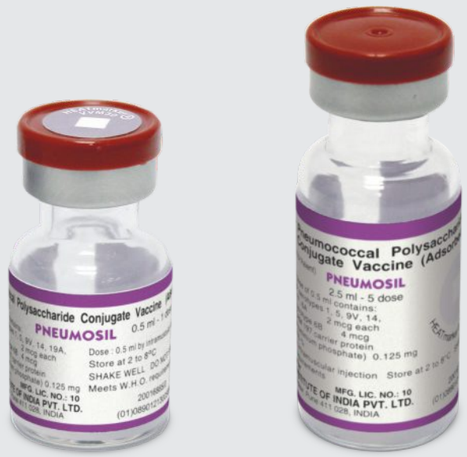
Pneumosil

Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed, 10-Valent)

Relevant Serotypes, Comprehensive Protection



Single dose 0.5ml Vial

Multidose 2.5ml Vial

A Tailored PCV with 6A and 19A
"Affordable Protection"

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WHO Pre-Qualified

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PNEUMOCOCCAL DISEASE

The Organism

Pneumococcal disease is the name given to a group of diseases caused by a bacterium called *Streptococcus pneumoniae* (also known as pneumococcus). S. pneumoniae is a Gram-positive encapsulated diplococcus. The polysaccharide capsule is an essential virulence factor for invasive pneumococcal disease. Pneumococcus is classified into 93 known serotypes, based on the identification of differences in the composition of its outer capsule[1]. The different serotypes have varying potential to cause disease with relatively few serotypes associated with severe disease in children. Globally, about 20 serotypes are associated with >80% of invasive pneumococcal disease occurring in all age groups; the 13 most common serotypes included in the PCV cause at least 70–75% of invasive disease in children[2]. Most illnesses are sporadic. Outbreaks of pneumococcal disease are uncommon, but may occur in closed populations, such as nursing homes, childcare centres or other institutions.

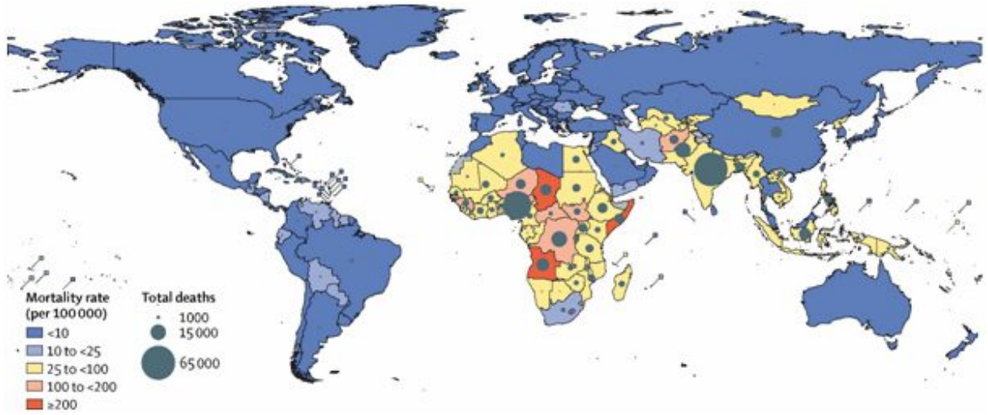
Different Types of Diseases Caused by Pneumococcus

Diseases caused by pneumococcus *(Streptococcus pneumoniae)* are a major public health problem worldwide. Diseases that are often caused by pneumococcus include:

- Pneumonia: inflammation of the lungs;
- Bacteraemia/sepsis: bloodstream infection, with or without infection of secondary sites, e.g., meningitis;
- Bacterial meningitis: infection of the membranes that cover and protect the spinal cord and brain;
- Otitis media: Middle ear infection; and
- Sinusitis, Bronchitis

About 75% of invasive pneumococcal disease and 83% of pneumococcal meningitis occur in children aged <2 years, among which many cases occur in neonates and children under 6 months of age.

Country-specific mortality rates and deaths attributable to pneumococcus in 2015[3]



Mortality rates and deaths in children aged 1–59 months are HIV-negative deaths only. Mortality rates are deaths per 100 000 children aged 1–59 months. Pneumococcus = *Streptococcus pneumoniae*.

PNEUMOSIL

Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-valent) is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F individually conjugated by using 1-cyano-4-dimethylamino pyridinium tetrafluoroborate chemistry (CDAP) to non-toxic diphtheria CRM197 protein. The polysaccharides are chemically activated and then covalently linked to the protein carrier CRM197 to form the glycoconjugate.

- PNEUMOSIL (Pneumococcal Conjugate Vaccine - adsorbed, 10 Valent), a well-designed vaccine with relevant serotypes by targeting the most prevalent serotypes of the bacterium causing serious illness in countries with high disease burden.
- PNEUMOSIL safety and immunogenicity profile is favourably comparable to both currently available licensed and WHO pre-qualified PCVs worldwide.
- Various seroprevalence assessment estimates PNEUMOSIL serotype coverage comparable to other PCVs in high disease burden countries including countries with high seroprevalence of 6A and 19A.
- PNEUMOSIL is WHO pre-qualified for its procurement by United Nations Agencies and Gavi.

Description

Individual conjugates are compounded and then polysorbate 20 and aluminium phosphate are added to formulate the vaccine.

Composition

Each dose of 0.5 ml of vaccine contains:

Active Ingredients	Quantity
Saccharide for serotypes 1, 5, 6A, 7F, 9V, 14, 19A, 19F and 23F	2 μg
Saccharide for serotype 6B	4 μg
Conjugated to CRM 197 carrier protein	19 to 48 μg

Inactive Ingredients	Quantity
Aluminium (as Aluminium phosphate)	0.125 mg
L-Histidine	1.55 mg
Succinic acid	1.18 mg
Sodium Chloride	4.50 mg
Polysorbate-20	0.05 mg
Thiomersal*	0.005 %
Water for Injection	q.s. to 0.5 ml

* Added only in multi-dose presentation

PNEUMOSIL Clinical Trials

PNEUMOSIL (10-valent) has been extensively evaluated in 7 randomized controlled clinical trials and has demonstrated comparable safety and immunogenicity against licensed pneumococcal vaccines across diverse populations of India and Africa, where PNEUMOSIL was administered to adults, toddlers and infants using different vaccination schedules, with all sera samples being tested (WHO standard ELISA and MOPA) at the WHO Pneumococcal Reference Laboratory in the UK;

Study No. / Phase / Location	Study Population	Schedule of vaccination / Control	No. Subjects PNEUMOSIL	No. Subjects Comparator
PCV-10-001 / Phase 1 / India (Data on file)	PCV-naïve adults (18-40 years inclusive)	Single dose / PPSV23	17	17

In a Prospective, Randomized, Two-Arm, Active Controlled, Double-Blind Study; A single dose of PNEUMOSIL was well tolerated and showed no safety concerns in healthy Indian adults, demonstrating a safety profile comparable with the licensed comparator.

Study No. / Phase / Location	Study Population	Schedule of vaccination / Control	No. Subjects PNEUMOSIL	No. Subjects Comparator
VAC-017 / Phase 1/2 / The Gambia (https://pubmed.ncbi.nlm.nih.gov/31843266/)	PCV-naïve adults (18-40 years inclusive)	Single dose / PPSV23	17	17
	PCV-primed toddlers (12-15 months inclusive)	Single dose / PCV13	56	56
	PCV-naïve infants (6 to 8 weeks inclusive)	3-dose primary vaccination series (at 6, 10 and 14 weeks of age) / PCV13	100	100
		Booster vaccination at 10-14 months of age in a subset / PCV13	49	47

In a Phase 1/2, Prospective, Single Centre, Randomized, Active-Controlled, Double-Blind, Age De-escalation Study;

- **PNEUMOSIL** demonstrated similar safety and tolerability profile in all three age groups to the licensed comparator/s.
- **PNEUMOSIL** was immunogenic in all three age groups as measured both with IgG antibody level and functional activity (OPA).
- IgG GMCs were > 1μg/ml for all serotypes in both PNEUMOSIL and the licensed comparator group. Post booster GMCs were comparable between groups.
- **PNEUMOSIL** elicited a strong booster response for all 10 serotypes, comparable to the licensed comparator.
- **PNEUMOSIL** did not appear to interfere with the responses to concomitantly administered vaccinations.
- Pre booster vaccination IgG GMCs were generally comparable between both **PNEUMOSIL** and licensed comparator groups, and were lower than the respective post primary series GMCs for both groups.

Study No. / Phase / Location	Study Population	Schedule of vaccination / Control	No. Subjects PNEUMOSIL	No. Subjects Comparator
PCV-10-002 / Phase 2 / India (Data on file)	PCV-naïve toddlers (12-15 months inclusive)	Two dose Catch-up schedule, 8 weeks apart / PCV13	57	57

In a Phase 2, Prospective, Multi-centre, Randomized, Two-arm, Active Controlled, Double-blind Study;

- **PNEUMOSIL** was well tolerated and no safety signals were identified, demonstrating a similar safety and tolerability profile to the licensed comparator.
- Overall immune responses (both IgG by ELISA, as well as functional responses by OPA) following **PNEUMOSIL** were robust and comparable to those following the licensed comparator, with IgG GMCs > 1μg/ml for all 10 serotypes in both treatment groups.

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Study No. / Phase / Location	Study Population	Schedule of vaccination / Control	No. Subjects PNEUMOSIL	No. Subjects Comparator
VAC-056 / Phase 3 / The Gambia (3 + 1) (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30735-0/fulltext)	PCV-naïve infants (6 to 8 weeks inclusive on Day 0)	3-dose primary vaccination series (at 6, 10 and 14 weeks of age) / PHiD-CV	1,503	747
		Booster vaccination at 9-10 months of age in a subset / PHiD-CV	428	213

In a Pivotal Phase 3, Randomized, Double-Blind Study;

- Lot-to-Lot consistency was established with equivalence demonstrated for the 3 lots of **PNEUMOSIL** evaluated in the study.
- Non-inferiority was demonstrated for all 10 serotypes in **PNEUMOSIL** in comparison to the immune responses induced by the licensed comparator, after a 3-dose primary series, on the basis of both % IgG responders (≥ 0.35 μg/ml) as well as IgG GMC ratios.
- Robust functional responses were demonstrated for all 10 serotypes in **PNEUMOSIL** by both % OPA responders (≥ 1:8) as well as OPA GMT ratios, favourably comparable to those induced by the licensed comparator.
- Robust booster IgG and OPA responses were demonstrated for all 10 serotypes in **PNEUMOSIL**, favourably comparable to those induced by the licensed comparator.
- Non-inferior non-interference to all co-administered EPI vaccines was established in comparison to the licensed comparator group.
- **PNEUMOSIL** had an acceptable safety and tolerability profile, with no notable difference in comparison with the licensed comparator.
- Antibodies elicited by the booster dose were shown to persist at least as well following **PNEUMOSIL** as following the licensed comparator for all serotypes over the 1 year follow-up period post booster.

Study No. / Phase / Location	Study Population	Schedule of vaccination / Control	No. Subjects PNEUMOSIL	No. Subjects Comparator
PCV-10-003 / Phase 3 / India (3 + 0) (Data on file)	PCV-naïve infants (6 to 8 weeks inclusive on Day 0)	3-dose vaccination series (at 6, 10 and 14 weeks of age) / PCV13 and PHiD-CV	225	223

In a Phase 3, Randomized, Double-Blind Study;

- **PNEUMOSIL** was highly immunogenic in Indian infants and induced robust serotype specific IgG and functional OPA responses for all 10 serotypes.
- The study data indicates comparable immunogenicity of **PNEUMOSIL** to both licensed comparators using either of the WHO defined IgG endpoints and/or OPA endpoints for all 10 serotypes and thus demonstrates comparability of **PNEUMOSIL** with both currently licensed PCVs in India, in Indian infants.
- The robust OPA results are clinically significant in light of increasing clinical importance assumed by OPA over IgG, as opsonophagocytosis is considered as the primary mechanism of host defence against pneumococcal disease, and is being increasingly observed to correlate well with protection offered against IPD.
- **PNEUMOSIL** was safe and well tolerated in a 3 + 0 vaccination schedule in Indian infants, with a safety and reactogenicity profile favourably comparable to both licensed comparators.

Study No. / Phase / Location	Study Population	Schedule of vaccination / Control	No. Subjects PNEUMOSIL	PHiD-CV	PCV13
CVIA-074 Phase 3 The Gambia (2 + 1) (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00734-4/fulltext)	PCV-naïve infants (6 to 8 weeks inclusive on Day 0)	3-dose vaccination series (at 6, 14 weeks and 9 months of age) / PHiD-CV and PCV13	220	220	220

OPA percentage responders 4 weeks post dose 3:

- In the **PNEUMOSIL** group, the observed proportion of OPA responders 4 weeks post-booster reached 100% for all serotypes except for serotype 19F (98.0%).
- No significant difference was observed in the proportion of OPA responders in the **PNEUMOSIL** group compared to the PHiD-CV group for any of the 8 common serotypes and no significant difference for PCV13 group for any serotype.

IgG percentage responders 4 weeks post dose 3:

- In the **PNEUMOSIL** group, the observed proportion of IgG responders (at the 0.35 μg/mL threshold) at 4 weeks post- booster was at least 97.5% for all serotypes.
- The observed proportion of IgG responders in the **PNEUMOSIL** group compared to the PHiD-CV group, no difference was observed for the 7 common serotypes and no significant difference in the proportion of IgG responders in the PNEUMOSIL group compared to the PCV13 group was evidenced for any of the 10 serotypes.

OPA GMTs 4 weeks post dose 3:

- The GMT at 4 weeks post-booster was significantly higher in the **PNEUMOSIL** group compared to the PHiD-CV group for 7 of the 8 common serotypes and the GMT was significantly higher in the PCV13 group compared to the **PNEUMOSIL** group for 4 serotypes; GMTs were similar for 6 serotypes.

IgG GMCs 4 weeks post dose 3:

- Post-booster IgG GMCs in the **PNEUMOSIL** group were statistically significantly higher compared to the PHiD-CV group for 7 of the 8 common serotypes and IgG GMC was significantly higher in the PCV13 group compared to the **PNEUMOSIL** group for 4 serotypes; IgG GMCs were similar for 5 serotypes.

All confirmatory primary and secondary objectives were met:

- **PNEUMOSIL** was shown to induce a robust immune response (by both ELISA and OPA) to all pneumococcal serotypes contained in the vaccine 4 weeks after completion of the 2 + 1 schedule.
- **PNEUMOSIL** has demonstrated to have an acceptable safety profile and be well-tolerated when co-administered with routine paediatric vaccines through 4 weeks after a booster vaccination.

References

1. Introduction of pneumococcal vaccine PCV13, A handbook for district and health facility staff. 2013. http://apps.who.int/iris/bitstream/10665/90380/1/WHO_IVB_13.10_eng.pdf
2. Pneumococcal vaccines WHO position paper – 2012. Weekly epidemiological record. No 14, 2012, 87, 129-144. http://www.who.int/wer/2012/wer8714.pdf?ua=1
3. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health. 2018;6(7):e744-e57.

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Study No. / Phase / Location	Study Population	Schedule of vaccination / Control	No. Subjects PNEUMOSIL	PHiD-CV	PCV13
PCV-10-004 Phase 3 India (2 + 1) (Data on file)	PCV-naïve infants (6 to 8 weeks inclusive on Day 0)	3-dose vaccination series (at 6, 14 weeks and 9 months of age) / PHiD-CV and PCV13	168	85	83

This was a prospective, multi-center, randomized, active-controlled, double-blind, Phase 3 Indian experience study in pneumococcal conjugate vaccine (PCV)-naïve infants (6 to 8 weeks).

- Data from this descriptive Indian Phase 3 experience study designed to support use of PNEUMOSIL in a 2 + 1 schedule (including in the Indian UIP) demonstrated that **PNEUMOSIL** on its own elicited strong total as well as functional immune responses against all 10 serotypes contained in the vaccine when given to Indian infants in a 2 + 1 schedule.
- The treatment group comparison with two Indian licensed and WHO prequalified PCVs using either (or both) of the WHO defined IgG criteria and/or WHO defined OPA criteria conclusively demonstrated **PNEUMOSIL** to be comparable to both PCV13 and PHiD-CV for all 10 serotypes contained in the vaccine.
- **PNEUMOSIL** was safe and well tolerated when administered in Indian infant population in a 2 + 1 vaccination schedule, with a safety and reactogenicity profile comparable to both PCV13 and PHiD-CV.

Indication: Active immunization against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in infants and toddlers from 6 weeks up to 2 years of age. The use of vaccine should be determined on the basis of relevant recommendations and taken into consideration the disease impact by age and regional epidemiology.

Contraindications: Hypersensitivity to any component of the vaccine, including diphtheria toxoid.

Precautions: Do not administer intradermally, subcutaneously or intravenously. Avoid injecting into or near nerves or blood vessels. Do not inject into gluteal area. Appropriate treatment and supervision must be available in case of rare anaphylactic event. Adrenaline Injection (1:1000) must be Immediately available should an Acute Anaphylactic reaction occur due to any component of the Vaccine. Hydrocortisone and antihistaminics should also be available in addition to supportive measures such as oxygen inhalation and IV fluids. Minor illnesses, such as mild respiratory infection, with or without low grade fever, are not generally contraindications to vaccination. The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. As with any intramuscular injection, PNEUMOSIL (10-valent) should be given with, caution to infants or children with thrombocytopenia or any coagulation disorder, or to those receiving anticoagulant therapy. This vaccine is not intended to be used for treatment of active infection. PNEUMOSIL (10-valent) may not protect all individuals receiving the vaccine from pneumococcal disease.

Adverse Effects: Very common / common: injection site reaction; pain, fever; Irritability; Decreased appetite; Drowsiness; rash. Uncommon / Rare: Diarrhoea; Fever > 39ºC (axillary). Others see full package insert.

Dose: PNEUMOSIL (10-valent) 0.5 mL I.M. is to be administered as a three-dose primary series at 6, 10, and 14 weeks of age or 2, 3 and 4 months of age or 2, 4 and 6 months of age, with or without, depending on recommended dosing schedule, a booster dose at 9-10 or 12-15 months of age. The minimum interval between doses should be 4 weeks. If a booster dose is given, it should be at least 6 months after the last primary dose.

Alternatively, Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-valent) is given as a two-dose primary series with booster dose. The first dose may be administered from the age of 6 weeks, with a second dose at age of 14 weeks. The third (booster) dose is recommended between 9-18 months of age.

For unvaccinated children 7-11 months of age, The vaccination schedule consists of two primary doses of 0.5 ml with an interval of at least 1 month between doses. A booster (third) dose is recommended in the second year of life with an interval of at least 2 months after the last primary dose.

For unvaccinated children 12-24 months of age, The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

Medicine Classification: Prescription Medicine