.

Any data discrepancies generated by the system will be flagged in the OpenClinica database system for the PI to provide a satisfactory resolution within the OpenClinica database system. The data management team will review all the data discrepancy responses by the site to ensure the correctness of data. The AEs will be coded using MedDRA dictionary version 21.0 or later and the concomitant medications will be coded using standard nomenclature. After completion of data coding and resolution of all the queries in the database pertaining to subject visits through completion of Visit 4 by the last subject, the database will be declared to be accurate and statistical analysis of secondary immunogenicity objectives, and safety and tolerability, through V4 will take place. A final database lock will occur after completion of data coding and resolution of all the queries in the database following completion of Visit 6 by the last subject (LSLV).

## 11.1. Case Report Form Development and Completion

Based on the final protocol of the study, a comprehensive set of paper CRFs will be prepared to capture all the relevant data required for analysis and reporting. This study will utilize the OpenClinica system such that the entire study data can be maintained in a secure electronic system. No written or electronic data recorded prior to the study will be included in the paper CRFs or OpenClinica system respectively.

All study data will be collected by the clinical study staff using designated source documents, wherever applicable, and will be entered in the appropriate CRFs and OpenClinica system in an anonymized form. In some cases, the CRF will be the source document. The study database will identify study subjects only by unique study ID numbers through screening (screening number) and randomization assignments (randomization ID) and will not contain any identifying information such as name, address or personal contact information, or any other national ID number. CRFs will be reviewed by the clinical team who are responsible for ensuring that they are accurate and complete.

The data management activities will be performed as per the CRO's SOPs. The appropriately trained site personnel will ensure double data entry of the study data recorded on the CRFs into the OpenClinica system. To ensure that data are entered in a timely fashion so as to monitor safety of the study, it is expected that the site will maintain data entry with a minimal expectation of 3 business days from subject clinic visit or last home visit. The study monitor plan will include assessments of data entry timeliness.

The study site will maintain the source documents for each study subject. The source documents and other supporting documents will be kept in a secure location. Source documentation will be available for review by the study monitor to ensure that the source data are consistent with the CRFs.

## 11.2. Record Archival

### 11.2.1. Archiving Data at Study Site

The study site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory, sponsoring organization and institutional requirements for the protection of confidentiality of subjects. The site will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. The final database will be locked and transferred to the Sponsor for long-term storage.

### 11.2.2. Data Storage and Archival

The PI will maintain an Investigator Site File, which will be used to file the IB, protocol, vaccine accountability records, correspondence with the EC/IRB, Sponsor, CRO, and other study-related documents. The PI will maintain, and store securely, complete, accurate and current study records throughout the study.

As required by ICH GCP guidelines, the PI will keep essential documents until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The documents will be archived either in the MRCG at LSHTM Archive or at any other secure location as agreed upon with the Sponsor. It is the responsibility of the Sponsor to inform the PI/institution as to when these documents no longer need to be retained.

Following completion of the study, serum samples and nasal swabs collected during respiratory-related adverse events will be stored at an appropriate place in a designated freezer at the [redacted] until it is determined whether the samples are to be retained or destroyed under the direction of PATH. During the informed consent procedures, additional consent for the use of any serum remaining at the end of the trial and nasal swabs collected during respiratory-related adverse events for other ethically approved research will be sought from subjects' parents by the PI. Any such use must be with the consent/approval of PATH. When such additional consent has not been obtained the PI will destroy remaining serum and nasal swab samples based on the Sponsor's instructions (with proper audit documentation, reconciliation, and certification).

No data will be destroyed without the agreement of the Sponsor. The applicable records include source documents, site registration documents and reports, correspondence, ICFs, and notations of all contacts with the subject. The Sponsor will inform the PI in writing of the need for record retention and will notify the PI in writing when the trial-related records are no longer needed. Subjects' medical records and other original data will be archived in accordance with the local regulations or facilities of the investigational site.

### 11.3. Posting of Information on Public Registries

Study information from this protocol will be posted on Clinicaltrials.gov and www.pactr.org.

### 11.4. Publication

PATH will work with the PI and other relevant personnel at MRCG at LSHTM on the publication of the complete Phase 3 study outlined in this protocol in a timely fashion. Primary publication of the trial results will be shared between the MRC and PATH. Other individuals having input into the study justifying authorship from MRCG at LSHTM, from collaborators and from PATH will similarly be included in publication(s). Additional publications resulting from the analysis of the study data will be agreed between PATH and the MRCG at LSHTM on a case-by-case basis but will generally include authors from both organizations. PATH will be acknowledged in all publications as the Sponsor of the trial.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement, is executed between PATH and the study site, that contract's publication provisions shall apply rather than this statement.

## 12. STATISTICAL DESIGN AND ANALYSIS

This section describes study size calculations and the planned analysis of study objectives as envisioned at the time of the protocol. Any substantive changes to these planned analyses (e.g., definitions of analysis populations, endpoint definitions, or analysis methods) will be documented in a detailed Statistical Analysis Plan (SAP) developed and approved prior to interim unblinding of the CRO statistical personnel.

### 12.1. Sample Size Considerations

Previous clinical studies have provided the necessary immunogenicity, safety, and tolerability data to support WHO pre-qualification (PQ) of PNEUMOSIL. The current study is intended to provide additional data to assist WHO-PQ and regulatory authorities in making recommendations regarding the immunogenicity and safety of PNEUMOSIL when delivered in a 2+1 dosing schedule. Since there are no hypothesis tests specified in this supportive study, sample size considerations are based on expected

precision of immunogenicity-related parameter estimates, rates of AEs, and descriptive comparisons between treatment groups in these measures, which are considered sufficient by the study team to generate actionable data by regulatory authorities.

All sample size calculations assume the use of descriptive 95% CIs (both for treatment group-specific measures and differences between groups), with no adjustment for multiple comparisons. Unless otherwise noted, asymptotic Wald-type CIs will be used when describing proportions, and asymptotic likelihood Score-type intervals for differences in proportions. Log-normality will be assumed when computing CIs for GMCs, GMTs, and their ratios between groups.

**Primary Immunogenicity Objective**:

The VAC-056 study observed coefficients of variation (CV) that ranged from 0.89 to 1.46 for serotype-specific serum IgG antibody levels measured 4 weeks after a booster dose of PNEUMOSIL in infants. In the VAC-017 study, the variability of serotype-specific IgG antibody levels observed in infants boosted between approximately 10-14 months of age was consistent with this range. Assuming the CVs for all 10 PNEUMOSIL serotypes measured 4-weeks after booster in the current study are at most 1.5, then the lower and upper 95% confidence bounds for each serum IgG GMC are expected to be at most 14% below and 16% above the GMC based on the study size of 220 per group (assuming no more than 10% of subjects are not evaluable due to loss to follow-up or other exclusions) (Table 17). For example, if the observed serotype-specific GMC = 1.0 μg/mL, then the 95% confidence interval (CI) is expected to be no wider than (0.86, 1.16); if the GMC = 3.0 μg/mL then the 95% CI is expected to be no wider than (2.58, 3.49). Similarly, the expected lower and upper 95% confidence bounds for descriptive GMC ratios (PNEUMOSIL versus either comparator) are expected to be no more than 19% below and 24% above the ratio. For example, if the observed GMC ratio equals 1.0, then the 95% CI is expected to be no wider than (0.81, 1.24), so long as the CV in the comparison group does not exceed 1.5.

**Table 17. Expected precision of serotype-specific GMCs (µg/mL) and GMC ratios (PNEUMOSIL vs. reference) for a range of possible true GMCs and GMC ratios**

| GMC in PNEUMOSIL group | Expected 95% CI for GMC | GMC ratio (PNEUMOSIL vs. comparator) | Expected 95% CI for GMC Ratio[†] |
|---|---|---|---|
| 0.5 | 0.43-0.58 | 0.75 | 0.60-0.93 |
| | | 1.00 | 0.81-1.24 |
| 1.0 | 0.86-1.16 | 0.75 | 0.60-0.93 |
| | | 1.00 | 0.81-1.24 |
| 3.0 | 2.58-3.49 | 0.75 | 0.60-0.93 |
| | | 1.00 | 0.81-1.24 |
| 5.0 | 4.29-5.82 | 0.75 | 0.60-0.93 |
| | | 1.00 | 0.81-1.24 |

[†] Precision of GMC ratio is independent of the GMC in column 1.

**Secondary Immunogenicity Objectives**

The precision of IgG GMCs at secondary time points is expected to be as for the primary objective, under the same assumptions about CV of serotype-specific IgGs and follow-up rates at different sampling times. The expected precision of other secondary immunogenicity objectives (IgG and OPA response rates, and OPA GMTs) is as follows:

*Precision of IgG Response Rates and Differences in Rates*

With a sample size of 220 per group (up to 10% of whom may not be evaluable), the half-width of 95% CIs for serum IgG response rates (IgG ≥ 0.35 µg/mL or IgG ≥ 1.0 µg/mL) will be no more than 0.07, and the half-width of 95% CIs for differences in proportions should not exceed 0.10.

*Precision of Serum OPA Titer Response Rates and Differences in Rates*

With a sample size of 50 per group (and no more than 10% excluded), the half-width of 95% CIs for OPA response rates (titer ≥ 1:8) will be no more than 0.15, and the half-width of 95% CIs for differences in proportions responding (PNEUMOSIL versus a comparator) should not exceed 0.21.

*Precision of OPA GMTs and GMT ratios*

The VAC-056 study observed CV values that ranged from 0.97 to 2.11 for serotype-specific OPA titers measured 4 weeks after a booster dose of PNEUMOSIL in infants. Assuming the CVs for all 10 PNEUMOSIL serotypes in the current study are at most 2.11 at any given secondary analysis time point, then the lower and upper 95% confidence bounds for each GMT are expected to be at most 32% below and 48% above the observed GMT based on the study size of 50 per group (assuming no more than 10% of subjects are not evaluable due to loss to follow-up or other exclusions). For example, if the observed serotype-specific GMT = 100, then the 95% CI is expected to be no wider than (68, 148). Similarly, the expected lower and upper 95% confidence bounds for descriptive GMT ratios

(PNEUMOSIL versus either comparator) are expected to be no more than 42% below and 73% above the ratio. For example, if the observed GMT ratio equals 1, then the 95% CI is expected to be no wider than (0.58, 1.73), so long as the CV in the comparison group does not exceed 2.11.

**Safety**

With a sample size of 220 infants vaccinated per group, there is an 89% chance of observing at least 1 safety endpoint (e.g., a solicited AE) which occurs with probability 0.01 or more; if no events of a specific classification occur then the 95% upper confidence bound for the event rate will be 0.017.

### 12.2. Analysis Populations

The Enrolled Population will include all screened subjects who provide informed consent, regardless of whether the subject is randomized to receive a study treatment. This population will be used to account fully for subject disposition, starting with the informed consent.

The Safety Population will include all subjects who were randomized, received a vaccination, and provided at least some post-vaccination safety data; all treated subjects are expected to contribute to this population. Treatment groups for safety analyses will be assigned according to the actual treatment received at Visit 1. This population will serve as the primary analysis population for demographics and study disposition as well as safety.

The Full Immunogenicity Population (FIP) includes subjects in the enrolled population who were randomized, received a study vaccination, and have one or more post-vaccination immunogenicity measurement(s). Analysis will be according to the treatment received by each subject, even if different from that to which the subject was randomized.

The Primary Per Protocol Immunogenicity (PP_IMM) Population will include all subjects in the FIP who received all 3 study vaccine doses (including booster) and have post-booster immunogenicity measurements. The Secondary PP_IMM Population (used for the analysis of Visit 4 data) will include all subjects who received both primary series doses and contribute immunogenicity measurement(s) 4 weeks post primary series.

Any exclusion from these populations (e.g., due to major protocol deviations that could potentially interfere with immune responses or the interpretability of findings) will be established in blind review of data by the Clinical Lead alone. To minimize the possibility of unintentional un-blinding, participant identifiers will be masked by the statistician providing relevant data listings on protocol deviations.

### 12.3. Handling of Dropouts or Missing Data

Immunogenicity values falling below the lower limit of quantitation or the lower limit of detection will be assigned a value of ½ the applicable limit. Values above an upper limit of quantification will be assigned the upper limit. Rules for imputing incomplete AE onset dates will be documented in the SAP. No other missing data imputation is planned for the study. If any is necessary, however, appropriate imputation rules will be established in blind review.

### 12.4. Multiple Comparisons/Multiplicity

There will be no type I error control of multiple comparisons in this descriptive study. All tests will be two-sided and conducted at the 0.05 significance level, and a coverage level of 95% will be used for all confidence intervals.

### 12.5. Timing of Interim and Final Analyses

An interim analysis of immunogenicity objectives through the end of V4 will occur when all subjects have completed V4, at which time the CRO statisticians responsible for the analysis will be unblinded. The Sponsor, Principal Investigator, site team, other CRO personnel and laboratory staff performing immunogenicity assays, will remain blinded until the completion of the trial. The final analysis of other endpoints will be conducted when all subjects have completed V6 and the database is locked.

### 12.6. Assessment of Study Populations

Disposition, demographic, and other baseline characteristics will be provided for the Safety and PP_IMM Populations.

#### 12.6.1. Participant Disposition

The numbers of participants enrolled, participants enrolled but not randomized (and reason), participants who withdraw early (and reason), and participants who complete the study will be summarized using descriptive statistics.

#### 12.6.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequencies and percentages for categorical data, and means, standard deviations, medians, and range for continuous variables. Data listings will be sorted by treatment group and subject ID number. Tabular summaries will be presented by subject ID.

### 12.7. Immunogenicity Analyses

##### 12.7.1.1. Primary Objective

The primary immunogenicity objective is to evaluate serum IgG antibody responses (GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to antibody responses to these serotypes induced by Prevenar 13 and Synflorix at 4 weeks post booster dose. Serum IgG GMCs will be reported by PNEUMOSIL serotype and treatment group, together with 95% CIs. For each serotype, GMC ratios (PNEUMOSIL vs. each comparator) and associated 95% CIs for the GMC ratio will be reported based on log-linear models, with no adjustment for multiple comparisons.

#### 12.7.2. Secondary Objectives

**Secondary Objective 1** is to evaluate – in a subset of subjects in the Primary PP_IMM Population – functional antibody responses to the 10 serotypes in PNEUMOSIL as measured by OPA at 4 weeks post the booster dose. Serotype-specific OPA GMTs will be reported by PNEUMOSIL serotype and treatment group, together with 95% CIs. Serotype-specific GMT ratios (PNEUMOSIL versus each comparator) and associated 95% CIs will be reported based on log-linear models.

**Secondary Objective 2** is to evaluate the proportion of subjects with serotype-specific serum IgG concentrations ≥ 0.35 μg/mL, serum IgG concentrations ≥ 1.0 μg/mL, and serum OPA titers ≥ 1:8 at 4 weeks post the booster dose by treatment group, together with 95% CIs. Serotype-specific differences in response rates (PNEUMOSIL vs. each comparator) will be reported with 95% CIs.

**Secondary Objective 3** is to evaluate serum IgG antibody responses to the 10 serotypes in PNEUMOSIL at 4 weeks post 2-dose primary series. The percentage of responders (subjects with serum IgG concentrations ≥ 0.35 μg/mL) will be reported by PNEUMOSIL serotype and treatment group, together with 95% CIs. Differences in response percentages (PNEUMOSIL vs. each comparator) will be reported with 95% CIs, with no adjustment for multiple comparisons. Serum IgG GMCs will be reported by PNEUMOSIL serotype and treatment group, together with 95% CIs. For each serotype, GMC ratios (PNEUMOSIL vs. each comparator) and associated 95% CIs for the GMC ratio will be reported based on log-linear models.

**Secondary Objective 4** is to evaluate – in a subset of subjects in the Secondary PP_IMM Population – functional antibody responses to the 10 serotypes in PNEUMOSIL as measured by OPA at 4 weeks post the 2-dose primary series. The proportion of subjects with serotype-specific serum OPA titers ≥1:8 and GMTs 4 weeks post dose 2 will be reported by PNEUMOSIL serotype and treatment group, together with 95% CIs. Serotype-specific differences in response percentages (PNEUMOSIL vs. each comparator) and GMT ratios will be reported with 95% CIs based on log-linear models.

**Secondary Objective 5** is to evaluate the persistence of serum IgG antibody responses to the 10 serotypes in PNEUMOSIL at 9-18 months of age, prior to the booster dose. The percentage of responders (IgG 0.35 μg/mL) and GMCs will be reported by PNEUMOSIL serotype and treatment group, together with 95% CIs. Serotype-specific differences in response rates (PNEUMOSIL vs. each comparator) and GMC ratios will be reported with 95% CIs.

**Secondary Objective 6** is to evaluate – in a subset of subjects in the Primary PP_IMM Population – the persistence of functional antibody responses to the 10 serotypes in PNEUMOSIL as measured by OPA at 9-18 months of age, prior to the booster dose. The proportion of subjects with serotype-specific serum OPA titers ≥1:8 and GMTs will be reported by PNEUMOSIL serotype and treatment group, together with 95% CIs. Serotype-specific differences in response percentages (PNEUMOSIL vs. each comparator) and GMT ratios will be reported with 95% CIs.

**Secondary Objective 7** is to evaluate booster responses (serum IgG concentrations and functional responses) from 4 weeks after the primary series (V4) to 4 weeks post booster dose (V6). For each PNEUMOSIL serotype, the ratio of post-booster to post-primary series IgG GMCs and OPA GMTs will be reported by treatment group with 95% CIs, restricted to subjects who provide response data at both V4 and V6.

In addition to the summary measures of immunogenicity responses described above for each of the primary and secondary objectives, reverse cumulative IgG concentration and OPA titer distribution curves will be presented by serotype and treatment group.

### 12.8. Safety and Tolerability Analyses

AEs will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version 21.0 or later).

The safety and tolerability of study vaccines will be evaluated by tabulating, by treatment group, the severity of solicited local and systemic AEs through Day 6 post each dose; the severity and relatedness of unsolicited AEs through 4 weeks after the booster dose; and the severity and relatedness of SAEs. All tabulations will include both the number of events in a given severity/relatedness category and the number (percentage) of subjects experiencing such events. Results will be tabulated separately through 4 weeks post primary series and through 4 weeks post booster (final analysis). Comparisons of event rates between groups will be made using descriptive 95% CIs and Chi-squared tests stratified on field

site, with no adjustment for multiple comparisons (exact methods will be used if there are fewer than 5 events in one or both groups being compared for a given outcome).

# 13. STUDY MONITORING

Sponsor monitoring responsibilities will be provided by the CRO. A site initiation visit will be conducted prior to beginning the study, and monitoring will be during and at closeout of the study by the study monitor or designee. See Section 7.4 for a discussion of the roles of blinded and unblinded study monitors in this study.

During the course of the study, the monitor will visit the site (including field sites) at intervals to verify compliance to the protocol; completeness, accuracy, and consistency of the data and study vaccine accountability; adherence to protocol and regulatory obligations; and to ensure that conduct of the research follows GCP. The monitor should have access to subject medical records, study vaccine accountability and other study-related records needed to verify the entries on the CRFs.

The PI and the monitor will cooperate to ensure that any problems detected in the course of these monitoring visits, including OpenClinica database completion and query resolution, are resolved in a predefined time frame to be agreed in the Clinical Monitoring Plan.

To ensure the quality of clinical data for all subjects, a clinical data management review will be performed on subject data received by the CRO. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for resolution as soon as possible and within the time frame described in the Clinical Monitoring Plan; all queries must be resolved prior to database lock.

Essential documents must be filed in the site study file on an ongoing basis and be available for review by the Sponsor's contracted site monitor. Monitoring visits will be performed according to the Clinical Monitoring Plan.

## 13.1. Independent Auditing

PATH representatives may audit the study to ensure that study procedures and data collected comply with the protocol and applicable SOPs/SSPs of the site and the CRO, and that data are correct and complete. The PI will permit auditors (employees of the Sponsor or an external company designated by the Sponsor) to verify source data of the regularly monitored clinical study. The auditors will compare the entries in the CRFs with the source data (where applicable) and evaluate the study site for its adherence to the clinical study protocol and GCP guidelines and applicable regulatory requirements.

## 13.2. Regulatory Agency Auditing

The PI will notify the Sponsor within 24 hours following contact by a regulatory agency. The PI will make the relevant records available for inspection and will be available to respond to reasonable requests and audit queries made by authorized representatives of regulatory agencies. The PI will provide the Sponsor with copies of all correspondence that may affect the review of the current study or his qualification as PI in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance in responding to regulatory audits or correspondence.

# 14. OBLIGATIONS AND ROLES OF THE SPONSOR, PI AND STUDY PERSONNEL

This study will be conducted according to GCP as well in accordance with Gambian regulations. The Sponsor will assure the trial is conducted in compliance with the protocol, GCP, and regulatory authority requirements. The Sponsor will provide the PI with the funding and information needed to conduct the trial properly, ensuring proper monitoring of trial activities, and that the trial is conducted in accordance with the general investigational plan and protocol contained in the submissions to the regulatory authorities. The Sponsor will ensure that the PI and regulatory authorities are immediately informed (within 24 hours of the Sponsor becoming aware) of significant new adverse effects or risks with respect to the study vaccine. The Sponsor will ensure that they will be immediately informed (within 24 hours of SIIPL becoming aware) of significant new adverse events in the Phase 3 trial in India or of any other safety concerns which could influence decisions regarding informed consent, enrollment and vaccination in this trial.

In addition, the PI will follow local and institutional requirements including, but not limited to, investigational vaccines, clinical research, informed consent and ethics regulations. The Sponsor will provide notification to the PI of protocol and amendment approvals by regulatory authorities when applicable. Any modifications to the research protocol, the ICF, and/or change in PI will be submitted for review and approval to regulatory authorities per their guidelines. The PI may deviate from the protocol without prior approval only when the deviation is necessary to eliminate an apparent immediate hazard to the study subject.

While the PI may delegate study duties to appropriate study personnel, the PI is ultimately responsible for the conduct of all aspects of the study.

## 15. ETHICAL CONSIDERATIONS AND INFORMED CONSENT

The study will be performed in accordance with SSPs and study plans generated and agreed between the Sponsor, Sponsor-designated CRO and the PI. The CRO has the responsibility for ensuring the site has the appropriate SSPs to perform the study. These SSPs have been developed in accordance with ICH Guidelines for GCP (1996), Directive 2001/20/EC, and GCPs for Clinical Research in The Gambia, which are consistent with the Ethical Guidelines outlined in the Declaration of Helsinki (2013), thus ensuring protection of the subjects. The study will commence only after receipt of a favorable opinion from the EC/IRB listed in this protocol and national authorities under Gambian law.

### 15.1. Institutional Review Board/Ethics Review Committee and Regulatory

The PI at the study site will be responsible for obtaining approval from the MRC Scientific Coordinating Committee (SCC) and The Gambia Government/MRC Joint Ethics Committee for the conduct of the study. The PI will submit the final protocol, IB, proposed ICF, any proposed advertising material, and all other relevant study-related information in writing for The Gambia Government/MRC Joint Ethics Committee and LSHTM Research Ethics Committee review and written approval, according to guidelines. The Sponsor will ensure approval to undertake the study is obtained from WIRB. The PI will obtain import authorization and clinical trials authorization from the NMRA in The Gambia. Recruitment and enrollment of subjects will not take place until all approvals from regulatory authorities involved in this trial are received. The PI will notify the EC/IRB of SAEs, protocol amendments, and protocol violations and deviations according to the EC/IRB requirements.

### 15.2. Informed Consent Process

Prior to any study-related screening procedures being performed on the subject, written (or thumb-printed) informed consent will be obtained from each subject's parent. Only one parent (usually the

mother) will provide written consent but in general both parents should agree to a subject's participation. If either parent specifically states that they do not want their infant to participate, the infant will not be enrolled. Consent will only be obtained from birth parents. Consent will not be obtained from guardians in this study. Once informed consent has been obtained the subject will be considered to be enrolled. The method of explanation to the subject's parent or impartial witness, and obtaining of parental consent will comply with the ICH GCP Guidelines and the ethical principles in the amended Declaration of Helsinki (2013), whichever represents the greater protection for the individual. The PI will obtain and document the informed consent process in accordance with the requirements for source documentation in PATH-sponsored clinical trials. See Section 6.1.2 for a detailed explanation of the informed consent process. Of note, consent in many cases will be obtained through verbal translation of the ICF from English into the local language. Individuals at The MRCG at LSHTM have longstanding expertise in this area. The local languages are not written therefore translation and back-translation has been proven to be unreliable/ineffective. The approach taken has been approved by The Gambia Government/MRC Joint Ethics Committee.

### 15.3. Research Involving Children

Before undertaking research involving children, the PI must ensure that the research has the goal of bettering the health of children. PNEUMOSIL contains 10 pneumococcal serotypes chosen specifically because of their prevalence in low-resource countries such as The Gambia. This Phase 3 study aims to assist WHO-PQ and regulatory authorities in making recommendations regarding the immunogenicity and safety of PNEUMOSIL when delivered in a 2+1 dosing schedule. Because of the early successful introduction of PCV into the national EPI program, and continued high coverage rates for Prevenar 13, rates of vaccine-type IPD are low in The Gambia. This fact, together with the substantial immune response to all 10 serotypes in PNEUMOSIL seen in infants in the Phase 1/2 trial (VAC-017), and the demonstrated efficacy and effectiveness of Synflorix against IPD and pneumonia in randomized controlled trials, provides assurance that it is safe for infants to be vaccinated with a 2-dose primary series and booster dose of PNEUMOSIL or Synflorix. Additionally, infants who are enrolled in the PNEUMOSIL and Synflorix groups will be offered a dose of Prevenar 13 outside the study after visit 6 for all study subjects have been completed and the study has been unblinded for the site team to ensure all recruited infants gain maximal long-term pneumococcal protection.

### 15.4. Insurance and Indemnity

Subjects will be insured against injury caused by the study according to legal requirements. The parent will be informed about the insurance and the responsibilities on their part. In the event that a subject suffers injury or death directly attributable to participation in this study, appropriate treatment and/or compensation will be provided by and/or paid to the subject by the Sponsor.

### 15.5. Risk/Benefit

No benefits can be guaranteed to subjects for their participation in this research study. As with any vaccine, severe allergic reaction is a potential rare event. In the VAC-017 and VAC-056 studies, conducted in The Gambia, PNEUMOSIL was well-tolerated, and no meaningful safety signals were identified, in 1,603 infants who have received a 3-dose primary series of PNEUMOSIL (at 6, 10, and 14 weeks of age), and in 500 infants total who have received a booster dose of PNEUMOSIL (between 9 and 14 months of age), in all cases co-administered with standard EPI vaccines. When observed, reactogenicity was primarily mild or moderate and of short duration. There were no related SAEs in

either study and no meaningful trends in SAEs, vaccine-related TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death.

As in the VAC-017 and VAC-056 trials, additional risk mitigation will be provided in the planned Phase 3 trial by clinical monitoring and access to clinical evaluation and management.

Potential health benefits include the clinical assessments and physical examinations by a study clinician outlined in the protocol which may identify illnesses or other medical issues, thus allowing for their prompt treatment. Medical issues will also be investigated and managed by the study team according to good clinical practice in The Gambia and within the limits of the regular practice of the MRCG at LSHTM clinical services department and associated laboratory, radiology and pharmacy facilities. Certain issues beyond this (including in particular, but not limited to, any surgical issues) would instead be referred to the appropriate government health facility for management, in which case transport and other small costs would generally be covered by the study team (note that these limitations do not apply to study-related injury, which are covered by clinical trial insurance).

Infants who participate in the study will receive a booster dose, which is expected to provide additional protection against pneumococcal disease by boosting immunity. A booster dose of PCV is not currently offered by the Gambian EPI program. The overall aim of the program is to see if the vaccine can be delivered in a 2+1 dosing schedule.

Infants who participate in the study will have some discomfort and slight bruising when the blood sample is taken.

### 15.6. Subject Confidentiality

Every effort will be made to protect subject privacy and confidentiality. Personal identifiers will not be included in any study reports. All study records will be kept confidential to the extent provided by national laws. Medical records containing identifying information will be made available for review when the study is monitored by the Sponsor or an authorized regulatory agency. Direct access may include examining, analyzing, verifying, and reproducing any records and reports that are important in the evaluation of the study.

All study-related information will be stored securely at the study site. All subject information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, and other reports will be identified only by a unique trial-related subject ID code (screening/randomization ID) to maintain subject confidentiality. Laboratory reports may include the name and date of birth of the subject to minimize the risk of errors in the busy clinical laboratories. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link subject ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Subjects' study information will not be released without their written permission, except as necessary for monitoring, or as required/permitted by law/regulatory authorities.

### 15.7. Reimbursement

Pending EC approval, parents of subjects will be compensated for travel to study visits. In addition, appropriate food during a visit and services to allow phone contact for follow-up purposes will be provided. The study ICF will explain this. Parents of study subjects will not be charged for vaccines,

research clinic visits, research-related examinations, or research-related laboratory tests or health care in line with good practice in The Gambia while on follow-up in the study.

## 15.8. Storage of Specimens

### 15.8.1. Use of Specimens during the Study

Each blood sample drawn for a subject will be uniquely labeled at the subject level to allow the site, the laboratories performing the assays, and the Sponsor to remain blinded to treatment assignment until the blind is broken during the primary and secondary immunogenicity analyses. After the blind is broken, the laboratories performing the assays will continue to be blinded for the additional analysis. Stored study research samples will be labeled by screening number. All stored research samples will be logged into a secure database that tracks total samples collected and used. The transport of samples to any laboratory outside of the clinical site will be traceable and logged at the time of transit (at the package level) and receipt (at the sample level) and temperature monitored when appropriate to ensure sample integrity. Any deviations identified during transport that might affect the integrity of the sample analysis will be reported to the data management system for logging. Refer to the SSP for specifics on sample labeling, transport, tracking and logging. After the completion of immune testing, all remaining samples at the central laboratory will be destroyed.

### 15.8.2. Future Use of Stored Specimens

Some serum samples and nasal swab samples will be retained at the [redacted] in case testing needs to be repeated. When these samples are no longer needed for the purposes of the study, they will be kept or destroyed, depending on whether subjects' parents consented to any remaining samples being used for other, ethically approved research which could be of benefit to the people of The Gambia. Samples that will remain at the [redacted] will have the same label as was used in the current study. Their use will be governed by a repository plan that is mutually agreeable to PATH and MRCG at LSHTM. The samples will be used in accordance with what is stated in the study consent form and with review by relevant ethics committees in accordance with laws of [redacted] and PATH policies. No genetic testing will be done on the samples.

# 16. APPENDICES

## 16.1. Appendix 1: Solicited Local and Systemic Reactions Toxicity Grading Table

| Local Reaction to Injectable Product | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| Tenderness[a] | Minor reaction to touch | Cries / protests on touch | Cries when limb is moved / spontaneously painful | Hospitalization |
| Erythema/Redness[b] | Erythema present but ≤ 2.5 cm diameter | Erythema >2.5cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh) | Erythema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage | Necrosis (involving dermis and deeper) of tissue OR Hospitalization |
| Induration/Swelling[b] | Induration OR Edema present but ≤ 2.5 cm diameter | Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh) | Induration OR Edema involving > 50% surface area of the extremity segment (e.g., upper arm/thigh) or Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage | Necrosis (involving dermis and deeper) of tissue OR Hospitalization |
| Temperature (axillary) | ≥ 37.5°C (99.5°F) to ≤ 38.0°C (100.4°F) | > 38.0°C (100.4°F) to ≤ 39.0°C (102.2°F) | > 39.0°C (102.2°F) to ≤ 40.0°C (104.0°F) | > 40.0°C (104.0°F) |
| Irritability[a] | Crying more than usual / no | Crying more than usual / | Crying that cannot be | Hospitalization |

| Local Reaction to Injectable Product | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| | effect on normal activity | interferes with normal activity | comforted / prevents normal activity | |
| Drowsiness | Drowsiness easily tolerated | Drowsiness that interferes with normal activity | Drowsiness that prevents normal activity | Hospitalization |
| Decreased Appetite[a] | Eating less than usual / no effect on normal activity | Eating less than usual / interferes with normal activity | Not eating at all | Hospitalization |
| Cutaneous Rash | Localized macular rash (not directly associated with the injection site – i.e. not a local reaction at the site of injection) | Diffuse macular; maculopapular, or morbilliform rash OR Target lesions | Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site | Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal Necrolysis (TEN) |

Note: The preferred route for recording temperature in this study will be axillary.

[a] Standard pediatric reactogenicity scales used in PCV studies.

[b] Record redness and swelling at greatest surface diameter in millimeters using a ruler.

NOTE: The above table is derived from Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.0, November 2014).

## 16.2. Appendix 2: Vital Signs Toxicity Grading Table

| Vital Signs[a]/Terms | Normal Range | Criteria / Info | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|---|---|
| Temp ($^{o}$C) / Fever | ≤ 37.4 | High | 37.5 - 38.0 | 38.1 - 39.0 | 39.1 - 40.0 | >40 |
| Respiratory Rate (breaths/min) [b] / Tachypnoea | 30 – 50*<br><br>(30 to 60 if less than or equal to 8 weeks of age) | High | Wheezing OR minimal increase in respiratory rate for age | Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95% | Dyspnoea at rest causing inability to perform usual social and functional activities OR Pulse oximetry < 90% | Hospitalization |
| Respiratory Rate (breaths/min) [b] / Bradypnoea | | Low* | Mild | Moderate | Severe | Life-threatening |
| Heart rate (beats/min)[c] / Tachycardia | 95 - 160 | High | Asymptomatic, intervention not indicated | Symptomatic, non-urgent medical intervention indicated | Severe, medically significant, medical intervention indicated | Life-threatening consequences; urgent intervention indicated |
| Heart rate (beats/min)[c] / Bradycardia | | Low | Asymptomatic, intervention not indicated | Symptomatic; non-urgent medical intervention indicated | Severe, medically significant, medical intervention indicated | Life-threatening consequences; urgent intervention indicated |

* Low respiratory rates should be graded based on the severity grading for unsolicited AE (1=mild; 2=moderate; 3=severe; 4=life threatening) but note that an infant cannot be vaccinated with any vital sign which is out of range (high OR low)

[a] Subject should be at rest for all vital sign measurements.

[b] Derived from the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.0, November 2014).

[c] Derived from Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, Published May 28, 2009 (v4.03: June 14, 2010).

## 16.3. Appendix 3: References

[1] World Health Organization. Estimated Hib and pneumococcal deaths for children under 5 years of age; 2008. March 2012. http://www.who.int/immunization/monitoring_surveillance/burden/estimates/Pneumo_hib/en/ (accessed 8/26/16).

[2] Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2014; 385(9966):430–40.

[3] Levine OS, Cherian T. Pneumococcal vaccination for Indian children. *Indian Pediatr*. 2007 Jul; 44(7):491-496

[4] O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *Lancet* 2009;374:893–902.

[5] Klugman KP. Contribution of vaccines to our understanding of pneumococcal disease. *Philos Trans R Soc Lond B Biol Sci*. 2011 Oct 12;366(1579):2790-8.

[6] Simell B, Auranen K, Käyhty H, Goldblatt D, Dagan R, O'Brien KL; Pneumococcal Carriage Group. The fundamental link between pneumococcal carriage and disease, *Expert Rev Vaccines*. 2012 Jul;11(7):841-55

[7] Feigin RD, McCracken GH Jr, Klein JO. Diagnosis and management of meningitis, *Pediatr Infect Dis J. 1992*; 11(9):785

[8] Tan TQ, Mason EO Jr, Barson WJ, Wald ER, Schutze GE, Bradley JS, Arditi M, Givner LB, Yogev R, Kim KS, Kaplan SL. Clinical characteristics and outcome of children with pneumonia attributable to penicillin-susceptible and penicillin-nonsusceptible Streptococcus pneumoniae, *Pediatrics* 1998;102(6):1369

[9] O'Dempsey TJ, McArdle TF, Lloyd-Evans N, Baldeh I, Lawrence BE, Secka O, et al. Pneumococcal disease among children in a rural area of west Africa. *Pediatr Infect Dis J*. 1996;15: 431-37.

[10] Campbell JD, Kotloff KL, Sow SO, Tapia M, Keita MM, Diallos S, et al. Invasive pneumococcal infections among hospitalized children in Bamako, Mali. *Pediatr Infect Dis J*. 2004; 23: 642-49.

[11] Berkley JA, Lowe BS, Mwangi I, Williams T, Bauni E, et al. Bacteremia among children admitted to a rural hospital in Kenya. *NEJM*. 2005; 352: 39-47.

[12] Obaro SK. Prospects for pneumococcal vaccination in African children. *Acta Trop*. 2000; Mar 25; 75(2):141-153.

[13] Cutts FT, Zaman SMA, Enwere G, Jaffar S, Levine OS, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomized, double-blind, placebo-controlled trial. *Lancet*. 2005 Mar 26; 365: 1139-1146.

[14] Mackenzie GA, Hill PC, Jeffries DJ, Hossain I, Uchendu U, et al. Effect of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease in The Gambia: a population-based surveillance study. *Lancet Infect Dis*. 2016 Jun;16(6):703-11

[15] Johnson HL, Deloria-Knoll M, Levine OS, Stoszek SK, Freimanis Hance L, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Med*. 2010 Oct 5;7(10). pii: e1000348. doi: 10.1371/journal.pmed.1000348.

[16] Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med*. 1991; 325: 1453-1460.

[17] Temple K, Greenwood B, Inskip H, Hall A, Koskela M, Leinonen M. Antibody response to pneumococcal capsular polysaccharide vaccine in African children. *Pediatr Infect Dis*. 1991; 10: 386-390.

[18] Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, et al. For the Active Bacterial Core Surveillance/Emerging Infections Program Network. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *JID*. 2010; 201: 32-41.

[19] Gavi The Vaccine Alliance. The Gambia introduces vaccine against pneumococcal disease. Gavi The Vaccine Alliance website http://www.gavi.org/library/news/press-releases/2009/the-gambia-introduces-vaccine-against-pneumococcal-disease/ (accessed 8/26/16).

[20] Gavi The Vaccine Alliance. Pneumococcal AMC. Gavi The Vaccine Alliance website http://www.gavi.org/funding/pneumococcal-amc/ (accessed 8/26/16).

[21] Vaccine Information Management System Report on Global Introduction (updated June 2016) http://www.jhsph.edu/research/centers-and-institutes/ivac/view-hub/IVAC-VIEW-hub-Report-2016-06.pdf (accessed 8/26/16)

[22] United Nations. Transforming Our World: the 2030 Agenda for Sustainable Development, 2015. https://sustainabledevelopment.un.org/content/documents/21252030%20Agenda%20for%20Sustainable%20Development%20web.pdf

[23] Drugs and Cosmetics (IInd Amendment) Rules, Ministry of Health and Family Welfare, New Delhi, the 20th January, 2005.

[24] ICH Harmonized Tripartite Guideline S6. Preclinical safety evaluation of biotechnology-derived pharmaceuticals, recommended for adoption by the ICH Steering Committee on 16 July 1997. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf

[25] WHO guidelines on nonclinical evaluation of vaccines. TRS 927, Annex 1, 2005. http://www.who.int/entity/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1

[26] WHO. Annex 3: Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines. Replacement of WHO Technical Report Series, No. 927, Annex 2. WHO Technical Report Series: World Health Organization; 2013

[27] WHO. Target Product Profile (TPP) for the Advance Market Commitment (AMC) for Pneumococcal Conjugate Vaccines. February 22, 2008. http://www.who.int/immunization/sage/target_product_profile.pdf

[28] Pneumococcal vaccines WHO position paper – 2012. http://www.who.int/wer/2012/wer8714.pdf?ua=1

[29] WHO. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019. Weekly Epidemiological Record. No. 8, 2019, 94, 85-104. February 22, 2019. https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf

[30] Goldblatt D et al. Immunogenicity of a reduced schedule of pneumococcal conjugate vaccine in healthy infants and correlates of protection for serotype 6B in the United Kingdom. The Pediatric Infectious Disease Journal, 2010, 29:401–405.

[31] J. McLellan, B. Ebruke, R. Saluadeen, E. Machuka, S. Jarju, M. Antonio, S. Howie, N. PERCH Study Group. Carriage Prevalence, Serotype Distribution and Antibiograms of Streptococcus Pneumoniae Isolates from the PERCH Study, The Gambia Site. [Abstract ISPPD-0455]. Pneumonia 2014; 3:267.

[32] CBER/FDA. Prevenar 13® (13vPnC): Pneumococcal 13-valent Conjugate Vaccine (Diphtheria $CRM_{197}$ Protein), Vaccines and Related Biological Products Advisory Committee. November 18, 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM190734.pdf

[33] Jokinen J, Rinta-Kokko H, Siira L, Palmu AA, Virtanen MJ, et al. Impact of tenvalent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children–a population-based study. *PLoS One* 2015; 10(3):e0120290.

[34] Domingues CM, Verani JR, Montenegro Renoiner EI, de Cunto, et al. Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched casecontrol study. *Lancet Respir Med* 2014 June; 2(6):464-71.

[35] Deceuninck G, De Serres G, Boulianne N, Lefebvre B, De Wals P. Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada.*Vaccine* 2015 May 28; 33(23):2684-9.

[36] Chevallier B, Vesikari T, Brzostek J, Knuf M, Bermal N, et al. Safety and Reactogenicity of the 10-Valent Pneumococcal Non-typeable *Haemophilus influezae* Protein D Conjugate Vaccine (PHiD-CV) when Coadministered with Routine Childhood Vaccines. *Pediatr Infect Dis J* 2009;28: S109-S118

[37] Synflorix. Annex I Summary of Product Characteristics. GlaxoSmithKline Biologicals s.a., Rixensart, Belgium, 2014

[38] Prevenar 13 (package insert). Philadelphia, PA: Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc.; 2014

[39] WHO. Best practices for injections and related procedures toolkit, 2010. http://whqlibdoc.who.int/publications/2010/9789241599252_eng.pdf

[40] Guidance for Industry. E3 Structure and Content of Clinical Study Reports. U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research, CBER, January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM336889.pdf