



Pneum^osil

Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed, 10-Valent)

Relevant Serotypes, Comprehensive Protection

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



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. 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. 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:

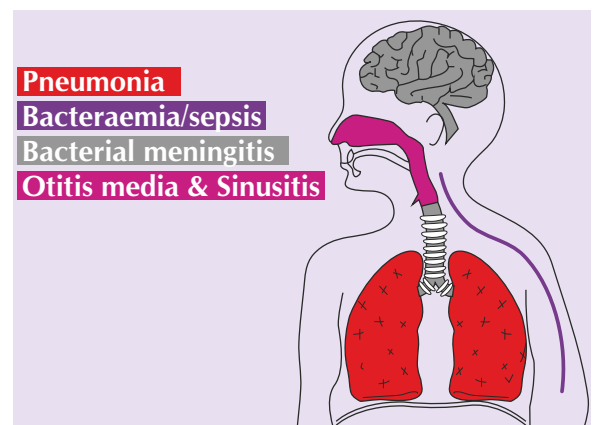
Pneumonia: inflammation of the lungs;

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.



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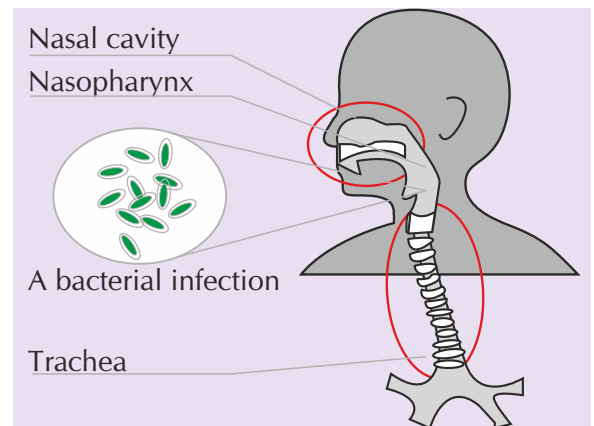
TRANSMISSION

Pneumococcal infection is transmitted by direct contact with respiratory secretions from patients and healthy carriers. Transient nasopharyngeal colonization – not disease – is the normal outcome of exposure to pneumococcus. Disease is caused either by contiguous spread to the sinuses or the middle ear, aspiration into the lower respiratory tract causing pneumonia, or by invasion of the bloodstream with or without spread to other sites. Most acute respiratory infections result in mild illnesses. In vulnerable children, infections that begin with mild symptoms may sometimes lead to more severe illnesses, such as pneumonia – especially when they coincide with other illnesses like diarrhoea or malaria. HIV infection and other conditions associated with immune deficiency greatly increase the likelihood of contracting pneumococcal disease.

PNEUMOCOCCAL PNEUMONIA

Pneumonia is a form of acute respiratory infection that causes inflammation or fluid in the lungs. It makes breathing difficult and limits oxygen intake. Symptoms include cough, chest in-drawing, difficult and rapid breathing, and wheezing. If infants are severely ill, they may also be unable to feed or drink and may experience unconsciousness, convulsions and even death.

The figure 1 depicts show pneumococcal disease spreads.



RISK FACTORS

The figure 2 depicts who is most at risk of pneumococcal disease. While most healthy individuals can fight the infection with their natural defences, the children most at risk of pneumococcal disease are:

- Children under 5 years of age and especially those under 2 years of age are the most at risk of developing and dying from the disease.
- Children who are immunocompromised (HIV infection, sickle cell disease, renal diseases, e.g., nephrotic syndrome) or have history of previous influenza or another respiratory virus infection.
- Infants and children who are exposed to additional risk factors: Malnutrition, lack of breastfeeding, exposure to indoor smoke and crowded living conditions.
- Elderly and immunocompromised people
- Poor and marginalized populations with poor access to health care



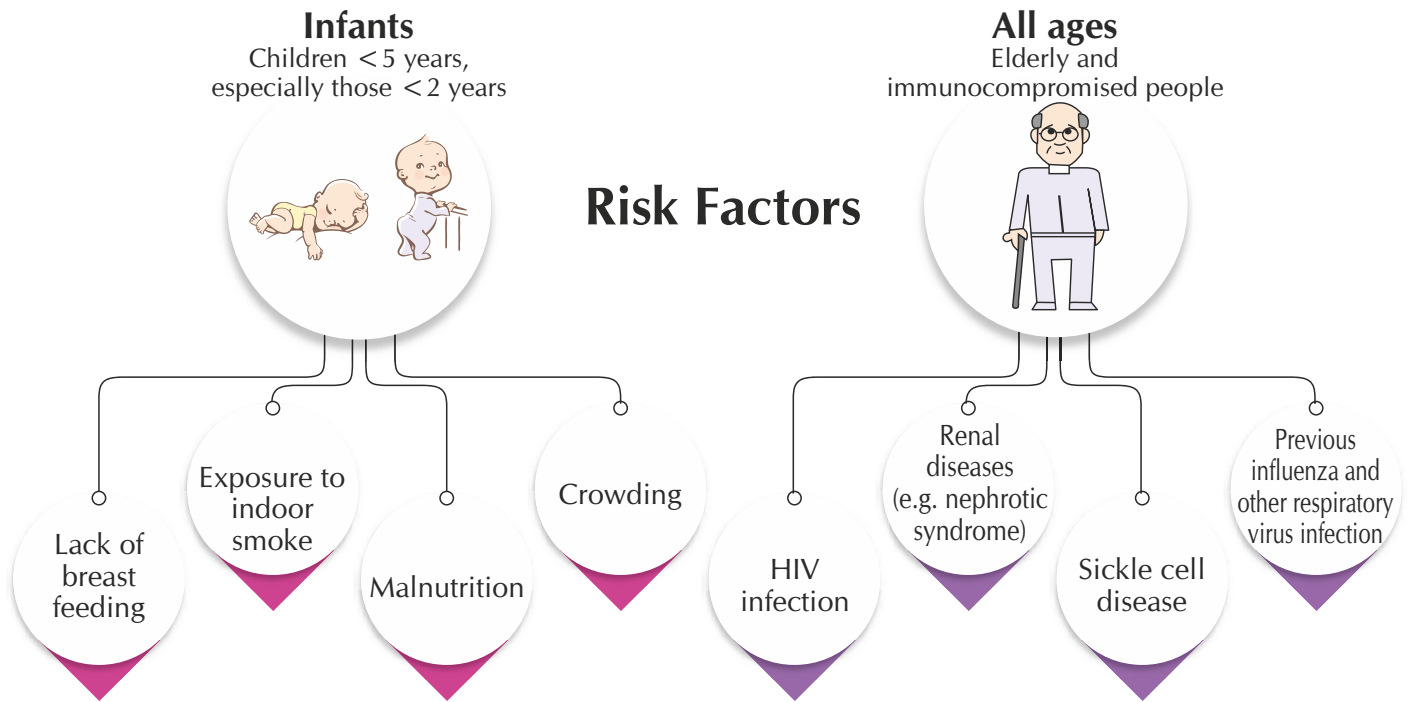
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Who is most at risk of pneumococcal diseases



SIGNS AND SYMPTOMS

Pneumococcal disease can occur in multiple organ systems, causing pneumonia, meningitis, bacteraemia/ sepsis, sinusitis, bronchitis and middle ear infection. Pneumococcal pneumonia in particular is a major public health concern for children globally.

The presenting features of viral and bacterial pneumonia are similar. However, the symptoms of viral pneumonia may be more numerous than the symptoms of bacterial pneumonia. In children under 5 years of age, who have cough and/or difficult breathing, with or without fever, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall in-drawing where the chest moves in or retracts during inhalation (in a healthy person, the chest expands during inhalation). Wheezing is more common in viral infections. Very severely ill infants may be unable to feed or drink and may also experience unconsciousness, hypothermia and convulsions.

Type of pneumococcal disease	Signs/Symptoms
All types of pneumococcal disease	fever, chills
Pneumonia	fever, chills, cough, difficult and rapid breathing, chest wall in drawing
Meningitis	fever, headaches, sensitivity to light, neck stiffness, convulsions and sometimes confusion or altered consciousness
Bacteraemia and sepsis	fever, chills, low alertness
Otitis and sinusitis	fever, pain and discharge from the ears (otitis), tenderness over sinuses and/or persistent discharge from the nose

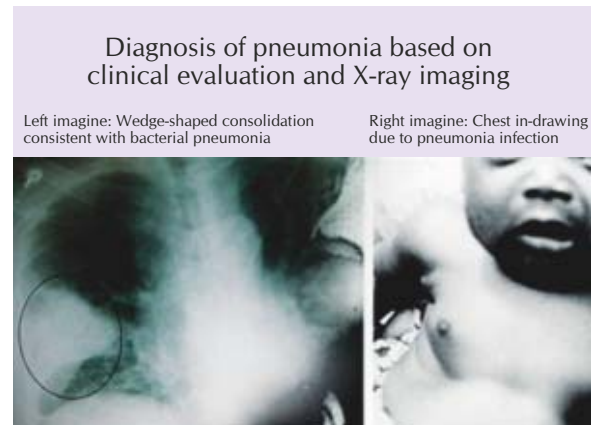


SEVERITY OF DISEASE

Pneumonia is a severe form of acute lower respiratory tract infection. The lungs are made up of small sacs called alveoli, which fill with air when a healthy person breathes. When an individual has pneumonia, the alveoli are filled with pus and fluid, which makes breathing difficult and limits oxygen intake. Severe pneumonia or sinusitis can progress to bacteraemia/sepsis or meningitis, which require antibiotic treatment and have high mortality rates.

DIAGNOSIS

Pneumonia is diagnosed based on clinical evaluation and X-ray imaging when available. The figure depicts clinical signs of pneumonia and X-ray imaging. It can be difficult to establish whether pneumococcal infection is the cause of the patient's symptoms because even in true pneumococcal cases, the specimens collected often do not yield the bacterium. This is particularly true of pneumococcal pneumonia because specimens from the actual site of infection (i.e., the lung) cannot be collected and in only a small fraction of pneumococcal pneumonia cases is the blood also infected.



When laboratory testing is possible, pneumococcal infections may be identified through testing of the blood (for bacteraemia and bacteraemic pneumonias) or in the case of suspected meningitis by performing a lumbar puncture, which involves inserting a needle into the epidural space to obtain a sample of cerebrospinal fluid (CSF).

Pneumococcus is a difficult bacterium to grow in the laboratory and frequently goes undiagnosed even when blood or CSF samples are truly infected with the pneumococcus. Testing to determine the pneumococcal serotype is used primarily for research purposes and is not available for patient diagnosis in most clinical settings.

PREVENTION

Preventing pneumococcal diseases, particularly pneumonia, in children is an essential component of a strategy to reduce child mortality. Immunization against Hib, pneumococcus, measles and whooping cough (pertussis) is the most effective way to prevent pneumonia.

Adequate nutrition is the key to improving children's natural defences, starting with exclusive breastfeeding for the first 6 months of life. In addition to being effective in preventing pneumonia, it also helps to reduce the length of the illness, if a child does become ill. Addressing environmental factors such as indoor air pollution (by providing affordable clean indoor stoves, for example) and encouraging good hygiene in crowded homes also reduces the number of children who fall ill with pneumonia.

The Global Action Plan for Prevention and Control of Pneumonia (GAPP, 2009) aims to accelerate pneumonia control with a combination of interventions to protect, prevent and treat pneumonia in children with actions to:



CHILDHOOD PNEUMONIA

Pneumonia disease is the biggest vaccine-preventable cause of death in children under five, globally. India accounts for one-fifth (20%) of the global pneumonia deaths in 2015. The figure 3 illustrates global causes of deaths among children under 5 years, 2018. Despite advances in fighting childhood illnesses, infectious diseases remain a leading cause of death for children under the age of 5, particularly in Sub-Saharan Africa and Southern Asia. Pneumonia (15%) [deaths among children aged 1-59 months 12% + neonatal deaths 3%], diarrhoea (8%) and malaria (5%) remain among the leading causes of death globally among children under age 5 – accounting for almost a third of global under five deaths.

Infectious diseases remain a leading cause of death among children under age 5

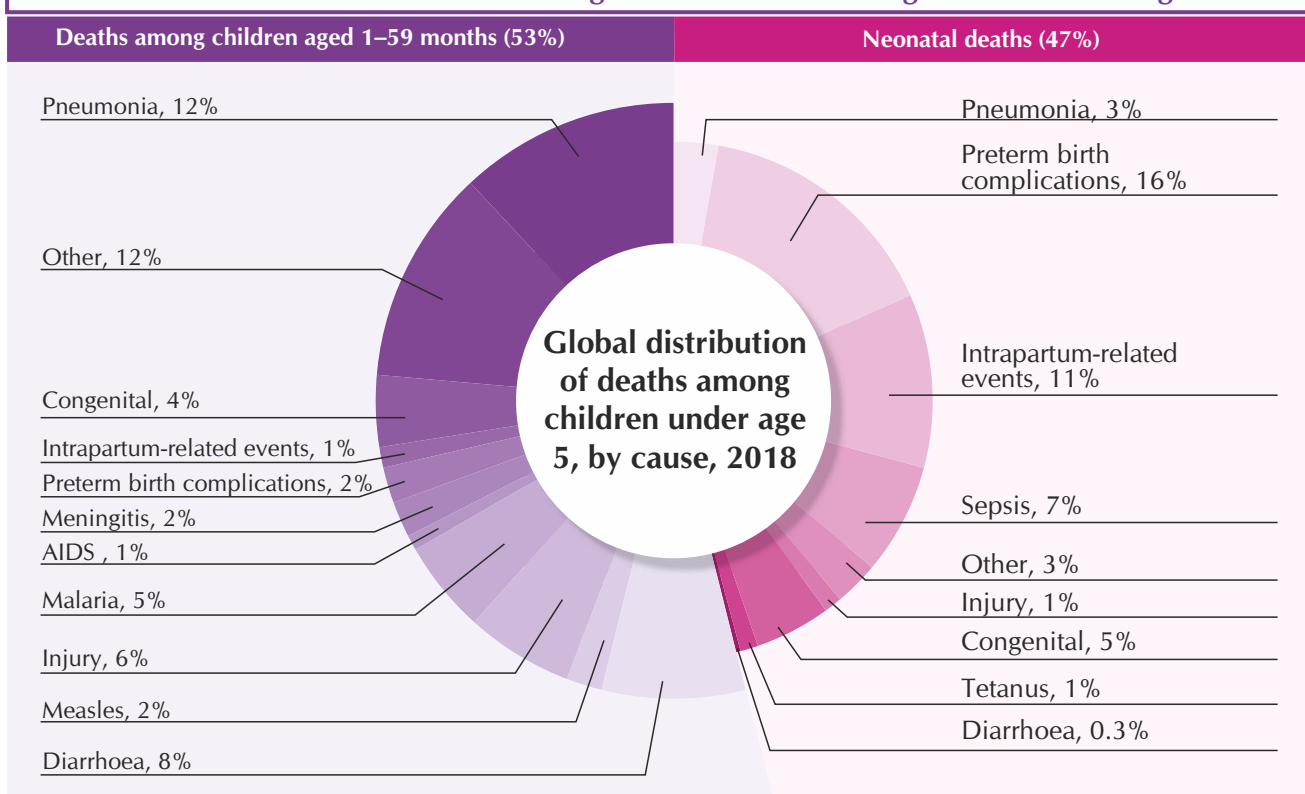
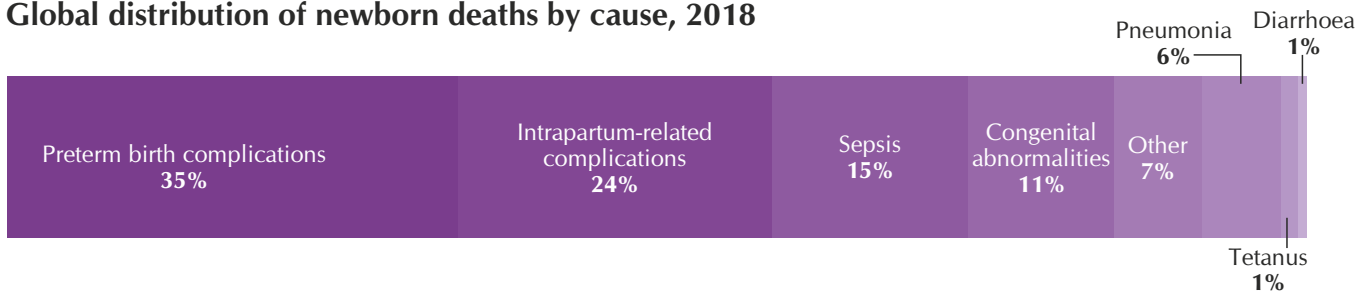


Fig 3, Reference: <http://www.indiaenvironmentportal.org.in/files/file/Child-Mortality-Report-2019.pdf>, Levels and Trends in Child Mortality Report 2019
Note: Estimates are rounded and therefore may not total 100 percent.

Global distribution of newborn deaths by cause, 2018





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Young children are at particularly high risk of developing severe pneumonia disease and death. More than 80% of deaths associated with pneumonia occurs in children during the first 2 years of life.

Pneumonia affects children and families everywhere, but most prevalent in the developing World in South Asia and sub-Saharan Africa. Children infected with pneumonia require early diagnosis and treatment. Many cases of pneumonia are vaccine-preventable.

Pneumonia is caused by a number of infectious agents, including viruses, bacteria and fungi.

The most common are:

- Streptococcus pneumoniae – the most common cause of bacterial pneumonia in children
- Hib – the second common cause of bacterial pneumonia.
- Pneumococcal disease is the name given to a group of disease caused by a bacterium called Streptococcus pneumoniae. Pneumococcal disease can occur in multiple organ systems, causing pneumonia, meningitis, bacteraemia / sepsis, sinusitis, bronchitis and middle ear infection.

GLOBAL SCENARIO OF PNEUMOCOCCAL DISEASE

Pneumococcal disease is the name given to a group of diseases caused by a bacterium called Streptococcus pneumoniae (also known as pneumococcus). Pneumococcal disease can occur in multiple organ systems, causing pneumonia, meningitis, bacteraemia/sepsis, sinusitis, bronchitis and middle ear infection. Figure 4 looks at how child pneumonia death rates are changing over time. The vertical axis charts the death rate and the size of the bubble indicates the number of deaths caused by pneumonia in 2018 for each country, while the horizontal axis measures the rate of decline. It shows that in too many countries with a high burden of child pneumonia deaths the rate of decline is too slow.¹

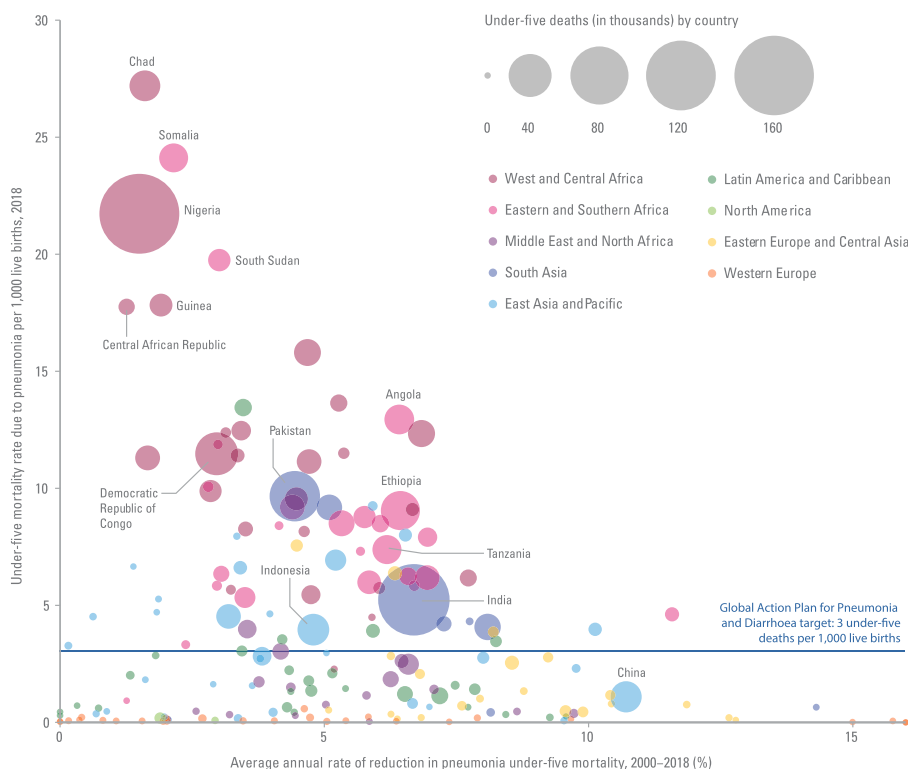


Fig. 4 Average annual rate of reduction in pneumonia under-five mortality, 2000 – 2018 (%)

(Source: UNICEF analysis based on WHO and Maternal and Child Epidemiology Estimation Group interim estimates produced in September 2019, applying

cause fractions for the year 2017 to United Nations Inter-Agency Group for Child Mortality Estimation estimates for the year 2018).



Pneumonia is a single largest infectious cause of death among children under five worldwide, accounted for nearly 8,02,000 deaths in under five children in 2018. Of those 1,53,000 (19%) died within their first month of life.¹

Pneumococcal mortality is a significant contributor to the under-five mortality rate worldwide. *Most children who died of pneumococcus (81%) and Hib (76%) presented with pneumonia. Less conservative assumptions result in pneumococcal death estimates that could be as high as 515 000 deaths in 2015. Approximately 50% of all pneumococcal deaths in 2015 occurred in four countries in Africa and Asia: India (68 700 deaths), Nigeria (49 000 deaths), the Democratic Republic of the Congo (14 500 deaths), and Pakistan (14 400 deaths). India (15 600 deaths), Nigeria (3600 deaths), China (3400 deaths), and South Sudan (1000 deaths) had the greatest number of Hib deaths in 2015. We estimated 3.7 million episodes of severe pneumococcus and 340 000 episodes of severe Hib globally in children in 2015.

The high concentration of pneumonia deaths among poor and marginalized populations is a key marker of inequality both across and within countries, and much more needs to be done to reach the most vulnerable children.

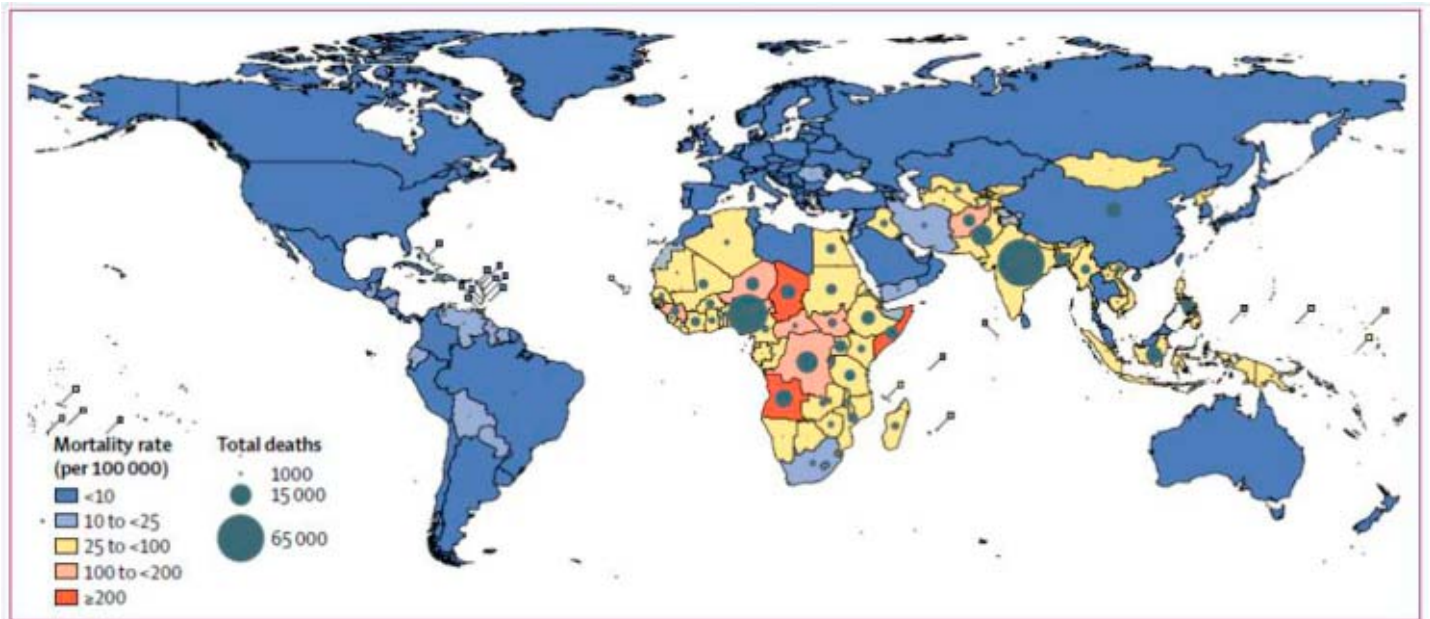


Fig. 5 Country-specific mortality rates and deaths attributable to pneumococcus in 2015

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*.

Nigeria had the largest number of child pneumonia deaths in 2018, followed by India, Pakistan, the Democratic Republic of Congo (DRC) and Ethiopia. Together, these five countries account for more than half of all deaths due to pneumonia among children under five years. (Fig. 5)

References:

1: Adopted from <https://data.unicef.org/resources/every-childs-right-to-survive-an-agenda-to-end-pneumonia-deaths/>

*: Adopted from [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(18\)30247-X/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30247-X/fulltext)



INDIA SCENARIO

Pneumococcal infection, a common cause of pneumonia, remains the leading cause of vaccine-preventable deaths and illness among children under 5 globally and in India.

In 2015; 68,700 pneumococcal deaths and 15,600 Hib deaths were estimated to have occurred in children aged 1–59 months in India. (Fig. 6)

Of the three syndromes associated with pneumococcal and Hib infection, pneumonia accounted for the greatest burden of pathogen-specific mortality in India and in every state between 2000 and 2015. Pneumonia accounted for 78% (53,300) of the all-syndrome pneumococcal deaths estimated in 2015, whereas meningitis accounted for 12% (8200) and NPNM accounted for 11% (7200).

Severe pneumococcal disease in India manifests primarily as severe pneumonia. There were 1.6 million estimated cases of severe pneumococcal pneumonia in 2015, accounting for more than 97% of all severe pneumococcal disease.²

Severe pneumonia frequently requires hospitalization for treatment, leading to emotional and financial burden for caregivers and stress on the public healthcare system. Risk of pneumonia is largely driven by factors associated with malnutrition, poverty, air pollution and other environmental factors. As mentioned above India contributes to a substantial portion of pneumococcal pneumonia across the globe. Within India, the states

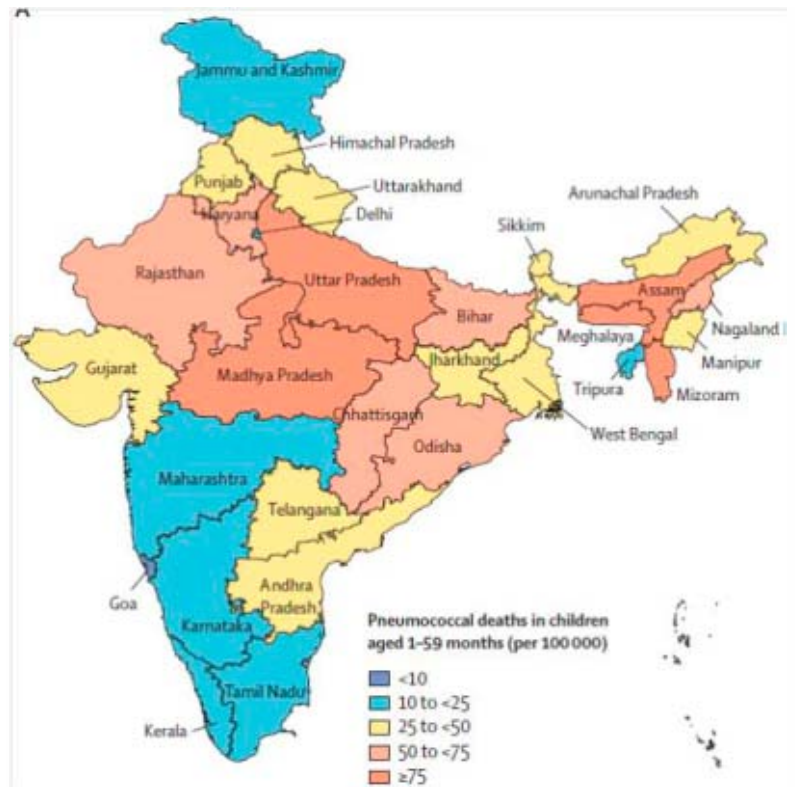


Fig. 6 Mortality rates for Streptococcus pneumoniae in 2015 by state

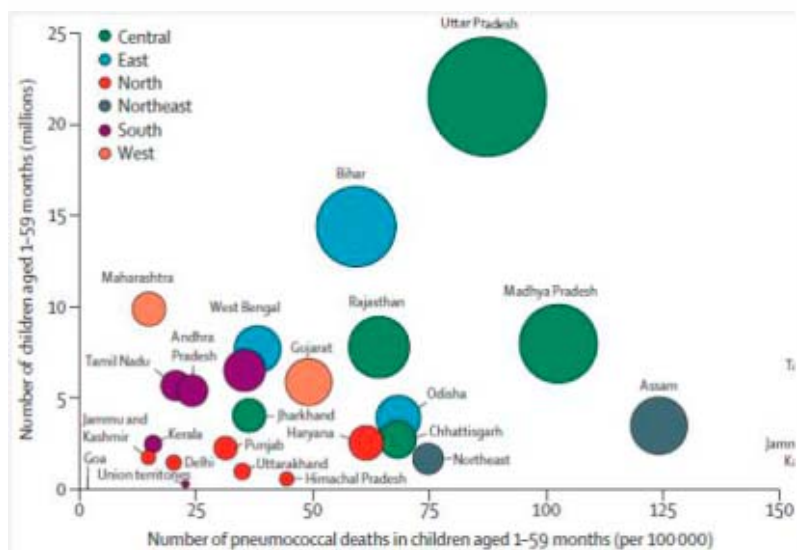


Fig. 7 Burden of Streptococcus pneumoniae deaths and mortality by state in 2015. Size of bubble indicates absolute number of pathogen-specific deaths. Y-axis shows number of children aged 1–59 months living in each state.

References:

2: Adopted from - www.thelancet.com/lancetgh Vol 7 June 2019 e735



with the greatest estimated pneumococcal pneumonia burden are Bihar, Madhya Pradesh, Rajasthan and Uttar Pradesh. These four states account for an estimated 59.24% of all pneumonia deaths. Above figure depicts the selected Indian States with the highest number of pneumococcal pneumonia deaths in children younger than 5 years in India, 2015. The bubble size indicates the number of pneumococcal pneumonia deaths. (Fig. 7)

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.

Description:

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

Composition:

Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-valent) 0.5 ml - 1 dose

Each dose of 0.5 ml contains: Saccharide for serotypes 1, 5, 9V, 14, 19A, 19F, 23F, 7F, 6A - 2 mcg each Saccharide for serotype 6B - 4 mcg

Conjugated to CRM197 carrier protein Aluminium (as Aluminium phosphate) 0.125 mg

Dose: 0.5 ml by intramuscular injection.

Serum Institute – A Leader in Conjugate Vaccines

Broad and diverse Conjugate vaccine portfolio which is well established:

- ◆ Hib Conjugate Vaccine (and also as combination product with DTP)
- ◆ MenAfriVac[®] (Men A-TT Conjugate Vaccine)
- ◆ PNEUMOSIL (Pneumococcal Conjugate Vaccine)
- ◆ Poly Meningococcal Conjugate Vaccine
- ◆ Maximum number of WHO pre-qualified Vaccines (# 25 Vaccines)
- ◆ Excellent supply track record with UNICEF and PAHO for many decades
- ◆ Network and Reach to 170+ countries
- ◆ Largest supplier of Hib and Meningococcal A Conjugate Vaccines to UNICEF at affordable prices
- ◆ Polysaccharides (Hib and Meningococcal A polysaccharides - as process intermediate) produced at SIPL are used by WHO Reference Laboratory i.e. National Institute of Biological Standards and Control (NIBSC) UK as Reference (Gold) Standards for testing and release of Vaccines from different manufacturers. This is a recognition of the Scientific expertise that exists at SIPL.



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Key Points

- ◆ Pneumosil is a well-designed vaccine with relevant serotypes yet more affordable than existing PCVs and provide comparable protection by targeting the most prevalent serotypes of the bacterium causing serious illness in developing countries.
- ◆ As a PCV, Pneumosil is the same kind of vaccine as the paediatric pneumococcal vaccine already on the market and targets serotypes 1,5,6A,6B,7F,9V,14,19A,19F and 23F.
- ◆ Pneumosil is a WHO prequalified for its procurement by United Nations Agencies and GAVI. This marks an important milestone towards accelerated access of this much needed affordable vaccine for the countries with high disease burden.
- ◆ Pneumosil developed through a collaboration spanning over a decade between Serum Institute of India Pvt Ltd and PATH and with funding from Bill and Melinda Gates foundation. Through the collaboration, the vaccine has advanced from preclinical and clinical development to WHO pre-qualification.
- ◆ Pneumosil safety and immunogenicity profile is favourable to both currently available licensed and WHO pre-qualified PCVs worldwide. Various seroprevalence assessment estimates Pneumosil serotype coverage similar to other PCVs in high disease burden countries including countries with high seroprevalence of 6A and 19A.
- ◆ WHO pre-qualification opens door for this vaccine being accessible that countries can afford and sustain their pneumococcal immunization programme.

**RELEVANT SEROTYPES,
COMPREHENSIVE PROTECTION**

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SERUM INSTITUTE OF INDIA

CYRUS POONAWALLA GROUP

212/2 Hadapsar, Pune 411 028, India. Tel.: +91 20 26993900/04 Fax: +91 20 26993924.
website: www.seruminstitute.com E-mail: exports@seruminstitute.com