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REVIEW

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Clinical and evidence-based considerations for choosing a pneumococcal conjugate vaccine in India: A narrative review

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ABSTRACT

Immunization plays a crucial role in protecting children from life-threatening conditions such as pneumococcal disease. Pneumococcal disease can affect multiple organ systems and manifest as an invasive or noninvasive disease. Despite being preventable by vaccines, it remains a public health concern in India. The development of pneumococcal conjugate vaccines (PCVs) has helped reduce the burden of pneumococcal disease by overcoming the limitations of polysaccharide vaccines, especially in young children. Although immunogenicity is used as a proxy for the evaluation and approval of PCVs, results from immunogenicity studies have been bridged back to vaccine trial efficacy. Post-approval effectiveness and impact of new PCVs must be established. This review aims to consolidate evidence-based considerations that play a role in the evaluation of PCVs. Critical aspects related to the assessment of vaccines, their importance, and limitations in real-world contexts are discussed in this review.

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Introduction

Pneumococcal disease is a group of diseases caused by *Streptococcus pneumoniae* that can affect multiple organ systems.[1] Pneumococcal disease can be invasive when *S. pneumoniae* enters sterile sites (e.g., blood or cerebrospinal fluid), resulting in bacteremia, pneumonia, septicemia, meningitis, empyema, and osteomyelitis. Noninvasive pneumococcal disease (non-IPD) occurs when bacteria invade nonsterile parts of the body and cause noninvasive pneumonia, sinusitis, bronchitis, and otitis media. The causative bacteria can also be carried asymptomatically by about 50% of the population.[2] The risk of mortality is higher with invasive disease, and survivors may experience sequelae.[3] India accounts for 20% of worldwide deaths due to pneumonia.[4] A 2010 estimate indicated that 560,000 episodes of severe pneumococcal pneumonia and 105,000 deaths occur in Indian children <5 years of age.[5]

Immunization is considered one of the most cost-effective public health interventions for protecting children from life-threatening conditions, particularly for those under 5 years of age.[4] Although preventable by vaccines, pneumococcal disease remains a public health concern in India, with an estimated 1.6 million severe pneumococcal pneumonia cases and 68,700 deaths (in patients <5 years of age) occurring in a year (estimates from 2015).[6] Infants and young children (<5 years of age) in India are vulnerable to pneumococcal disease, with an estimated national mortality rate of 56 per 100,000 due to pneumococcal infection.[6] Social factors such as bed-sharing, nutrition, living in overcrowded homes, households with individuals at risk, attendance in daycare centers, etc., can play a considerable role in exposing children to the risk of pneumococcal disease.[7] Regional variations in serotype prevalence and conditions that compromise the immune system (e.g., low birth weight and pre-term birth) also play a critical role and need to be taken into consideration.[8,9] Comorbid viral infection can enhance the tissue-invasive capabilities of pneumococcal infections.[10] Those infected with the hepatitis C virus have been reported to be vulnerable to pneumococcal disease.[11] Vaccination against pneumococcal disease can be especially important among such individuals at risk. The currently available pneumococcal conjugate vaccines (PCVs) in India are PCV-10 (GlaxoSmithKline), PCV-10 (Serum Institute of India), PCV-13 (Pfizer), and PCV-14 (BE). The introduction of PCVs into the national immunization program reflects an important step in combating the disease. This review aims to consolidate and present critical aspects associated with the assessment of PCVs, offering insights and an in-depth understanding of outcomes from a private healthcare practice perspective.

Materials and methods

An extensive search on pneumococcal disease and pneumococcal conjugate vaccines in India was carried out using databases such as Embase, PubMed, and Google Scholar.

Results

The search results were collated and have been presented in this narrative review.

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Discussion

Important factors to be considered while choosing a PCV

Although pneumococcal disease is endemic in many areas around the world, the serotype distributions of *S. pneumoniae* are dynamic and vary over time. In addition, population age, clinical manifestations, and geographic location also affect the severity of the disease.[12,13] More than 100 *S. pneumoniae* serotypes have been identified based on the composition of the polysaccharide capsules of *S. pneumoniae*, with a subset of serotypes capable of causing severe disease.[8,14] The emergence of antibiotic resistance in *S. pneumoniae* is also a cause for concern as it can make the treatment of pneumococcal pneumonia challenging.[15] Therefore, vaccination can be crucial in preventing *S. pneumoniae* strains with antimicrobial resistance (AMR) from becoming prevalent.

In addition to the serotype prevalence of the *S. pneumoniae* strains causing IPD and non-IPD, data from carriage studies can also be important. Asymptomatic carriage of bacteria, including *S. pneumoniae*, in the human nasopharynx is a common and natural phenomenon.[16] Vaccines reduce the carriage of vaccine-type strains.[17] Nasopharyngeal colonization is commonly observed to precede disease.[18] Several studies from India have reported high levels of colonization with *S. pneumoniae* in the pediatric population.[19–21] Nasopharyngeal colonization not only plays a role in the development of infections and invasive diseases but also serves as a source of transmission to other individuals.[15]

In summary, the selection of an appropriate PCV requires careful consideration of the dynamics of *Streptococcus pneumoniae*, including local serotype distribution and nasopharyngeal carriage, as well as disease characteristics such as invasiveness, mortality, and antimicrobial resistance associated with the serotypes.

Factors while choosing a PCV

- Serotype distribution
- Immunogenicity
  - Seroresponse rates
  - IgG GMC
  - OPA GMT
  - Booster response; GMFR
- Vaccine efficacy, effectiveness, and impact
- Cross-protection vs. direct protection
- Herd protection
- Antimicrobial resistance

Pneumococcal serotype distribution

Although pneumococcal disease is caused by different serotypes, only a small subset of the pathogenic serotypes primarily contribute to the disease burden.[22,23] In addition, the pneumococcal serotype distribution varies over time depending on the age of the population, clinical manifestation, and geography.[8] The seven serotypes included in the first PCV (PCV-7) were selected based on the most commonly isolated strains of *S. pneumoniae* with the potential to cause an invasive form of the disease.[24] Prior to the introduction of PCV7, those seven serotypes accounted for 80% of the infections among children <5 years of age and about 50% among older children and adults in the US.[24] In a surveillance study from India (prior to the introduction of PCV), the most common serotypes that accounted for approximately 74% of all IPD cases included serotypes 14, 1, 5, 19F, 6B, 19A, 23F, 6A, 9 V, 10F, and 35F.[25,26] Serotypes 1, 5, 14, and 19F were predominant in children >2 years of age and serotypes 14, 1, 19F, 5, 6B, 19A, 23F, and 9 V were prevalent among children <2 years of age.[25] Serotype 1 is known to be the most common serotype causing IPD in India.[27] Singh et al. report that serotypes 14, 1, 19F, 6B, 5, 6A, 9 V, and 23F were the most frequent serotypes causing IPD in children under 5 years.[26] Serotype 4, which is associated with invasive potential, was reported to be among the top five serotypes found in carriage isolates (in the age group of 6–24 years) and in a few disease isolates.[28] The common circulating serotypes identified in studies from Indian settings are listed in Table 1.[25–26,28–33]

A study analyzing pneumococcal disease and carriage epidemiology across India reported the presence of serotype 6A in disease-causing isolates among children and seniors.[28] Although initially typed as serotype 6A by the quelling reaction, serotype 6C was identified as a distinct subtype within the previously established serogroup. Serotype 6C was identified as a distinct serotype from 6A in 2007. Classical serotyping methods did not distinguish between 6A and 6C, but retrospective work showed that serotype 6C has been circulating for many years. Serotype 6C is both genetically and biochemically different from serotypes 6A and 6B. Studies have identified the

Table 1. The top five *Streptococcus pneumoniae* serotypes identified in different studies from India.

Study	Location	Most common serotypes
Manoharan A et al. 2016[25]	Representing 11 states in India	14, 1, 5, 19F, 6B
Jaiswal N et al. 2014[29]	SAARC countries (only the results from India are included)	14, 5, 1, 19F, 6B
Balaji V et al. 2015[30]	Multispecialty tertiary care hospital	14, 19F, 5, 6A, 6B
Nagaraj G et al. 2021[28]	14 regions across India	Disease isolates: ≤2 years: 19F, 1, 14, 6A, 6B 3–5 years: 19F, 19A, 5, 1, 9 V Carriage isolates: ≤2 years: 6A, 23F 3–5 years: 18C, 19A, 23F, 6B, 6A
Singh J et al. 2017[26]	Systematic literature review of hospital-based observation studies from India	14, 1, 19F, 6B, 5
Nisarga R et al. 2015[31]	South Bangalore, India	6A, 14, 5, 6B, 1
Vandana G et al. 2016[32]	Pan India	1, 6B, 14, 19F, 23F
Jayaraman Y et al. 2018[33]	India (children with suspected bacterial meningitis)	6B, 14, 6A, 19F, 4

SAARC: South Asian Association for Regional Cooperation.

presence of serotype 6C in India as well, most recently from a study assessing the circulating serotypes of bacterial pneumococcal disease in Assam, India.[34] The serotype epidemiology is dynamic and may vary with geography. Countries with PCV-10 (GlaxoSmithKline) as a part of their immunization program have a higher proportion of PCV13–preventable disease burden, especially those associated with serotype 19A.[23,35] This serotype, known to affect all age groups, is not only prevalent worldwide but can also be multidrug resistant.[36–38] In Belgium, a switch from PCV-13 to PCV-10 resulted in a significant increase in serotype 19A infections.[39–41]

In summary, pneumococcal serotype distribution varies by factors such as age and geography, with only a few serotypes contributing the most to the disease burden. It is important to consider the prevalence and relevance of the serotypes included in the vaccine rather than just the number of serotypes. It is also important to have continued monitoring and consider the impact of vaccination on serotype distribution.

Vaccine-related factors for consideration

Due to ethical considerations and the lack of feasibility in conducting randomized controlled trials to determine the efficacy of newer higher valent PCVs, immunogenicity is used as a proxy for the evaluation and approval of such PCVs. The approval criteria require an immune response that is non-inferior (at least equivalent) to that of existing PCVs. The assessments for gauging immune responses to vaccines are shown in Figure 1.

Post-primary series assessment

The outcome variables used include the seroresponse rates and the serotype-specific immunoglobulin G (IgG) geometric mean concentration (GMC) ratios.[42]

Seroresponse rate. While seroconversion indicates the development of antibodies after vaccination in a person who did not have antibodies prior to exposure, the seroresponse rate is the proportion of subjects with IgG concentrations greater than or equal to the reference concentration (≥0.35 µg/mL) for the assessment against IPD (Figure 2). The antibody concentrations for preventing mucosal disease and carriage are considerably higher than those for IPD, regardless of serotype or population.[43] The standard practice is to use the aggregate protective concentration of antibodies against the PCV-7 serotypes (0.35 µg/mL) to compare the effectiveness of both the serotypes covered by PCV-7 and the additional serotypes not covered by PCV-7, whose efficacies have not been tested in trials.[44] However, such aggregate values may not precisely predict the effectiveness of a vaccine against individual serotypes.[45] Any alternative threshold value that is proposed should be shown to correspond to 0.35 µg/mL in a well-conducted bridging assay against the World Health Organization (WHO) reference ELISA.[42]

IgG GMCs. The IgG GMCs are calculated by taking the geometric mean of the concentrations of antibodies; these values represent the average values of antibodies in the study population (Figure 3). A higher IgG GMC generally indicates a more robust immune response to the vaccine.

Post-booster assessments

In addition to the seroresponse rate and IgG GMCs, the booster response rates and geometric mean fold rise (GMFR) are calculated for post-booster assessment. GMFR indicates the fold increase in antibody concentrations after the booster dose, offering insight into the memory response of the immune system.

Functional antibody response

The functional antibody responses indicate the ability of the body to mediate bacterial clearance and are assessed based on opsonophagocytic assay (OPA) data. These include the OPA seroresponse rates (defined as the percentage of participants with a reciprocal OPA titer of ≥8) and the OPA geometric mean titers (GMTs). The OPA assay, which is based on phagocytosis triggered by opsonins, is a qualitative test carried out on a randomized

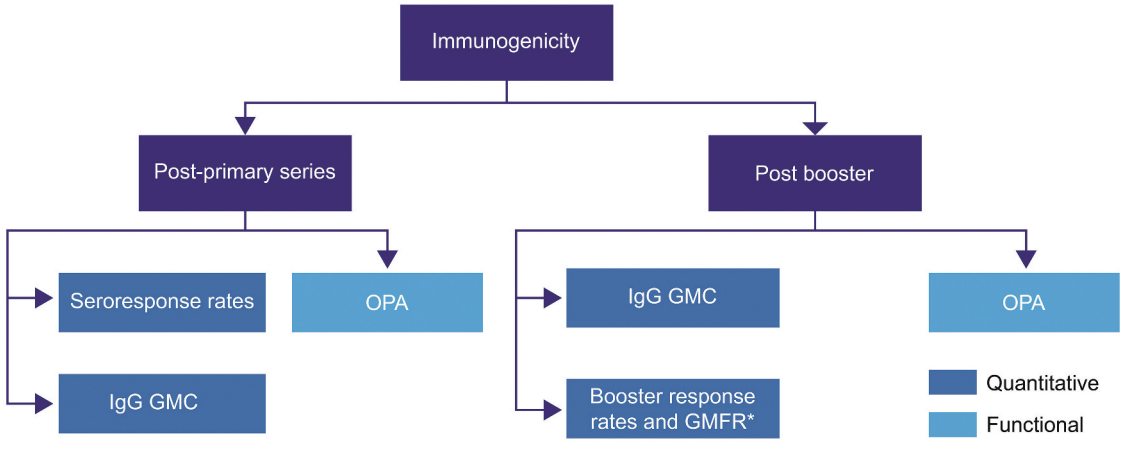

Figure 1. The primary and secondary analysis recommended by the World Health Organization for the comparison of immune responses between vaccines. GMC: Geometric mean concentration; GMT: Geometric mean titer; IgG: Immunoglobulin G; GMFR: Geometric mean fold rise; OPA: Opsonophagocytic assay. *Booster response rates and GMFR are also indirect markers for memory function

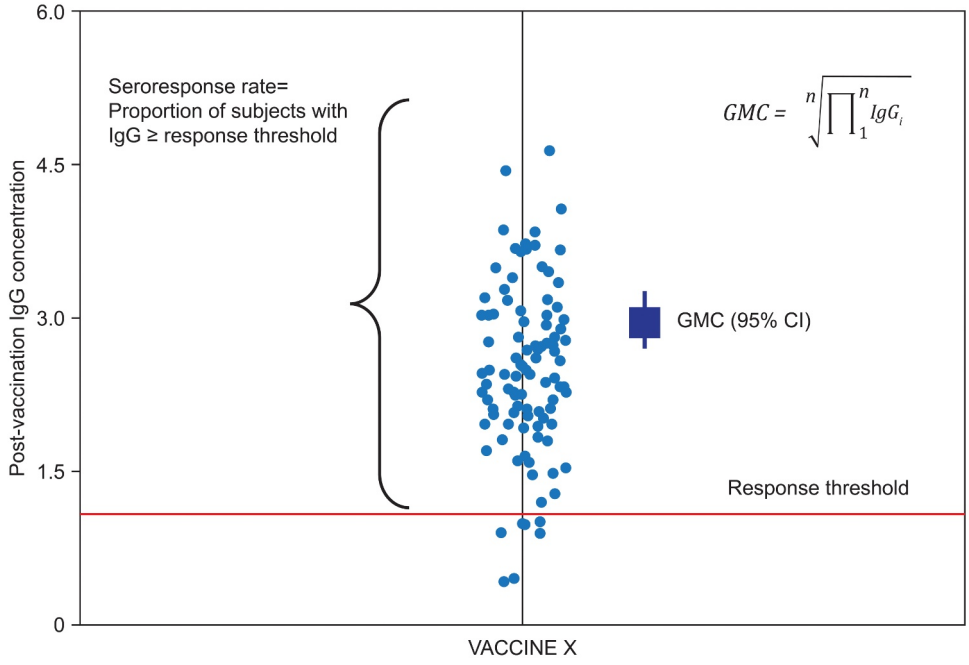

Figure 2. A representation of the calculations for seroresponse rate and geometric mean concentration (GMC) for a hypothetical vaccine X. CI: Confidence interval; IgG: Immunoglobulin; i: Individual subject; n: Total number of subjects.

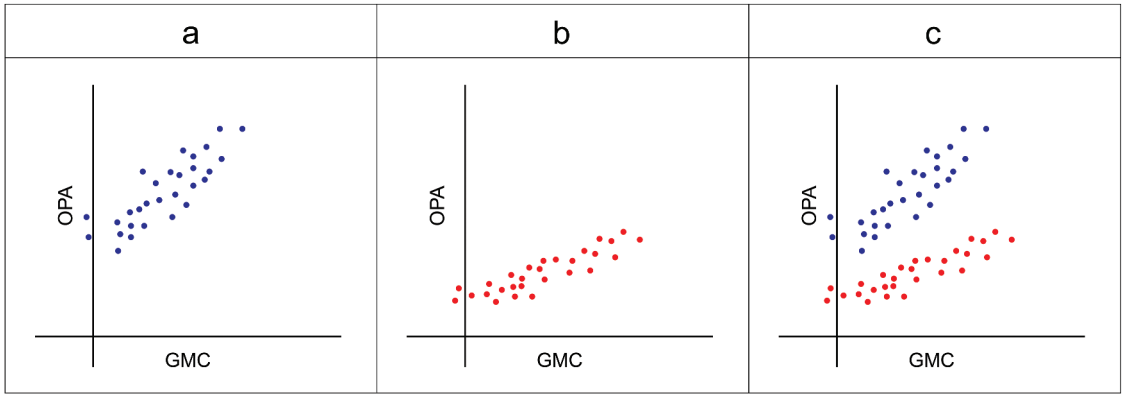

Figure 3. A representation of the concordance analysis between antipolysaccharide binding IgG and functional OPA response for a serotype. Blue scatter plot represents higher potency compared to red scatter plot.

subset of vaccinated subjects. An OPA titer of ≥ 1:8 is used as an indication of functional antibody response. However, the OPA titer of ≥1:8 is linked to the lower limit of quantification (LLOQ) of the assay and is not universally applicable to all serotypes or all assay platforms. Using this as a threshold, the OPA seroresponder rates are calculated. The OPA GMTs that are common to the new vaccine are also compared. Like GMCs, a titer that correlates with protection for specific serotypes is unknown; therefore, comparisons of OPA titers are recommended. Earlier studies have demonstrated the use of concordance between functional antibody response (OPA GMTs) and antipolysaccharide response.[46] Sample results from such concordance analyses are shown in Figure 2.

Limitations of immunogenicity criteria for evaluation of PCVs

Although the assessments described above are used to determine if a newer vaccine fulfills the noninferiority criteria, there is room for misinterpretation of the results of these analyses, especially if the PCVs differ in their immunogenicities.[44]

The correlation of protection can vary with serotype and population, which needs to be taken into consideration when determining effectiveness based on differences in immunogenicity.[45,47] In addition, the reference concentration (≥0.35 µg/mL) is not consistent for all serotypes. In randomized controlled clinical trials, a non-inferiority criterion is pre-defined when comparing the immunogenicity of 2 PCVs. These criteria can differ between trials and settings; hence, immune titers from one study cannot be directly compared to immune titers from another study.[48,49]

Moreover, the reference concentration of IgG recommended by the WHO is for IPD.[42] The antibody levels for protection against mucosal infections (nonbacteremic pneumonia, otitis media, and sinusitis), however, are several-fold higher than those required for protection against IPD.[50,51] Although the need for a framework that contextualizes differences in PCVs and expresses the differences in terms of vaccine effectiveness has been proposed, such a system is not yet available.[44] It remains crucial to generate real-world evidence to understand the broader impact of PCVs.

Immunogenicity is vital for assessing and approving new PCVs. Primary analysis offers an initial immune response overview and secondary analysis provides a deeper insight into the vaccine's protective capabilities. However, the reference threshold used is for IPD and is not serotype-specific. Despite the differences in serotype and population, the antibody concentrations for preventing mucosal disease and carriage are significantly higher than those for IPD. The use of immunogenicity as a measure of vaccine efficacy is limited by variabilities in immune responses, incomplete understanding of immune correlates, lack of correlation with clinical protection, and failure to capture real-world effectiveness.

Vaccine efficacy, effectiveness, and impact

Vaccine efficacy is a measure of vaccine performance under controlled experimental conditions, such as a randomized clinical trial (Figure 4). However, practical and ethical considerations may pose limitations to the measurement of vaccine efficacy. For example, when a population already uses PCVs, the small number of disease events may limit meaningful comparisons between vaccines.[44] Additionally, there are ethical considerations associated with placebo-controlled trials when an effective vaccine is available.[52] The ethical considerations, challenges, and impact of vaccine clinical trials in resource-limited settings have been reviewed by Kochhar *et al.* (2013).[53]

Vaccine effectiveness measures the performance of the vaccine outside of controlled clinical trials and assesses the reduction in the risk of disease in vaccinated populations.[52,53] Although some studies have observed that GSK PCV-10 and PCV-13 have comparable immunogenicities, it is possible that factors such as the vaccines' effectiveness against specific serotypes, local serotype distribution, and local population characteristics may affect their performance in specific areas.[54] The levels of antibodies required to achieve effectiveness in real-world settings may vary according to the density of nasopharyngeal colonization of pneumococci.[51] This colonization has been reported to be more common and denser in low- and middle-income countries (LMICs), especially in young children.[51]

A critical endpoint used to assess the effectiveness of PCVs is IPD, which typically involves infections in the bloodstream, meninges, or other normally sterile sites in the body. The effectiveness of pneumococcal vaccines in reducing the incidence of IPD has been demonstrated in several studies.[55] In addition to IPD, pneumonia, and otitis media have also been used as endpoints to assess vaccine effectiveness. However, challenges in obtaining accurate microbiological confirmation of the infectious causes can limit the accuracy of diagnosis.[56] For example, tympanocentesis is the gold standard for acquiring middle ear fluid, but very few studies have reported such data.[51,57] Additionally, otitis media, in particular, can be caused by pathogens other than *S. pneumoniae*, such as *Haemophilus influenzae* and *Moraxella catarrhalis*. Consequently, assessing vaccine effectiveness against otitis media based solely on clinical diagnosis may not provide an accurate assessment of vaccine effectiveness unless the endpoint specifically targets the prevention of all-cause acute otitis media. Therefore, the challenge in evaluating vaccine

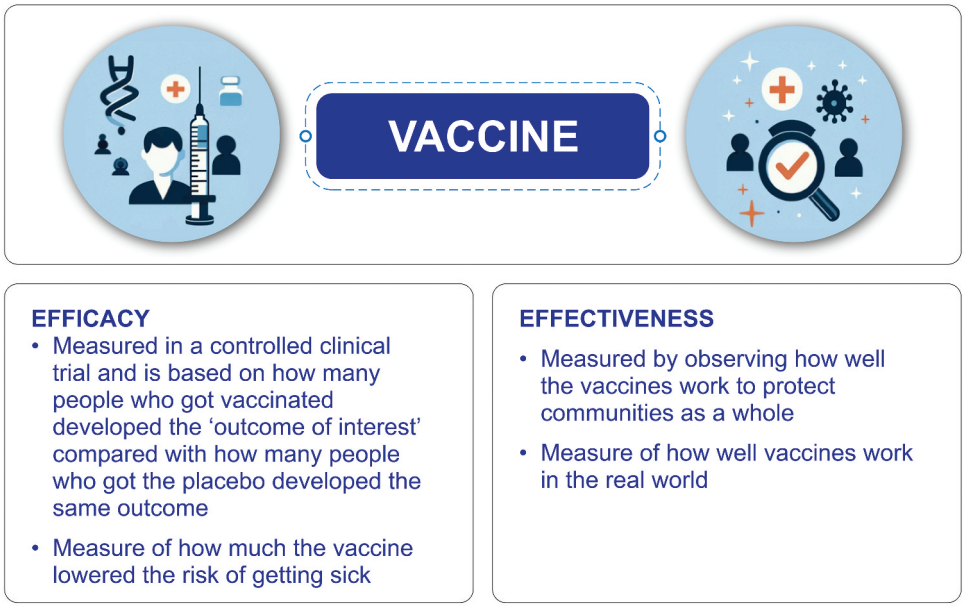

Figure 4. Vaccine efficacy and effectiveness.

effectiveness extends beyond reliance on clinical diagnosis alone to the inherent complexity of distinguishing the specific causative pathogen, further complicating the assessment.[51]

Vaccine impact is a broader measure than efficacy and effectiveness and involves the assessment of the overall reduction in the burden of disease in a population as a result of vaccination. As IPD cases may be underreported or subject to surveillance bias, particularly in resource-limited settings or areas with inadequate surveillance systems, the actual burden of IPD can be underestimated and affect the accuracy of impact estimates.[58] LMICs often face challenges in assessing the impacts of vaccines due to limited resources and weak surveillance systems.[58] However, the use of nasopharyngeal carriage data has been proposed as a proxy measure for monitoring the impact of PCVs, as these data are less expensive and technically easier to gather than population-based IPD data.[18,58,59]

Pneumococcal vaccines have been effective in reducing the burden of pneumococcal disease in many regions of the world.[60] However, multiple factors influence vaccine efficacy, effectiveness, and overall public health outcomes. Age plays a critical role, as immune responses may differ in infants, young children, adults, and the elderly.[17] Vaccine coverage rates determine the extent of direct and herd protection, with suboptimal coverage limiting the full potential of vaccination programs.[17] Underlying health conditions, such as immunosuppression, malnutrition, and chronic illnesses, can impact individual immune responses to vaccination.[61] Additionally, local epidemiology, including regional serotype distribution and antibiotic resistance patterns, affects vaccine protection against circulating strains.[8] Sociodemographic, environmental, and genetic factors may also play a role in limiting the impact of pneumococcal vaccines in LMICs.[62,63] Addressing these factors is essential for optimizing vaccine strategies and ensuring maximal protection in diverse populations, particularly in LMICs.

In summary, it is essential to consider all three assessments, encompassing efficacy, effectiveness, and impact, to derive a comprehensive comparison of vaccine potential and their implications. While immunogenicity is a critical aspect of vaccine development, assessing effectiveness and impact provides a more complete picture of how well a vaccine works in diverse populations and under real-world conditions.

Cross protection

In addition to the vaccine-covered serotypes, there is some evidence of cross-reactivity to related serotypes that are not directly covered.[64] The cross-protective response of a pneumococcal vaccine refers to the ability of a vaccine to provide protection against pneumococcal serotypes that are not included in the vaccine formulation. For example, although PCV-7 contained a serotype 6B conjugate (but no serotype 6A conjugate), it displayed a strong opsonophagocytic assay (OPA) response to serotype 6B and a partial OPA response to 6A.[65] However, cross-protection requires high levels of antibodies against the parent antigens.[43] Such a requirement, in combination with the need for higher levels of antibodies for carriage protection compared to that required for protection against IPD, may result in insufficient protection.[43] The cross-protection against IPD elicited by cross-reacting serotypes may not be sufficient against mucosal disease and carriage.[43] Lack of serotype 6A in PCV formulations (PCV-7 and PCV-10 [GSK]) led to ambiguous results because 6A carriage was often but not universally reduced.[43] Having serotype 6B coverage has been shown to elicit reductions in serotype 6A, but not serotype 6C. Serotype 6C, though biochemically and genetically different from 6A and 6B, has serologic similarities to serotype 6A. Hence, it can be cross-protected by serotype 6A but not serotype 6B. This is supported by evidence from Belgium, where the transition to a PCV program not covering serotype 6A was associated with an increase in serotype 6C.[66]

Therefore, while some vaccines exhibit cross-reactivity against non-included serotypes, as seen in immunogenicity studies, such cross-protection may not always be sufficient for the reduction of carriage and disease. This underscores the significance of vaccine composition and real-world evidence to accept or refute the extent of cross-protection offered by PCVs. In light of this, ongoing surveillance is essential, especially with newer vaccines. Comprehensive data from the use of the PCV-13 and the earlier PCV-10 (GSK) vaccines have significantly enhanced our understanding of their impact, guiding more informed decisions.

Importance of booster doses

The available PCVs have shown serotype-specific antibody responses and are known to reduce vaccine-serotype carriage and transmission.[43] Studies have reported that the prevention of nasopharyngeal carriage requires higher levels of antibodies than those for protection against IPD.[67–70] The IgG levels after vaccination may decline over time, due to which susceptibility to carriage and disease can increase.[71–73] Polysaccharide vaccines only elicit B-cell response, resulting in a lack of long-term memory.[74] However, conjugate vaccines induce a T-cell-dependent response, leading to higher antibody and immune memory responses after subsequent exposures.[74] Waning serum IgG levels have been shown by comparing IgG levels after the primary series with the prebooster IgG levels (Figure 5).[46,73] A considerable increase in antibody levels after the toddler dose can be observed. Booster doses result in elevated antibody levels that might confer a longer duration of protection compared to that seen with a schedule in which booster doses are not administered.[75] These heightened antibody levels could be instrumental in preventing the carriage of vaccine-serotype pneumococci (e.g., among 1-year – old babies who are often known to spread infection in many communities). Population-based impact assessments of PCV13 indicate that booster dose regimens, such as the 2 + 1 and 3 + 1 schedules, may offer enhanced herd immunity benefits.[76] This is likely attributable to the sustained immune response beyond the age of 2 years, which coincides with the peak colonization levels for PCV13 serotypes. It has been reported that the 2 + 1 schedule may have advantages over the 3 + 0 schedule due to higher antibody titers induced in the second year of life.[77] The 2 + 1 schedule, due to its booster dose given at an older age, may offer more prolonged protection and have more significant indirect effects than the 3 + 0 schedule.[78] Such protection is particularly significant for serotype 1, the predominant serotype responsible for IPD in India.[27,79] The results of a study from Malawi showed that a 3 + 0 schedule failed to elicit sustained population-level

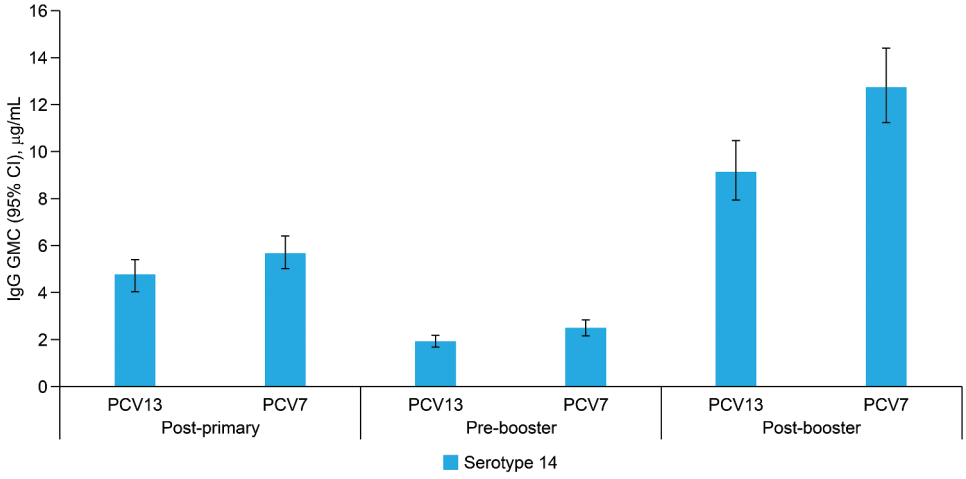

Figure 5. IgG GMCs associated with serotype 14 (common to PCV-7 and PCV-13) assessed after the primary series, before the toddler dose, and after the toddler dose. Source: figure created using data from Yeh et al. CI: Confidence interval; GMC: Geometric mean concentration; IgG: Immunoglobulin G; PCV: Pneumococcal conjugate vaccine.

antibody levels beyond the first year.[80] A study in Australian children showed that when given at a schedule of three doses at 2, 4, and 6 months of age with no booster dose, the ability of PCV to prevent IPD appeared to wane over time.[75] The chances of contracting vaccine-type IPD are five times higher in children vaccinated two years previously than in those vaccinated within the past 12 months.[75] Such results highlight the need for administering a booster dose within 11 months of the last vaccination to sustain vaccine-induced antibody titers.[73] Although more data are needed to enhance our understanding of outcomes associated with different vaccination schedules, the evidence seems to support that including a booster dose for children is beneficial.[81]

It is recommended that immune response comparisons be carried out approximately 4 weeks after the booster dose.[42] The induction of immune memory during infancy should be associated with higher post-booster antibody concentrations.[42] Owing to the high booster responses, comparisons based on the proportions of subjects reaching predefined thresholds (e.g. IgG concentrations ≥0.35 µg/mL or OPA titers ≥ 1:8) may not adequately detect differences between different vaccines.[42] The WHO recommends comparisons based on the ratios of post-booster values to post-primary values for IgG GMCs or OPA GMTs. Assessing the divergence in curves from reverse cumulative distribution plots can also be of assistance.[42]

In summary, the vaccine efficacy can wane over time, making booster doses crucial for maintaining and enhancing protection. These doses elevate antibody levels, ensuring a long duration of protection and helping to prevent carriage and spread, particularly among high-risk groups.

Herd protection

The PCVs not only benefit those vaccinated but also provide indirect protection to unvaccinated populations, such as older adults and those at high risk of pneumococcal disease.[82] Evidence suggests that nasopharyngeal carriage is a precursor of pneumococcal disease and the source of transmission between individuals.[83] It is hypothesized that the protection provided by the herd effect is a result of the reduction in the nasopharyngeal carriage of vaccine-type strains in immunized children. This effect leads to the restriction of subsequent transmission to their nonimmunized contacts.[84] In the United States, the 13-valent pneumococcal vaccine (PCV13) was launched for children in 2010 and was subsequently introduced for immunocompromised adults aged 19 years or more in 2012, in conjunction with the 23-valent polysaccharide vaccine (PPSV23). A study utilizing the Active Bacterial Core surveillance system and the National Health Interview Survey found that the incidence of IPD significantly reduced among all adult age groups after introducing PCV13 for children.[85] This decline was observed both in adults with direct indications for PCV13 use and those without. The data suggest that the noted benefits were primarily a result of the indirect effects stemming from children's vaccination with PCV13 rather than its direct application in the adult population.

PCVs confer not only direct protection to vaccinated individuals but also indirect protection to the unvaccinated, such as older adults, by reducing nasopharyngeal carriage of vaccine-type strains in children, which limits transmission.

Antimicrobial resistance

According to a 2019 study assessing the global burden of AMR, *S. pneumoniae* was one of the six leading pathogens contributing to deaths.[86] Analysis of Antimicrobial Testing Leadership and Surveillance (ATLAS) data from India, spanning 2018 to 2021, indicated an increase in AMR among *S. pneumoniae* isolates, with observed decreases in susceptibility to key antibiotics such as penicillin, erythromycin, levofloxacin, meropenem, and clindamycin.[87] Such reports highlight the need for vaccines with broader serotype coverage. The use of PCVs contributes toward reducing AMR by preventing pneumococcal infections, which are significant drivers of antibiotic use. Vaccines help decrease the need for antibiotic treatment by reducing the incidence of pneumococcal diseases, thus potentially reducing the selective pressure required for resistant strains to emerge and spread.[88] The use of PCVs has decreased the proportion of circulating pneumococci resistant to first-line antibiotic treatment for pneumonia.[88] A study from India

Table 2. Key highlights from the article.

Section	Key messages
Choosing PCV	• The selection of an appropriate PCV requires careful consideration of the dynamics of *Streptococcus pneumoniae*, including local serotype distribution and nasopharyngeal carriage, as well as disease characteristics such as invasiveness, mortality, and antimicrobial resistance associated with the serotypes.
Serotype distribution	• It is important to consider the prevalence and relevance of serotypes included in the vaccine rather than just the number of serotypes. • It is also important to have continued monitoring and consider the impact of vaccination on serotype distribution.
Vaccine-related factors	• The reference threshold used for immunogenicity studies is for IPD and is not serotype-specific. • Regardless of the differences in serotype and population, the antibody concentrations for preventing mucosal disease and carriage are significantly higher than those for IPD. • The use of immunogenicity as a measure of vaccine efficacy is limited by variabilities in immune responses, incomplete understanding of immune correlates, lack of correlation with clinical protection, and failure to capture real-world effectiveness.
Vaccine efficacy, effectiveness, and impact	• It is essential to consider all three assessments, encompassing efficacy, effectiveness, and impact, to derive a comprehensive comparison of vaccine potential and its implications. • While immunogenicity is a critical aspect of vaccine development, assessing effectiveness and impact provides a more complete picture of how well a vaccine works in diverse populations and under real-world conditions.
Cross-protection	• While some PCVs exhibit cross-reactivity against non-included serotypes, such cross-protection may not always be sufficient for the reduction of carriage and disease. • This underscores the significance of vaccine composition and real-world evidence to accept or refute the extent of cross-protection offered by PCVs. • Ongoing surveillance is essential, especially with newer vaccines. Comprehensive data from the use of the PCV-13 and the earlier PCV-10 (GSK) vaccines have significantly enhanced our understanding of their impact, guiding more informed decisions.
Importance of booster	• The vaccine efficacy can wane over time, making booster doses crucial for maintaining and enhancing protection. • These doses elevate antibody levels, ensuring a long duration of protection and helping to prevent carriage and spread, particularly among high-risk groups.
Herd protection	• PCVs confer not only direct protection to vaccinated individuals but also indirect protection to the unvaccinated, such as older adults, by reducing nasopharyngeal carriage of vaccine-type strains in children, which limits transmission.
Antimicrobial resistance	• *Streptococcus pneumoniae* is a major contributor to AMR-related deaths globally. Evidence indicates rising resistance to several antibiotics in India, emphasizing the critical role of PCVs in preventing infections and curbing the spread of resistant pneumococcal strains.

AMR: Antimicrobial resistance; GSK: GlaxoSmithKline; IPD: Invasive pneumococcal disease; PCV: Pneumococcal conjugate vaccine.

investigating the serotype distribution, antibiotic resistance profile, and expected vaccine coverage among children <5 years of age has reported the presence of *S. pneumoniae* strains that are resistant to cotrimoxazole (96.4%), erythromycin (30%), penicillin (5.2%), and cefotaxime (0.8%).[30] A majority of these strains arise from the serotypes targeted by PCV-13, which highlights the importance of pneumococcal vaccines in preventing the spread of resistant strains of *S. pneumoniae*. A global susceptibility surveillance study reported that serotypes 19A, 6A, 19F, 6B, 15A, 9 V, and 14 exhibited higher levels of erythromycin resistance, while serotypes 19A, 19F, 35B, 6A, 6B, 23A, 9 V, 15A, and 14 displayed higher rates of penicillin resistance.[89] The use of PCVs (pneumococcal vaccines) plays a crucial role in reducing antibiotic resistance by preventing pneumococcal infections, which drive antibiotic use. By decreasing the incidence of these diseases, vaccines lower the chance for resistant strains to develop and spread.

In summary, *S. pneumoniae* is a major contributor to AMR-related deaths globally. Evidence indicates rising resistance to several antibiotics in India, emphasizing the critical role of PCVs in preventing infections and curbing the spread of resistant pneumococcal strains.

Conclusion

Pneumococcal diseases pose a significant health risk, particularly to vulnerable populations such as the young, the elderly, and those with compromised immune systems. Factors like malnutrition, crowded living conditions, limited healthcare access, and poverty can amplify the risk of infection. Vaccination against pneumococcal diseases is essential for safeguarding health and curbing transmission within communities. When choosing an appropriate PCV, it is vital to consider various factors beyond serotype coverage and immune response efficacy. Assessment of aspects such as the volume of participants in clinical studies that establish its safety, co-administration data with other vaccines, information on catch-up vaccination, and data supporting the vaccine's efficacy in high-risk groups are equally important. The flexibility of the vaccine schedule is another practical consideration, allowing for adjustments if an appointment is missed, thereby maintaining the integrity of the vaccination program. Key highlights from different sections of the article are summarized in Table 2.

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Data availability statement

All the data included in the manuscript is from previously published sources.

References

1. Randle E, Ninis N, Inwald D. Invasive pneumococcal disease. Archiv Disease In Child - Educ And Pract. 2011;96(5):183–190. doi: 10.1136/adc.2010.11718.
2. Austrian R. Some aspects of the pneumococcal carrier state. J Antimicrob Chemother. 1986;18(Supplement_A):35–45. doi: 10.1093/jac/18.Supplement_A.35.
3. Huang SS, Johnson KM, Ray GT, Wroe P, Lieu TA, Moore MR, Zell ER, Linder JA, Grijalva CG, Metlay JP, et al. Healthcare utilization and cost of pneumococcal disease in the United States. Vaccine. 2011;29(18):3398–3412. doi: 10.1016/j.vaccine.2011.02.088.
4. National Operational Guidelines. [accessed 2023 June 19]. https://main.mohfw.gov.in/sites/default/files/PCV_Operational.
5. Farooqui H, Jit M, Heymann DL, Zodpey S. Burden of severe pneumonia, pneumococcal pneumonia and pneumonia deaths in Indian states: modelling based estimates. In: Hill P, editor. PLOS ONE. Vol. 10(6):2015. p. e9191. doi: 10.1371/journal.pone.09191.
6. Wahl B, Sharan A, Deloria Knoll M, Kumar R, Liu L, Chu Y, McAllister DA, Nair H, Campbell H, Rudan I, et al. National, regional, and state-level burden of streptococcus pneumoniae and haemophilus influenzae type b disease in children in India: modelled estimates for 2000–15. The Lancet Global Health. 2019;7(6):e735–e747. doi: 10.1016/S2214-109X(19)30081-6.
7. Howie SRC, Schellenberg J, Chimah O, Ideh RC, Ebruke BE, Oluwalana C, Mackenzie G, Jallow M, Njie M, Donkor S, et al. Childhood pneumonia and crowding, bed-sharing and nutrition: a case-control study from the Gambia. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2016;20(10):1405–1415. doi: 10.5588/ijtld.15.0993.
8. Grant LR, Slack MPE, Theilacker C, Vojicic J, Dion S, Reinert R-R, Jodar L, Gessner BD. Distribution of serotypes causing invasive pneumococcal disease in children from High-income countries and the impact of pediatric pneumococcal vaccination. Clin Infect Dis. 2023;76(3):e1062–e1070. doi: 10.1093/cid/ciac475.
9. Sadeck LDSR, Kfouri RDÁ. An update on vaccination in preterm infants. Jornal de Pediatria. 2023;99 Suppl 99(Suppl 1):S81–S86. doi: 10.1016/j.jped.2022.12.004.
10. Frenkel LD. The global burden of vaccine-preventable infectious diseases in children less than 5 years of age: implications for COVID-19 vaccination. How can we do better? Allergy Asthma Proc. 2021;42(5):378–385. doi: 10.2500/aap.2021.42.20065.
11. Marrie TJ, Tyrrell GJ, Majumdar SR, Eurich DT. Concurrent infection with hepatitis C virus and streptococcus pneumoniae. Emerg Infect Dis. 2017;23(7):1118–1123. doi: 10.3201/eid2307.11858.
12. Who Publication. Pneumococcal vaccines WHO position paper – 2012 – recommendations. Vaccine. 2012;30(32):4717–4718. doi: 10.1016/j.vaccine.2012.04.093.
13. Kalin M. Pneumococcal serotypes and their clinical relevance. Thorax. 1998;53(3):159–162. doi: 10.1136/thx.53.3.159.
14. Lister AJJ, Le CF, Cheah ESG, Desa MNM, Cleary DW, Clarke SC. Serotype distribution of invasive, non-invasive and carried streptococcus pneumoniae in Malaysia: a meta-analysis. Pneumonia. 2021;13(1):9. doi: 10.1186/s1479-021-00086-7.
15. Sutcliffe CG, Shet A, Varghese R, Veeraraghavan B, Manoharan A, Wahl B, Chandy S, Sternal J, Khan R, Singh RK, et al. Nasopharyngeal carriage of streptococcus pneumoniae serotypes among children in India prior to the introduction of pneumococcal conjugate vaccines: a cross-sectional study. BMC Infect Dis. 2019;19(1):605. doi: 10.1186/s2879-019-4254-2.
16. Belayhun C, Tilahun M, Seid A, Shibabaw A, Sharew B, Belete MA, Demsiss W. Asymptomatic nasopharyngeal bacterial carriage, multi-drug resistance pattern and associated factors among primary school children at Debre Berhan town, North Shewa, Ethiopia. Ann Clin Microbiol Antimicrob. 2023;22(1):9. doi: 10.1186/s2941-023-00557-3.
17. Berical AC, Harris D, Dela Cruz CS, Possick JD. Pneumococcal vaccination strategies. An update and perspective. Ann ATS. 2016;13(6):933–944. doi: 10.1513/AnnalsATS.21511-778FR.
18. Simell B, Auranen K, Käyhty H, Goldblatt D, Dagan R, O'Brien KL. The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines. 2012;11(7):841–855. doi: 10.1586/erv.12.53.
19. Rupa V, Isaac R, Manoharan A, Jalagandeeswaran R, Thenmozhi M. Risk factors for upper respiratory infection in the first year of life in a birth cohort. Int J Pediatr Otorhinolaryngology. 2012;76(12):1835–1839. doi: 10.1016/j.ijporl.2012.09.013.
20. Dhakal R, Sujatha S, Parija SC, Bhat BV. Asymptomatic colonization of upper respiratory tract by potential bacterial pathogens. Indian J Pediatr. 2010;77(7):775–778. doi: 10.1007/s2098-010-0118-x.
21. Coles CL, Kanungo R, Rahmathullah L, Thulasiraj RD, Katz J, Santosham M, Tielsch JM. Pneumococcal nasopharyngeal colonization in young South Indian infants. Pediatr Infect Disease J. 2001;20(3):289–295. doi: 10.1097/06454-203000-00014.
22. Ganaie F, Saad JS, McGee L, van Tonder AJ, Bentley SD, Lo SW, Gladstone RA, Turner P, Keenan JD, Breiman RF, et al. A new pneumococcal capsule type, 10D, is the 100th serotype and has a large cps fragment from an oral streptococcus. McDaniel LS, ed. mBio. 2020;11(3):e0937–20. doi: 10.1128/mBio.00937-20.
23. Wasserman MD, Perdrizet J, Grant L, Hayford K, Singh S, Saharia P, Horn EK, Farkouh RA. Clinical and economic burden of pneumococcal disease due to serotypes contained in current and investigational pneumococcal conjugate vaccines in children under five years of age. Infect Dis Ther. 2021;10(4):2701–2720. doi: 10.1007/s0121-021-00544-1.

24. Preventing pneumococcal disease among infants and young children. [Published online 2000 2024 Mar 27]. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr4909a1.htm.
25. Manoharan A, Manchanda V, Balasubramanian S, Lalwani S, Modak M, Bai S, Vijayan A, Shet A, Nagaraj S, Karande S, et al. Invasive pneumococcal disease in children aged younger than 5 years in India: a surveillance study. Lancet Infect Dis. 2017;17(3):305–312. doi: 10.1016/S1473-3099(16)30466-2.
26. Singh J, Sundaresan S, Manoharan A, Shet A. Serotype distribution and antimicrobial susceptibility pattern in children ≤5 years with invasive pneumococcal disease in India – a systematic review. Vaccine. 2017;35(35):4501–4509. doi: 10.1016/j.vaccine.2017.06.079.
27. Thomas K, Mukkai Kesavan L, Veeraraghavan B, Jasmine S, Jude J, Shubankar M, Kulkarni P, Steinhoff M. Invasive pneumococcal disease associated with high case fatality in India. J Clin Epidemiol. 2013;66(1):36–43. doi: 10.1016/j.jclinepi.2012.04.006.
28. Nagaraj G, Govindan V, Ganaie F, Venkatesha VT, Hawkins PA, Gladstone RA, McGee L, Breiman RF, Bentley SD, Klugman KP, et al. Streptococcus pneumoniae genomic datasets from an Indian population describing pre-vaccine evolutionary epidemiology using a whole genome sequencing approach. Microb Genomics. 2021;7(9). doi: 10.1099/mgen.0.00645.
29. Jaiswal N, Singh M, Das RR. Distribution of serotypes, vaccine coverage, and antimicrobial susceptibility pattern of streptococcus pneumoniae in children living in SAARC countries: a systematic review. In: Miyaji E, editor. PLOS ONE. Vol. 9(9):2014. p. e8617. doi: 10.1371/journal.pone.08617.
30. Balaji V, Jayaraman R, Verghese V, Baliga P, Kurien T. Pneumococcal serotypes associated with invasive disease in under five children in India & implications for vaccine policy. Indian J Med Res. 2015;142(3):286. doi: 10.4103/0971-5916.16588.
31. Nisarga R, Premalatha R, Shivananda S, Ravikumar KL, Shivappa U, Gopi A, Chikkadasarahalli SB, Batuwanthudawe R, Kilgore PE, et al. Hospital-based surveillance of invasive pneumococcal disease and pneumonia in South Bangalore, India. Indian Pediatr. 2015;52(3):205–211. doi: 10.1007/s3312-015-0607-0.
32. Vandana G, Feroze AG, Geetha N, Avid H, Ravi Kumar KL. Pan India distribution of pneumococcal serotypes (PIDOPS) causing invasive pneumococcal disease and pneumonia in children between 6 weeks and 5 years and their antimicrobial resistance – phase I. Pediatr Infect Disease. 2016;8(2):47–51. doi: 10.1016/j.pid.2016.06.004.
33. Jayaraman Y, Veeraraghavan B, Chethrapilly Purushothaman GK. Burden of bacterial meningitis in India: preliminary data from a hospital based sentinel surveillance network. In: Chaturvedi V, editor. PLOS ONE. Vol. 13(5):2018. p. e7198. doi: 10.1371/journal.pone.07198.
34. Mazumdar D, Sarma A, Medhi D, Dutta R, Kataki M, Baishya L, Dutta BS, Saikia L. Capsular typing of streptococcus pneumoniae isolated from clinical specimens in Gauhati Medical College and Hospital, Assam, India. Indian J Med Microbiol. 2023;44:10350. doi: 10.1016/j.ijmmb.2023.01.008.
35. Isturiz R, Sings HL, Hilton B, Arguedas A, Reinert RR, Jodar L. Streptococcus pneumoniae serotype 19A: worldwide epidemiology. Expert Rev Vaccines. 2017;16(10):1007–1027. doi: 10.1080/10584.2017.12339.
36. Kaplan SL, Barson WJ, Lin PL, Stovall SH, Bradley JS, Tan TQ, Hoffman JA, Givner LB, Mason EO. Serotype 19A is the most common serotype causing invasive pneumococcal infections in children. Pediatrics. 2010;125(3):429–436. doi: 10.1542/peds.2008-1702.
37. Reinert R, Jacobs MR, Kaplan SL. Pneumococcal disease caused by serotype 19A: review of the literature and implications for future vaccine development. Vaccine. 2010;28(26):4249–4259. doi: 10.1016/j.vaccine.2010.04.020.
38. Hulten KG, Kaplan SL, Lamberth LB, Barson WJ, Romero JR, Lin PL, Bradley JS, Givner LB, Tan TQ, Hoffman JA, et al. Changes in streptococcus pneumoniae serotype 19A invasive infections in children from 1993 to 2011. J Clin Microbiol. 2013;51(4):1294–1297. doi: 10.1128/JCM.00058-13.
39. Desmet S, Lagrou K, Wyndham-Thomas C, Braeye T, Verhaegen J, Maes P, Fieuws S, Peetermans WE, Blumental S. Dynamic changes in paediatric invasive pneumococcal disease after sequential switches of conjugate vaccine in Belgium: a national retrospective observational study. Lancet Infect Dis. 2021;21(1):127–136. doi: 10.1016/S1473-3099(20)30173-0.
40. Wouters I, Desmet S, Van Heirstraeten L, Herzog SA, Beutels P, Verhaegen J, Goossens H, Van Damme P, Malhotra-Kumar S, Theeten H. How nasopharyngeal pneumococcal carriage evolved during and after a PCV13-to-PCV10 vaccination programme switch in Belgium, 2016 to 2018. Eurosurveillance. 2020;25(5). doi: 10.2807/1560-7917.ES.2020.25.5.10303.
41. Wilson MR, McDade CL, Perdrizet JE, Mignon A, Farkouh RA, Wasserman MD. Validation of a novel forecasting method for estimating the impact of switching pneumococcal conjugate programs: evidence from Belgium. Infect Dis Ther. 2021;10(3):1765–1778. doi: 10.1007/s0121-021-00485-9.
42. Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines, annex 3. TRS No 977. [accessed 2023 Jul 24]. https://www.who.int/publications/m/item/pneumococcal-conjugate-vaccines-annex3-trs-977.
43. Dagan R. Relationship between immune response to pneumococcal conjugate vaccines in infants and indirect protection after vaccine implementation. Expert Rev Vaccines. 2019;18(6):641–661. doi: 10.1080/10584.2019.17207.
44. Ryman J, Weaver J, Hu T, Weinberger DM, Yee KL, Sachs JR. Predicting vaccine effectiveness against invasive pneumococcal disease in children using immunogenicity data. Npj Vaccines. 2022;7(1):140. doi: 10.1038/s1541-022-00538-1.
45. Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, Slack M, Ladhani SN, Miller E, Goldblatt D. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis. 2014;14(9):839–846. doi: 10.1016/S1473-3099(14)70822-9.
46. Yeh SH, Gurtman A, Hurley DC, Block SL, Schwartz RH, Patterson S, Jansen KU, Love J, Gruber WC, Emini EA, et al. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in infants and toddlers. Pediatrics. 2010;126(3):e493–e505. doi: 10.1542/peds.2009-3027.
47. Siber GR, Chang I, Baker S, Fernsten P, O'Brien KL, Santosham M, Klugman KP, Madhi SA, Paradiso P, Kohberger R. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. Vaccine. 2007;25(19):3816–3826. doi: 10.1016/j.vaccine.2007.01.119.
48. Platt HL, Greenberg D, Tapiero B, Clifford RA, Klein NP, Hurley DC, Shekar T, Li J, Hurtado K, Su S-C, et al. A phase II trial of safety, tolerability and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, compared with 13-valent pneumococcal conjugate vaccine in healthy infants. Pediatr Infect Disease J. 2020;39(8):763–770. doi: 10.1097/INF.0000002765.
49. Clarke E, Bashorun AO, Okoye M, Umesi A, Badjie Hydara M, Adigweme I, Dhere R, Sethna V, Kampmann B, Goldblatt D, et al. Safety and immunogenicity of a novel 10-valent pneumococcal conjugate vaccine candidate in adults, toddlers, and infants in the Gambia—results of a phase 1/2 randomized, double-blinded, controlled trial. Vaccine. 2020;38(2):399–410. doi: 10.1016/j.vaccine.2019.08.072.
50. Kaur R, Pham M, Pichichero M. Serum antibody levels to pneumococcal polysaccharides 22F, 33F, 19A and 6A that correlate with protection from colonization and acute otitis media in children. Vaccine. 2021;39(29):3900–3906. doi: 10.1016/j.vaccine.2021.05.089.
51. Pichichero M, Malley R, Kaur R, Zagursky R, Anderson P. Acute otitis media pneumococcal disease burden and nasopharyngeal colonization in children due to serotypes included and not included in current and new pneumococcal conjugate vaccines. Expert Rev Vaccines. 2023;22(1):118–138. doi: 10.1080/10584.2023.22506.

52. Ginsburg AS, Nahm MH, Khambaty FM, Alderson MR. Issues and challenges in the development of pneumococcal protein vaccines. Expert Rev Vaccines. 2012;11(3):279–285. doi: 10.1586/erv.12.5.
53. Kochhar S. Challenges and impact of conducting vaccine trials in Asia and Africa: new technologies in emerging markets, October 16th-18th 2012; world vaccine congress, Lyon. Hum Vaccines & Immunotherapeutics. 2013;9(4):924–927. doi: 10.4161/hv.23405.
54. Ceyhan M, Aykac K, Gurler N, Ozsurekci Y, Öksüz L, Altay Akısoglu Ö, Öz FN, Emiroglu M, TurkDagi H, Yaman A, et al. Serotype distribution of streptococcus pneumonia in children with invasive disease in Turkey: 2015-2018. Hum Vaccines & Immunotherapeutics. 2020;16(11):2773–2778. doi: 10.1080/25515.2020.17931.
55. Cohen O, O'brien K, Hosangadi D. Pneumococcal conjugate vaccine (PCV) review of impact evidence. PRIME. [accessed 2023 Apr 26]. https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Oct2017/9_session_PCV/Oct2019_session9_PCV_PRIMEsummary.pdf.
56. Blaschke AJ. Interpreting assays for the detection of streptococcus pneumoniae. Clin Infect Dis. 2011;52(suppl_4):S331–S337. doi: 10.1093/cid/cir048.
57. Kaur R, Czup K, Casey JR, Pichichero ME. Correlation of nasopharyngeal cultures prior to and at onset of acute otitis media with middle ear fluid cultures. BMC Infect Dis. 2014;14(1):640. doi: 10.1186/s2879-014-0640-y.
58. Weinberger DM, Bruden DT, Grant LR, Lipsitch M, O'Brien KL, Pelton SI, Sanders EAM, Feikin DR. Using pneumococcal carriage data to monitor postvaccination changes in invasive disease. Am J Epidemiol. 2013;178(9):1488–1495. doi: 10.1093/aje/kwt156.
59. Patel SM, Shaik-Dasthagirisaheb YB, Congdon M. Evolution of pneumococcal serotype epidemiology in Botswana following introduction of 13-valent pneumococcal conjugate vaccine. In: Melo-Cristino J, editor. PLOS ONE. Vol. 17(1):2022. p. e2225. doi: 10.1371/journal.pone.02225.
60. Usuf E, Bottomley C, Gladstone R, Bojang E, Jawneh K, Cox I, Jallow E, Bojang A, Greenwood B, Adegbola RA, et al. Persistent and emerging pneumococcal carriage serotypes in a rural Gambian community after 10 years of pneumococcal conjugate vaccine pressure. Clin Infect Dis. 2021;73(11):e3825–e3835. doi: 10.1093/cid/ciaa856.
61. Froneman C, Kelleher P, José RJ. Pneumococcal vaccination in immunocompromised hosts: an update. Vaccines. 2021;9(6):536. doi: 10.3390/vaccines0536.
62. Gjini E. Geographic variation in pneumococcal vaccine efficacy estimated from dynamic modeling of epidemiological data post-PCV7. Sci Rep. 2017;7(1):3049. doi: 10.1038/s1598-017-02955-y.
63. Muhammad RD, Oza-Frank R, Zell E, Link-Gelles R, Narayan KMV, Schaffner W, Thomas A, Lexau C, Bennett NM, Farley MM, et al. Epidemiology of invasive pneumococcal disease among high-risk adults since the introduction of pneumococcal conjugate vaccine for children. Clin Infect Dis. 2013;56(5):e59–e67. doi: 10.1093/cid/cis971.
64. Considerations for pneumococcal conjugate vaccine (PCV) product choice. Published online 2021. https://www.who.int/publications/i/item/considerations-for-pneumococcal-conjugate-vaccine-(pcv)-product-choice.
65. Cooper D, Yu X, Sidhu M, Nahm MH, Fernsten P, Jansen KU. The 13-valent pneumococcal conjugate vaccine (PCV13) elicits cross-functional opsonophagocytic killing responses in humans to streptococcus pneumoniae serotypes 6C and 7A. Vaccine. 2011;29(41):7207–7211. doi: 10.1016/j.vaccine.2011.06.056.
66. Ekinci E, Van Heirstraeten L, Willen L, Desmet S, Wouters I, Vermeulen H, Lammens C, Goossens H, Van Damme P, Verhaegen J, et al. Serotype 19A and 6C account for one-third of pneumococcal carriage among Belgian day-care children four years after a shift to a lower-valent PCV. J Pediatr Infect Dis Soc. 2023;12(1):36–42. doi: 10.1093/jpids/piac117.
67. Dagan R, Juergens C, Trammel J, Patterson S, Greenberg D, Givon-Lavi N, Porat N, Gruber WC, Scott DA. Modeling pneumococcal nasopharyngeal acquisition as a function of anticapsular serum antibody concentrations after pneumococcal conjugate vaccine administration. Vaccine. 2016;34(36):4313–4320. doi: 10.1016/j.vaccine.2016.06.075.
68. Dagan R, Givon-Lavi N, Fraser D, Lipsitch M, Siber GR, Kohberger R. Serum Serotype-Specific pneumococcal anticapsular immunoglobulin G concentrations after immunization with a 9-Valent conjugate pneumococcal vaccine correlate with nasopharyngeal acquisition of pneumococcus. J Infect Dis. 2005;192(3):367–376. doi: 10.1086/41679.
69. Mitsi E, Roche AM, Reiné J, Zangari T, Owugha JT, Pennington SH, Gritzfeld JF, Wright AD, Collins AM, van Selm S, et al. Agglutination by anti-capsular polysaccharide antibody is associated with protection against experimental human pneumococcal carriage. Mucosal Immunol. 2017;10(2):385–394. doi: 10.1038/mi.2016.71.
70. Ojal J, Hammitt LL, Gaitho J, Scott JAG, Goldblatt D. Pneumococcal conjugate vaccine induced IgG and nasopharyngeal carriage of pneumococci: hyporesponsiveness and immune correlates of protection for carriage. Vaccine. 2017;35(35):4652–4657. doi: 10.1016/j.vaccine.2017.05.088.
71. Vesikari T, Wysocki J, Chevallier B, Karvonen A, Czajka H, Arsène J-P, Lommel P, Dieussaert I, Schuerman L. Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-cv) compared to the licensed 7vCRM vaccine. Pediatr Infect Disease J. 2009;28(4):S66–S76. doi: 10.1097/INF.0b013e8199f8ef.
72. Kieninger DM, Kueper K, Steul K, Juergens C, Ahlers N, Baker S, Jansen KU, Devlin C, Gruber WC, Emini EA, et al. Safety, tolerability, and immunologic noninferiority of a 13-valent pneumococcal conjugate vaccine compared to a 7-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in Germany. Vaccine. 2010;28(25):4192–4203. doi: 10.1016/j.vaccine.2010.04.008.
73. Van Westen E, Knol MJ, Wijmenga-Monsuur AJ, Tcherniaeva I, Schouls LM, Sanders EAM, Van Els CACM, Berbers GAM, Rots NY. Serotype-specific IgG antibody waning after pneumococcal conjugate primary series vaccinations with either the 10-valent or the 13-valent vaccine. Vaccines. 2018;6(4):82. doi: 10.3390/vaccines0082.
74. Bröker M, Berti F, Schneider J, Vojtek I. Polysaccharide conjugate vaccine protein carriers as a "neglected valency" – potential and limitations. Vaccine. 2017;35(25):3286–3294. doi: 10.1016/j.vaccine.2017.04.078.
75. Whitney CG. Examining duration of protection: should a booster dose Be part of all infant pneumococcal conjugate vaccine programs? Clin Infect Dis. 2018;67(3):375–377. doi: 10.1093/cid/ciy135.
76. Jayasinghe S, Chiu C, Quinn H, Menzies R, Gilmour R, McIntyre P. Effectiveness of 7- and 13-valent pneumococcal conjugate vaccines in a schedule without a booster dose: a 10-year observational study. Clin Infect Dis. 2018;67(3):367–374. doi: 10.1093/cid/ciy129.
77. Lee J. Pneumococcal conjugate vaccines: choice of schedule and product development. Clin Exp Pediatr. 2020;63(7):259–260. doi: 10.3345/cep.2019.01739.
78. Weekly epidemiological record Relevé épidémiologique hebdomadaire. [Published online 2019 2023 Nov 2]. https://iris.who.int/bitstream/handle/10665/30968/WER9408.pdf?ua=1.
79. Klugman KP, Madhi SA, Adegbola RA, Cutts F, Greenwood B, Hausdorff WP. Timing of serotype 1 pneumococcal disease suggests the need for evaluation of a booster dose. Vaccine. 2011;29(18):3372–3373. doi: 10.1016/j.vaccine.2011.02.089.
80. Swarthout TD, Henrion MYR, Thindwa D, Meiring JE, Mbewe M, Kalizang'oma A, Brown C, Msefula J, Moyo B, Mataya AA, et al. Waning of antibody levels induced by a 13-valent pneumococcal conjugate vaccine, using a 3 + 0 schedule, within the first year of life among children younger than 5 years in Blantyre, Malawi: an observational, population-level, serosurveillance study. The Lancet

Infect Dis. 2022;22(12):1737–1747. doi: 10.1016/S1473-3099(22)00438-8.
81. Conklin L, Loo JD, Kirk J, Fleming-Dutra KE, Deloria Knoll M, Park DE, Goldblatt D, O'Brien KL, Whitney CG. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on vaccine-type invasive pneumococcal disease among Young children. Pediatr Infect Disease J. 2014;33(Supplement 2):S109–S118. doi: 10.1097/INF.0000000078.
82. Rodgers GL, Whitney CG, Klugman KP. Triumph of pneumococcal conjugate vaccines: overcoming a common foe. The J Infect Dis. 2021;224(Supplement_4):S352–S359. doi: 10.1093/infdis/jiaa535.
83. Weinberger DM, Dagan R, Givon-Lavi N, Regev-Yochay G, Malley R, Lipsitch M. Epidemiologic evidence for Serotype-Specific acquired immunity to pneumococcal carriage. J Infect Dis. 2008;197(11):1511–1518. doi: 10.1086/57941.
84. Oabrien K. The potential indirect effect of conjugate pneumococcal vaccines. Vaccine. 2003;21(17–18):1815–1825. doi: 10.1016/S0264-410X(02)00807-1.
85. Ahmed SS, Pondo T, Xing W, McGee L, Farley M, Schaffner W, Thomas A, Reingold A, Harrison LH, Lynfield R, et al. Early impact of 13-valent pneumococcal conjugate vaccine use on invasive pneumococcal disease among adults with and without underlying medical conditions—United States. Clin Infect Dis. 2020;70(12):2484–2492. doi: 10.1093/cid/ciz739.
86. Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, Han C, Bisignano C, Rao P, Wool E, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–655. doi: 10.1016/S0140-6736(21)02724-0.
87. Kulkarni N, Routray A, Taur S. A multicenter evaluation of overall susceptibility and antimicrobial resistance among streptococcus pneumoniae isolates. Cureus. [Published online 2023 Jul 17.] doi: 10.7759/cureus.41984.
88. Andrejko K, Ratnasiri B, Hausdorff WP, Laxminarayan R, Lewnard JA. Antimicrobial resistance in paediatric streptococcus pneumoniae isolates amid global implementation of pneumococcal conjugate vaccines: a systematic review and meta-regression analysis. Lancet Microbe. 2021;2(9):e450–e460. doi: 10.1016/S2666-5247(21)00064-1.
89. Hackel M, Lascols C, Bouchillon S, Hilton B, Morgenstern D, Purdy J. Serotype prevalence and antibiotic resistance in streptococcus pneumoniae clinical isolates among global populations. Vaccine. 2013;31(42):4881–4887. doi: 10.1016/j.vaccine.2013.07.054.