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REVIEW

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Streptococcus pneumoniae serotype distribution in low- and middle-income countries of South Asia: Do we need to revisit the pneumococcal vaccine strategy?

Priya Dhawale[a*], Sanket Shah[b*], Kaushal Sharma[c], Deepa Sikriwal[d], Varnik Kumar[d], Arnabjyoti Bhagawati[d], Sakshi Dhar[d], Pratiksha Shetty[e], and Syed Ahmed[f]

[a]Global Business Development, Techinvention Lifecare Private Limited, Mumbai, India; [b]Strategic Medical Affairs, Techinvention Lifecare Private Limited, Mumbai, India; [c]Strategic Projects, Techinvention Lifecare Private Limited, Mumbai, India; [d]Research and Development, Techinvention Lifecare Private Limited, Mumbai, India; [e]Regulatory Affairs, Techinvention Lifecare Private Limited, Mumbai, India; [f]Business Development and Strategy, Techinvention Lifecare Private Limited, Mumbai, India

ABSTRACT

S. pneumoniae serotypes responsible for pneumococcal disease differ with respect to disease severity, invasiveness, antimicrobial susceptibility, geographies, immunization history, age groups, and with time. Although PCVs have blunted the pneumococcal disease burden, they are plagued with numerous challenges, especially the emergence of NVTs. In this review, we show that there are diverse serotypes, especially NVTs, responsible for causing pneumococcal diseases in LMICs of South Asia across different studies conducted between 2012 and 2024. We propose that pharmaceutical/biotech companies should tailor/customize the PCVs as per the region-specific serotype prevalence based on surveillance data. Furthermore, protein-based vaccines, or WCVs, have been explored and can serve as viable alternatives to address the limitations associated with PCVs. However, robust studies are warranted in different geographies to demonstrate its efficacy and safety in clinical trials as well as the real-world effectiveness of these promising candidates.

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Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is a gram-positive bacteria that colonizes the upper respiratory tract of humans.[1,2] Globally, it represents an important cause of morbidity and mortality in children and adults.[3] It is responsible for causing invasive pneumococcal disease (IPD), viz., meningitis, septicemia, bacteremia, and bacteremic pneumonia, as well as non-IPD, such as acute otitis media (AOM) and non-bacteremic pneumonia, in both adults and children.[4,5] The disease burden (incidence and mortality rates) is highest in children <5 years and adults >65 years, as well as in individuals with compromised immune system or chronic medical conditions.[5,6] The World Health Organization (WHO) estimates that *S. pneumoniae* is responsible for killing > 300,000 children under 5 years of age globally every year, with the majority of them occurring in developing countries.[7] It is also the leading cause of bacterial pneumonia globally.[7] Antibiotics have been used as front-line agents for the treatment of *S. pneumoniae* infections, but the emergence of antibiotic-resistant strains is a major concern for clinicians.[8,9] The WHO has included *S. pneumoniae* as one of the 12 priority pathogens, exhibiting increased resistance to antibiotics.[10,11] *S. pneumoniae* produces several virulence factors, and the capsular polysaccharide is considered to be the most important one, enabling binding to the cells and evading the host immune system.[5,6,12,13] More than 90 serotypes have been identified based on these capsular polysaccharides, and only a subset of them are responsible for causing pneumococcal disease.[5,6,14] These serotypes also form the basis of pneumococcal conjugate vaccines (PCVs), and only a fraction of the serotypes are included in the vaccine formulation because of the complexity involved in the manufacturing of PCVs.[5,15,16] Pneumococcal disease is endemic globally, but the distribution of *S. pneumoniae* serotypes differs with respect to their disease severity, invasiveness, antimicrobial susceptibility, geographies, immunization history of individuals, age groups, and with time.[4,5,16–19]

Pneumococcal carriage is seen more frequently in children than adults, and thus children are considered to be the main reservoir and transmitter of this pathogen.[13] In low- and middle-income countries (LMICs), *S. pneumoniae* has three times higher colonization as compared to those in high- income countries (HICs).[20] The burden of pneumococcal diseases remains high in LMICs.[21] Globally, there are over 1,400 cases of pneumonia per 100,000 children annually, with the greatest incidence occurring in South Asia (2,500 cases/100,000 children) and West and Central Africa (1,620 cases/100,000 children).[22] South Asian countries have the highest mortality due to IPD.[23] Population-based studies in South Asian countries have shown that *S. pneumoniae* was responsible for 12.8% of invasive bacterial diseases, whereas retrospective hospital-based studies showed that 28% of them were due to *S. pneumoniae*.[23]

The implementation of PCVs has played a significant role in reducing the burden of pneumococcal disease globally through direct protection of vaccinated individuals and indirect protection of unvaccinated individuals by reducing the

CONTACT Syed Ahmed syed@techinvention.biz Business Development and Strategy, Techinvention Lifecare Private Limited, #1004, The Summit Business Park, Off WEH Metro Station, Andheri Kurla Road, Andheri East, Mumbai 400093, India.

*These authors contributed equally to this work and share first authorship.

nasopharyngeal carriage and transmission of vaccine-type (VT) pneumococci.[24,25] Vaccines also serve as an effective strategy to address the burgeoning issue of antimicrobial resistance (AMR) in *S. pneumoniae*.[9] As per the VIEW-hub Report: Global Vaccine Introduction and Implementation, 159 countries have introduced PCVs into their national immunization programs (NIPs) as of August 2024.[26] PCVs have also been introduced in many LMICs with the support of Gavi, the Vaccine Alliance[27] Evaluating the impact of vaccines in LMICs is of paramount importance because of differences in pneumococcal epidemiology, including transmission rates.[28]

Despite the remarkable success achieved with PCVs, the prevalence of IPD has increased by non-vaccine serotypes (NVTs), partially offsetting the total disease reduction.[4,29–32] This phenomenon, referred to as serotype replacement, is due to the greater serotype diversity observed in developing countries.[29] Although this phenomenon was initially considered controversial, it is now well established.[33] These NVTs may replace the VTs in the upper airways, resulting in increased transmission and disease, as well as undermining the effectiveness of the currently available PCVs.[19,34] They have the tendency to be highly invasive in nature as well as exhibit high levels of resistance to antibiotics.[29,35] Two mechanisms for serotype replacement have been suggested, which are described in detail by Lo et al. and van Tonder et al.[30,36] Hence, it becomes imperative to monitor the serotype data post-PCV introduction to identify new emerging serotypes and gain insights into the evolving epidemiology of *S. pneumoniae*.[4,37] Also, robust vaccine strategies are warranted to address the issue of NVTs.[38]

In this comprehensive review, we bring forth the distribution and distinctive characteristics of pneumococcal serotypes in LMICs of South Asia. It sheds light on the prevailing trend of NVTs gaining prominence globally, showcasing their distinct features across the region. An elaborate overview of the current pneumococcal vaccine landscape is provided, highlighting the merits and demerits of PCVs, along with alternative strategies (protein-based and whole-cell vaccines [WCVs]) that are being investigated to address the limitations of PCVs. Furthermore, we provide valuable recommendations for future vaccine design and development to mitigate the threat posed by these NVTs.

Methods

We conducted a comprehensive literature search on PubMed to identify relevant studies that were published between 2012 and 2024 (at the time of writing the mansucript) using the keywords, viz., "pneumococcal disease," "pneumococcal serotypes," "pneumococcal conjugate vaccines," "invasive pneumococcal disease," "non-invasive pneumococcal disease," and the respective South Asian country name (Afghanistan, Bangladesh, Sri Lanka, Nepal, Bhutan, Pakistan, India, and Maldives). Studies that were conducted between 2012 to 2024 were included in our analysis. Also, studies that commenced before 2012 but concluded in or after 2012 were also included in our analysis. Studies published in native/regional languages other than English were excluded. Table 1 highlights the *S. pneumoniae* serotypes reported in LMICs of South Asia from different studies conducted between 2012 and 2024 (at the time of writing this manuscript). Table 2 highlights the different characteristics of NVTs observed in this region.

Pneumococcal vaccine landscape

Approved pneumococcal polysaccharide vaccines (PPSVs) and PCVs

There are two types of pneumococcal vaccines available that are clinically available, viz., PPSVs and PCVs, targeting multiple serotypes.[12,102] PPSVs stimulate the B cells by cross-linking the B-cell receptors (BCR), which leads to the production of immunoglobulins.[103] This type of immune response is usually a T cell-independent response, which implies that these polysaccharides are capable of activating B cells in the absence of T helper cells.[104,105] These polysaccharides cannot be processed and presented in association with major histocompatibility complex (MHC) class II molecules and cannot be recognized by T helper cells.[104] Due to the lack of T cell collaboration, the antibodies are of low affinity and are composed mainly of immunoglobulin M (IgM) with limited isotype switching to immunoglobulin G (IgG) and immunoglobulin A (IgA).[104] It results in a lack of production of new memory B cells along with depletion of the memory B cell pool, resulting in hyporesponsiveness to future doses of vaccine.[103] PPSV23 was licensed in the United States of America (USA) in 1983.[5] It included 23 serotypes, which were responsible for 85% to 90% of IPD globally.[29] It is approved for use in individuals 50 years of age or older and persons aged ≥2 years who are at increased risk for pneumococcal disease.[106] PPS23's protective efficacy has been consistently demonstrated in several studies as well as meta-analysis.[107–111] In immunocompetent individuals, the vaccine has an efficacy of 65% against pneumococcal infections with serotypes included in it.[112] The effectiveness against IPD in immunocompetent adults ranges from 56% to 81% but is lower in individuals with compromised immune status.[12] It reduces the severity of community-acquired pneumonia (CAP) but does not prevent it. It does not reduce the incidence of noninvasive pneumonia.[12] Moreover, it does not generate immunological memory in children <2 years, and hence it is not effective in this population.[12] Also, it does not reduce pneumococcal carriage.[12,112]

To overcome this drawback and elicit a protective immune response in children <2 years, capsular polysaccharide vaccines conjugated to a protein carrier were developed.[5,112] Conjugation of the polysaccharide to a suitable carrier protein converts it into a T cell-dependent antigen.[113] This conjugation of the capsular polysaccharide directs the processing of the carrier protein by the polysaccharide-specific B cells, followed by the presentation of the peptides to carrier-peptide specific T cells in association with MHC class II molecules.[103] When B cells receive help from T cells, they proliferate and differentiate into plasma cells, with class switching to IgG, and memory B cells. These memory B cells undergo rapid proliferation and differentiate into plasma cells upon subsequent encounter with the antigen, producing high antibody titers.[103,113] A 7-valent PCV (Prevnar, Pfizer) conjugated to cross-reactive material 197 (CRM_{197}) was developed and licensed in the United States (U.S.) and the European Union (EU) in 2000 and 2001, respectively.[12,102] The vaccine

Table 1. Pneumococcal serotypes reported in LMICs of South Asia from different studies conducted between 2012 to 2024.

Studies included[1]	Age groups[2]	Serotypes/Serogroups reported[3]	Serotypes covered under PCV13[4]	NVTs	Mixed Serotypes	Countries and references	Remarks
• Serotype distribution and AMR patterns of pneumococcal isolates collected from individuals with IPD and non-IPD and from carriage studies • Customized PCR for invasive pneumococcal serotype determination • Comparison of *S. pneumoniae* serotype distribution, AMR patterns, and carriage from community children and children with clinical pneumonia; health care and non-healthcare workers; and pre- and post-Hajj pilgrims • Carriage of *S. pneumoniae* serotypes in vaccinated and unvaccinated populations • Evaluating the burden of bacterial meningitis • Distribution and comparison of *S. pneumoniae* serotypes in healthy and diseased individuals • Comparison of *S. pneumoniae* serotype distribution in individuals with and without pneumonia • Identification of risk factors associated with nasopharyngeal colonization of *S. pneumoniae* • Observation and/or comparison of *S. pneumoniae* serotype distribution, AMR patterns, and genomic changes observed before and after PCV introduction • *S. pneumoniae* carriage, serotype distribution, and AMR patterns in other disease conditions • Identifying pneumococcal serotypes and evaluating the prevalence and risk factors for non-IPD • Effect of antibiotics on invasive and non-invasive pneumococcal isolates • Molecular characterization and serotype distribution of antibiotic-resistant IPD isolates	0 to >65 years	1, 2, 3, 4, 5, 6, 7, 8, 11, 13, 14, 15, 16, 17, 18, 20, 21, 24, 27, 29, 31, 33, 34, 36, 37, 38, 39, 40, 41, 42, 45, 46, 48, 10A, 10A/B, 10B, 10C, 10C/F, 10F, 10F/C, 10F/C/33, 10F/C/33C, 11A, 11A/C/D, 11A/D, 11B, 11B/F, 11C, 11D, 11F, 12A, 12B, 12F, 12F/A/44/46, 12F/A/B/44/46, 13/28, 15A, 15A/F, 15B, 15B/C, 15C, 15F, 15F/A, 16A, 16C, 16F, 17A, 17F, 18A, 18A/B, 18A/B/C,18A/B/C/F, 18A/C/B/D, 18B, 18C,18C/F, 18C/F/B, 18C/F/B/A, 18F, 19A, 19B, 19C, 19F, 19V, 21/39, 22A, 22A/F, 22F, 22F/A, 23A, 23B, 23F, 24A, 24A/B/F, 24B, 24F, 24F/A/B, 25A, 25F, 25F/38, 25F/A/38, 28A, 28F, 32A, 32F, 33A, 33A/F, 33B, 33B/C, 33B/C/D, 33C, 33D, 33F, 33F/A/37, 34/47, 35A, 35A/B/C, 35A/C/42, 35B, 35C, 35D, 35F, 35F/47F, 35F/A/37, 37F/47F, 38/25F/A, 41F, 47F, 6A, 6A/B, 6A/B/C, 6A/B/C/D, 6B, 6B/C, 6C, 6C/D, 6D, 6F, 7A, 7A/5, 7B, 7B/C/40, 7C, 7C/B, 7C/B/40, 7F, 7F/A, 7F/A/B, 9A, 9A/L, 9A/V, 9B, 9B/L, 9L, 9N, 9N/L, 9V, 9V/A	1, 3, 4, 5, 14, 18C, 19A, 19F, 23F, 6A, 6B, 7F, 9V	2, 6, 7, 8, 11, 13, 15, 16, 17, 18, 20, 21, 24, 27, 29, 31, 33, 34, 36, 37, 38, 39, 40, 41, 42, 45, 46, 48, 10A, 10B, 10C, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 15A, 15B, 15C, 15F, 16A, 16C, 16F, 17A, 17F, 18A, 18B, 18F, 19B, 19C, 19V, 22A, 22F, 23A, 23B, 24A, 24B, 24F, 25A, 25F, 28A, 28F, 32A, 32F, 33A, 33B, 33C, 33D, 33F, 35A, 35B, 35C, 35D, 35F, 41F, 47F, 6C, 6D, 6F, 7A, 7B, 7C, 9A, 9B, 9L, 9N	10A/B, 10C/F, 10F/C, 10F/C/33, 10F/C/33C, 11A/C/D, 11A/D, 11B/F, 12F/A/44/46, 12F/A/B/44/46, 13/28, 15A/F, 15B/C, 15F/A, 18A/B, 18A/B/C, 18A/B/C/F, 18A/C/B/D, 18C/F, 18C/F/B, 18C/F/B/A, 21/39, 22A/F, 22F/A, 24A/B/F, 24F/A/B, 25F/38, 25F/A/38, 33A/F, 33B/C, 33B/C/D, 33F/A/37, 34/47, 35A/B/C, 35A/C/42, 35F/47F, 35F/A/37, 37F/47F, 38/25F/A, 6A/B, 6A/B/C, 6A/B/C/D, 6B/C, 6C/D, 7A/5, 7B/C/40, 7C/B, 7C/B/40, 7F/A, 7F/A/B, 9A/L, 9A/V, 9B/L, 9N/L, 9V/A	Afghanistan[39] Bangladesh[40–46] Sri Lanka[47,48] Nepal[49–52]Bhutan[53] Pakistan[54–64] India[17,40,46,64–101]	• There is no data available for Maldives.

[1]Studies included refers to the different types of studies that were carried out in the region and included in the analysis.
[2]Age groups refers to the combined age groups under investigation from all the studies carried out in the region.
[3]Serotypes/Serogroups reported refers to the serotypes/serogroups reported from all the studies included in the analysis.
[4]PCV13 refers to Pfizer's Prevnar 13.
Abbreviations: NVTs: Non-vaccine serotypes; AMR: Antimicrobial resistance; IPD: Invasive pneumococcal disease; Non-IPD: Non-invasive pneumococcal disease; PCR: Polymerase chain reaction; *S. pneumoniae*: *Streptococcus pneumoniae;* PCV: Pneumococcal conjugate vaccine.

Table 2. Characteristics of NVTs observed in LMICs of South Asia from different studies conducted between 2012 and 2024.

	Characteristics					
NVTs	IPD	Non-IPD	Drug resistance[1]	NP carriage	Unspecified (IPD/Non-IPD)[2]	References
2	✓	✓	✓	✓	✓	17,43–45,49,50,52,58,63,64,67,68,70,72,76,78,80,84,100
6				✓	✓	48
7	✓	✓				86
8	✓	✓	✓	✓	✓	41–46,49–52,57–59,62,61,63–67,69–75,77,84,88,89,92,93,99–101
11*		✓			✓	39,86
13	✓	✓	✓	✓	✓	17,43–47,50–54,56,58–63,67,69–71,73–75,77,80,83–85,89,92,94,100
15	✓					49
16	✓			✓		49,71
17	✓					59,69,77
18*	✓			✓	✓	39,42,65,92
20	✓	✓	✓	✓	✓	17,39,41,43–47,50–53,58,61–63,65,67,69–71,74,75,77,80,83,84,89,90,92,94
21	✓		✓	✓	✓	43,44,46,50–52,54,56,58,61–64,67,68,70–73,83,92
24	✓		✓	✓	✓	41,44,52,53,61,69,70,84
27	✓			✓	✓	17,43,46,50,64,66,71,72,74,75,84
29	✓	✓	✓	✓	✓	17,43,45,46,50–52,61,66,69–72,74,80,90,94,100
31	✓	✓	✓	✓	✓	17,43,44,46,50–52,56,58,62–65,67,70–72,75,78,84–86,89,92,94,100,101
33	✓					49,74
34	✓	✓	✓	✓	✓	39,41,43–47,50–54,56,58,60–65,67,70–75,80,83–85,89,93,94,100,101
36	✓		✓	✓	✓	46,50–52,64,70,72,80,84,90,94,100
37	✓			✓	✓	46,50–52,70,71,75
38	✓	✓	✓	✓	✓	17,43,44,46,50–52,61,64,65,69–75,80,84,89,94,100
39	✓	✓	✓	✓	✓	44–46,50–53,61,66,67,69–71,74,80,83,89,100
40	✓		✓	✓	✓	46,50,51,69,72,77,84
41	✓					52
42				✓	✓	46,50,52,80
45	✓	✓	✓	✓	✓	42,43,45,51,61,64,70,72,75,80,84,100
46	✓					67
48	✓			✓	✓	39,46,49–52,70–72,84,90,94
10A	✓	✓	✓	✓	✓	43–46,49–52,61,64,68–75,77,80,83,84,89,90,94,100
10B	✓		✓	✓	✓	46,50,52,61,70,71,93
10C	✓		✓	✓	✓	17,46,69,70,74,75,83,89,93,100
10F*	✓	✓	✓	✓	✓	43–46,50–52,61,64,66,69–74,77,83,84,92
11A	✓	✓	✓	✓	✓	17,43–46,50–52,61,66,69–75,77,78,80,83–85,89,92–94,101
11B				✓		50,51
11C	✓		✓	✓		46,75
11D	✓			✓		51,69,77,80
11F	✓			✓		43,80
12A	✓				✓	42,43,49,50,52,69,73,80,83
12B	✓			✓		46,70,75
12F	✓	✓	✓	✓	✓	39,41,43,44,46,50–52,57,61,64,69,70,72,74,77,83–85,92,101
15A	✓	✓	✓	✓	✓	43–46,49–52,61,64,68–75,77,80,83,84,89,90,94,100
15B	✓	✓	✓	✓	✓	39,41–43,45,46,50–52,64,66,69–75,77,78,80,83,84,89,90,92,93,99,101
15C*	✓	✓	✓	✓	✓	41,45,46,50–52,64,66,71–74,80,83,84,89,90,94
15F	✓			✓	✓	43,46,50,52,61,64,69,70,72,77,78,80,92
16A				✓		46,50
16C				✓		52
16F	✓	✓	✓	✓	✓	43–46,50–54,56,58,60–65,67,70–75,80,83,84,86,89,90,92,93,101
17A	✓			✓		46,50–52,69,73,77,90,92
17F*	✓	✓	✓	✓	✓	17,39,42–44,46,47,50–52,54,56,58,61–67,69–75,80,84,85,89,90,92,93,99–101
18A	✓	✓	✓	✓	✓	41–43,46,50–52,61,64,66,69,70,72,78,80,83,84,88,100
18B	✓	✓	✓	✓		45,46,50,57,64,69–72,84
18F	✓			✓	✓	43,46,50,61,64,69,70,72,77,93
19B*	✓	✓	✓	✓	✓	45,46,50–52,61,64,66,68,70–72,74,75,84,90,93
19C	✓			✓		49,51,70
19V				✓		97
22A	✓		✓	✓	✓	46,50–52,61,66,70,71,74,75,80,90,100
22F	✓	✓	✓	✓	✓	41,43,44,46,50–52,61,65,69,71–73,75,77,80,84,89,90,92,101
23A*	✓		✓	✓	✓	39,43,44,46,50–53,56,58,61–64,66,67,70–75,80,84,89,90,92,100
23B	✓	✓	✓	✓	✓	44,46,50–54,56–63,67,69–71,75,80,83,85,89,90,93
24A	✓		✓	✓		50–52,64,72,89
24B	✓		✓	✓	✓	17,49,51,52,66,69,74,75,77,80,86,89,90,92
24F	✓		✓	✓	✓	17,42,43,46,50,52,64,66,71–74,89,92–94,100
25A	✓			✓	✓	50,64,69,72,80,84
25F	✓		✓	✓	✓	43,51,52,61,70,78,84,100
28A	✓	✓	✓	✓	✓	43,46,50,51,61,69,70,73,84,85
28F	✓	✓	✓	✓	✓	45,46,50–52,64,70,72,75,80,84
32A				✓	✓	17,52
32F				✓		46,51
33A	✓			✓	✓	46,51,64,72,73,80,92,93
33B	✓		✓	✓	✓	43,46,50–52,61,64,69–73,77,80,84–86,93
33C*	✓		✓	✓	✓	41,43,50–52,66,69–71,74,75,96
33D	✓			✓	✓	41,46,50,52,80

(*Continued*)

Table 2. (Continued).

NVTs	Characteristics					References
	IPD	Non-IPD	Drug resistance[1]	NP carriage	Unspecified (IPD/Non-IPD)[2]	
33F	✓	✓	✓	✓	✓	43,44,46,49–52,64–66,69–72,74,77,80,84,100
35A	✓		✓	✓	✓	42,44,46,50–52,61,64,70–72,75,80,83,84,89,93,100
35B*	✓	✓	✓	✓	✓	17,39,41–47,50–54,56,58–65,67,69–73,75,77,80,83,84,86,89,92,93,101
35C		✓		✓	✓	17,46,50–52,73,80,85
35D	✓		✓			89
35F	✓	✓	✓	✓	✓	39,43,44,46,50–52,61,64,68,70,72,73,80,85,90
41F	✓					72
47F	✓					17,66,74
6C	✓	✓	✓	✓	✓	41,43–47,50–53,56–58,62,61,63,64,66,69–75,80,82,84,89,94,100
6D	✓	✓	✓	✓	✓	41,43,45–47,50–52,17,56,58,61–63,80,84
6F				✓		46
7A	✓			✓		50,69,70,74,75
7B	✓	✓	✓	✓	✓	41–43,45,46,50–52,61,70–72,84,89
7C*	✓		✓	✓	✓	44,46,50–52,61,64,65,70,72,84,89,96
9A	✓			✓	✓	46,64,71–73,80,93
9B	✓		✓			70,75
9L	✓	✓	✓	✓		45,46,50–52,61,84
9N	✓	✓	✓	✓	✓	17,50–52,61,66,69–71,74,77,80,88–90,101

[1]Drug resistance refers to resistance to one or more classes of antibiotics.
[2]Unspecified includes cases that have not mentioned whether the pneumococcal infection was invasive or non-invasive in nature.
[3]Serogroups/serotypes marked with *in South Asia were responsible for causing deaths.[39,68,74,96]
[4]Mixed serotypes, as observed in Table 1, have not been included in the analysis because of the inconsistency in how they are named and interpreted across the referenced research articles. This inconsistency limits the ability to accurately characterize mixed serotypes within the study's framework, thus warranting their exclusion to maintain clarity and analytical appropriateness.
Abbreviations: NVTs: Non-vaccine serotypes; IPD: Invasive pneumococcal disease; Non-IPD: Non-invasive pneumococcal disease; NP: Nasopharyngeal.

included serotypes, which were identified as causes of IPD in the U.S.[13] However, after the introduction of PCV7, a change in the epidemiology of pneumococcal diseases was observed, and NVTs (not included in PCV7) emerged as the most prevalent ones, a phenomenon known as 'serotype replacement.[5,112] For example, serotypes 1 and 5, which were not included in PCV7, were responsible for a high burden of illness and deaths in low-income settings.[13] Another example was 19A, a problematic serotype, which exhibited antibiotic resistance.[12,13] This serotype replacement led to the development of PCV10 (Synflorix, GlaxoSmithKline [GSK]) and PCV13 (Prevnar 13, Pfizer), which were introduced in 2009.[4,12] Surveillance data from different countries implementing PCVs in their NIPs has prevented disease not only in vaccinated individuals but also in unvaccinated adults and children through herd immunity.[13] Although PCVs were originally developed for pediatric use, clinical studies conducted in adults have shown their ability to prevent diseases in individuals of all ages through direct protection.[13] A systematic review and meta-analysis conducted to evaluate the impact of PCV10 and PCV13 in reducing the incidence of CAP in children <5 years demonstrated that these vaccines showed a reduction of 17% and 31% in the hospitalization rates for clinically and radiologically confirmed pneumonia, respectively, in children <24 months.[114] In children aged 24–59 months, these vaccines showed a reduction of 9% and 24% in the hospitalization rates for clinically and radiologically confirmed pneumonia, respectively.[114] A systematic review evaluating the impact of PCV10 and PCV13 on all-cause, radiologically confirmed, and severe pneumonia hospitalization rates and pneumonia mortality in children 0–9 years old across several WHO regions demonstrated reductions ranging from 7% to 60% for all-cause pneumonia hospitalization, 8% to 90% for severe pneumonia, 12% to 79% for radiologically confirmed pneumonia, and 45% to 85% for pneumococcal confirmed pneumonia.[115] Pneumonia-related mortality saw a reduction of 10% to 78% across different regions.[115] A study conducted by Bennett et al. evaluated the impact of PCV10/PCV13 on IPD incidence in children <5 years and adults ≥65 years compared to the pre-PCV period.[116] It evaluated 275,582 cases from 47 surveillance sites in 29 countries (primarily HICs [80%]). The study demonstrated that IPD declined by 58% to 79% in children <5 years and by 4% to 29% in adults.[116] The Serum Institute of India (SII) has developed an affordable 10-valent PCV (Pneumosil), which provides protection against serotypes that are responsible for causing serious illness in developing countries.[12] Walvax Biotechnology Co., Ltd. (Walvax) has developed and manufactured a 13-valent PCV (Weuphoria), which has been marketed in China, Morocco, and Thailand.[117]

However, after the introduction of PCV10 and PCV13, the issue of serotype replacement continued, and newer vaccines were required to prevent pneumococcal diseases caused by serotypes 8, 12F, and 22F.[5,118,119] A systematic review of the serotype distribution of *S. pneumoniae* causing IPD in children in countries that have introduced PCV13 revealed that non-PCV13 serotypes contributed to 42.2% of the childhood IPD cases in the post-PCV era.[37] There were differences as per geography, viz., 57.8% in North America, 71.9% in Europe, 45.9% in the Western Pacific, 28.5% in Latin America, and 42.7% in South Africa. The predominant non-PCV13 serotypes were 22F, 12F, 33F, 24F, 15C, 15B, 23B, 10A, and 38.[37]

In light of this grim situation, two new PCVs, viz., PCV15 (VAXNEUVANCE, Merck) and PCV20 (Prevnar 20, Pfizer), have been approved by the United States Food and Drug Administration (USFDA) in 2021.[5,12,120,121] PCV15 is indicated for active immunization for the prevention of invasive disease in individuals 6 weeks of age and older.[122] PCV20 is

approved for the prevention of invasive diseases in individuals 6 weeks of age and older; prevention of otitis media in individuals 6 weeks through 5 years of age; and active immunization for the prevention of pneumonia in individuals 18 years of age and older.[123] Prevnar 20, which was built using Prevnar 13, includes seven additional serotypes that have been associated with antibiotic resistance, heightened disease severity, invasive potential, high case fatality rates, and prevalence in pediatric pneumococcal cases.[124,125] Moreover, these seven serotypes are among the most common responsible for IPD in the pediatric population in the USA.[124,125] Biological E Ltd. has developed a 14-valent PCV, viz., PNEUBEVAX 14, which received approval from the Indian drug regulator, Drug Controller General of India (DCGI), in 2022 for manufacturing and commercialization in India.[126] It offers protection against two new serotypes, 22F and 33F.[126] A 15-valent PCV has been developed by Tergene Biotech Pvt. Ltd. and manufactured at AuroVaccines Pvt. Ltd., which is a wholly owned subsidiary of Aurobindo Pharma Ltd.[127] The Indian drug regulator has granted permission to Tergene in 2022 to manufacture and market the vaccine.[127] In 2024, the USFDA approved CAPVAXIVE (V116), a 21-valent PCV developed by Merck.[128] The vaccine is indicated for active immunization for the prevention of invasive disease and pneumonia in individuals 18 years of age and older.[128] It includes eight unique serotypes responsible for approximately 27% of IPD cases in adults 50 years of age and older and approximately 30% in adults 65 years of age and older, as per the Centre for Disease Control and Prevention (CDC) data.[128]

Investigational PPSVs and PCVs

Panacea Biotech has developed an 11-valent PCV, viz., NuCoVac-11, which is currently in phase 3 trial. The company has also developed a PPSV23, which is in preclinical development.[129] Techinvention Lifecare Pvt. Ltd. has developed a 16-valent PCV that is currently in preclinical studies.[130] GBP410 is a 21-valent PCV that is jointly developed by SK Bioscience and Sanofi. The vaccine has demonstrated immunogenicity and safety in phase II trials and is expected to enter phase 3 trials in H1 of 2024.[131] AFX3772, a 24-valent PCV developed by Affinivax (acquired by GSK), is currently in phase 2 development.[132] This vaccine candidate is based on the highly innovative multiple-antigen presenting system (MAPS) platform technology.[132] A 30-plus-valent pneumococcal candidate vaccine is also in preclinical development.[132] VAX-24, developed by Vaxcyte, is a 24-valent, broad-spectrum, carrier-sparing PCV that will be entering phase 3.[133,134] VAX-31, another vaccine developed by Vaxcyte, is a 31-valent PCV, which is expected to enter phase 1/2 clinical study during the fourth quarter of 2023.[135] VAX-31 and VAX-24 are designed to improve upon the standard-of-care PCVs for both children and adults by providing coverage for serotypes that are responsible for a significant portion of IPD as well as high case-fatality rates, antibiotic resistance, and meningitis.[134] Preclinical immunogenicity evaluation of a 24-valent PCV developed by Merck has been conducted in adult monkeys.[136] Inventprise Inc. has developed a 25-valent PCV that is currently in phase 2 trial.[137] Table 3 highlights the status of PCVs in LMICs of South Asia. Table 4 gives a list of investigational and approved PPSVs and PCVs, along with their composition as well as their clinical/commercial status.

In light of recent findings, it has become increasingly evident that a decline in immunogenicity against shared serotypes has been noted with the adoption of higher-valency PCVs.[155] This observed trend, while pointing toward a potential decrease in immune response, poses uncertainties regarding its clinical implications.[155] While reduced immunogenicity has been observed among higher- vs. lower-valency PCVs, the trend is inconsistent.[155] Different vaccine components, platforms, technologies, and manufacturing processes can affect serotype-specific immunogenicity.[155] Consequently, further exploration through additional research is needed to fully comprehend the impact and effectiveness of these new vaccines.[155]

Exploring various avenues to enhance immunogenicity and overall vaccine efficacy is key in this scenario.[155] Innovative conjugation processes, diverse carriers, strategic use of adjuvants, and advancements in vaccine platforms represent promising approaches that could potentially offset any reduction in immunogenicity.[155] Some of these strategies include choosing appropriate carrier proteins to prevent carrier-induced suppression, such as utilizing single or multiple conserved *S. pneumoniae* proteins or employing enhanced carrier protein (eCRM) to facilitate conjugation reactions outside the primary T cell epitope region.[155] Techniques like preserving the structural integrity of capsular polysaccharides through polysaccharide activation or using specific linker moieties between polysaccharides and proteins are also being explored.[155] Novel vaccine platforms, like MAPS, in vivo bioconjugation, virus-like particle (VLP) technology, and messenger ribonucleic acid (mRNA) technology are being investigated to enhance overall B cell and T cell responses while generating enhanced serotype-specific IgG levels without the need for adjuvants.[155] By striving to maintain or elevate immunogenicity levels and subsequently boost vaccine effectiveness, it's possible to extend the coverage and protection offered by PCVs, especially as their valency increases.[155]

VAX-24 contains eCRM, a proprietary carrier protein with non-native amino acids (para-azidomethyl-L-phenylalanine) that undergo site-specific conjugation to pneumococcal polysaccharides activated with a small-molecule linker (dibenzocyclooctyne).[156] Site-specific conjugation utilizing click chemistry allows consistent exposure of T cell epitopes, reduction in carrier protein to pneumococcal polysaccharide ratio, and augments manufacturing process consistency to improve PCVs by increasing the coverage of serotypes and minimizing carrier suppression.[156] VAX-24 has demonstrated promising results in a phase 1/2 trial by targeting a wide array of pneumococcal serotypes without compromising the immunogenicity.[157]

Despite the widespread use of PCVs in vaccination programs and continuous advancements in serotype coverage, the underlying reasons for decreased antibody responses, particularly in infants and the elderly, remain incompletely understood.[158] Deeper insights into the molecular and cellular mechanisms governing protective antibody responses against *S. pneumoniae* could potentially inform the development of adjuvants that enhance these responses.[158]

Table 3. PCV status in LMICs of South Asia.

Country	Introduced in NIP	Date of introduction	Type of PCV formulation	Dosing schedule[1]	References
Afghanistan	Yes	7th December 2013	Prevnar 13	3+0	138
Bangladesh	Yes	21st March 2015	Synflorix	3+0	
Sri Lanka	No	NA	NA	NA	
Nepal	Yes	19th January 2015	Synflorix	2+1	
Bhutan	Yes	1st January 2019	Prevnar 13	2+1	
Pakistan	Yes	9th October 2012	Prevnar 13	3+0	
India	Yes	13th May 2017	Pneumosil	2+1	

[1]3+0: Three primary doses without a booster; 2+1: Two primary doses with one booster.[139]
Abbreviations: NIP: National immunization program; PCV: Pneumococcal conjugate vaccine.

Table 4. List of investigational and approved PPSVs and PCVs.

Sr. No.	Vaccine/ Brand name	Company	Carrier protein	Serotype composition	Clinical/ Commercial status	WHO prequalification	Reference
1	Pneumovax	Merck	–	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F	Approved commercially	–	140
2	PPSV23	Sinovac Biotech Ltd.	–	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F	Approved commercially	–	140
3	PPSV23	Walvax Biotechnology Co. Ltd.	–	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F	Approved commercially	–	12,141
4	Prevnar	Pfizer	CRM_{197}	4, 6B, 9V, 14, 18C, 19F, and 23F	Approved commercially	–	12,140
5	Synflorix	GSK	Protein D for serotypes 1, 5, 6B, 7F, 9V, 14, 23F, and 4. TT for serotype 18C and DT for serotype 19.	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	Approved commercially	Yes	12,140,142
6	Pneumosil	SII	CRM_{197}	1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F	Approved commercially	Yes	12,140,142
7	Prevnar 13	Pfizer	CRM_{197}	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	Approved commercially	Yes	12,140,142
8	Weuphoria	Walvax Biotechnology Co., Ltd.	TT	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	Approved commercially	–	12, 117, 140
9	PNEUBEVAX 14	Biological E Ltd.	CRM_{197}	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F	Approved commercially	–	126,143
10	VAXNEUVANCE	Merck	CRM_{197}	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F	Approved commercially		12,140
11	PCV15	Tergene Biotech Pvt. Ltd. and AuroVaccines Pvt. Ltd.	CRM_{197}	1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 12F, 14, 18C, 19A, 19F, and 23F	Permission granted by Indian drug regulator to manufacture and market		127,144
12	Prevnar 20	Pfizer	CRM_{197}	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F	Approved commercially		12,140
13	CAPVAXIVE	Merck	CRM_{197}	3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B	Approved commercially		128,145
14	NuCoVac-11	Panacea Biotec	CRM_{197}	1, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	Phase 3		129,146
15	NuVac-23	Panacea Biotec	-	-	Preclinical		129
16	PneumoWin	Techinvention Lifecare Pvt. Ltd.	$rCRM_{197}$	1, 3, 4, 5, 6A, 6B, 7F, 9V, 12F, 14, 15A, 18C, 19A, 19F, 22F, and 23F	Preclinical		130,147
17	GBP410	SK Bioscience and Sanofi	Serotypes 1, 3 and 5 conjugated to TT. Serotypes 4, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F conjugated to CRM_{197}	1, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F	Completed phase 2		131,148
18	AFX3772	GSK	Rhizavidin-fused carrier proteins	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20B, 22F, and 33F	Currently in phase 2 development		132,140,149

(*Continued*)

Table 4. (Continued).

Sr. No.	Vaccine/ Brand name	Company	Carrier protein	Serotype composition	Clinical/ Commercial status	WHO prequalification	Reference
19	VAX-24	Vaxcyte	eCRM	1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23F, and 33F	Will be entering phase 3		133,134,140,150
20	PCV24	Merck	CRM_{197}	1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F	Preclinical development		136
21	PCV25	Inventprise Inc.	CRM_{197}	1, 2, 3, 4, 5, 6B, 6C, 7F, 8, 9N, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 24F, 33F, and 35B	Phase 2		151,152
22	VAX-31	Vaxcyte	eCRM	1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 16F, 17F, 18C, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 31, 33F, and 35B	Expected to enter phase 1/2 clinical trial		135,153,154
23	30-plus valent PCV	GSK	-	-	Preclinical development		132

Abbreviations: WHO: World Health Organization; PPSV: Pneumococcal polysaccharide vaccine; CRM_{197}: Cross-reactive material 197; GSK: GlaxoSmithKline; TT: Tetanus toxoid; DT: Diphtheria toxoid; SII: Serum Institute of India; $rCRM_{197}$: Recombinant cross-reactive material 197; eCRM: Enhanced carrier protein.

Moreover, in alignment with the guidelines set forth by the WHO, the evaluation of noninferiority between higher- and lower-valency PCVs relies on specific criteria related to IgG response rates and IgG geometric mean concentrations (GMCs).[159] Each serotype is individually assessed to determine noninferiority, with the WHO underscoring that meeting the predefined criteria for either IgG response rates or GMCs should suffice for regulatory approval.[159] The correlate of protection for IPD is typically measured by noting the levels of vaccine-induced, serotype-specific IgG, with a protective threshold set at 0.35 µg/ml.[159] In 2008, the WHO reviewed data on PCVs, including effectiveness studies in Canada, the United Kingdom (UK), and the USA.[159] The data indicated variability in IgG concentrations and thresholds, with some suggesting alternative thresholds and the correlation of opsonophagocytic activity (OPA) titers for a few serotypes for vaccine effectiveness.[159]

Drawbacks

Administration of additional pneumococcal vaccines may be required in adults due to waning immunity. For example, the effectiveness of PPSV23 wanes over several years, and high-risk individuals may require revaccination every 5–10 years.[111] As mentioned earlier, serotype replacement has been observed with the implementation of PCVs, where niches occupied earlier by VTs have now been colonized by NVTs.[29,38,160,161] Both PPSVs and PCVs are serotype-based vaccines and therefore elicit a serotype-specific immune response.[162] Geographical differences with respect to serotype distribution have led to reduced vaccine effectiveness when they were implemented in geographies where the serotypes were not covered by the vaccines.[29] PCVs have weak efficacy at mucosal sites, such as for pneumonia and otitis media.[12,38] *S. pneumoniae* undergoes phase variation, wherein the capsule shifts stochastically from high to low expression levels.[12,38] This is a result of anatomical-site-specific selective pressures in the host environment.[12,38] The pathogens present on mucosal surfaces are less encapsulated as compared to those present in the blood, thereby exposing surface adhesins.[12,38] Therefore, the antibodies directed at the capsule are not efficient in opsonophagocytosis at the mucosal level.[12,38] Serotype coverage by PCVs in developed countries is substantially higher compared to developing countries, where pneumococcal diseases are caused by a wider spectrum of serotypes.[162] Vaccine failures have been reported following immunization with PCV10 and PCV13.[162,163] A systematic review published by Oligbu et al. identified serotypes 19B, 6B, and 4 associated with vaccine failure in countries with established PCV programs.[164] PCVs cannot offer protection against the emergence of *S. pneumoniae* strains, which are found among non-typeable isolates.[165] Capsular switching has been observed post the introduction of PCVs.[29] Although PCVs provide protection from infection, but not all serotypes are covered with equal potency.[12] For some serotypes, viz., 1, 3, and 5, the levels of functional antibodies against capsular polysaccharides induced by the vaccines and detected by opsonophagocytic killing are not ideal.[12] PCV manufacturing is an extremely complex and expensive process, making it unaffordable for the developing countries, which can lead to low vaccination coverage.[102,162] One of the glaring examples is the sub-Saharan countries, which still have the highest mortality rates in children <5 years, even after 10 years post-PCV licensure.[102] Increasing the valency of PCV also poses challenges with respect to conjugation.[102] A crucial issue of PCV is the binding of the carrier protein to the capsular polysaccharide to elicit a robust immune response as compared to the capsular polysaccharide alone.[102] Adding additional serotypes to the formulation results in blunting of the immune response to individual serotypes due to carrier suppression.[12] An increase in valency as well as the dosage of the carrier protein in the formulation can lead to immune response interference, both in the vaccine itself and other vaccines that are administered previously, jointly, or subsequently.[102,166] These interferences result in an imbalance in several arms of the immune response and hence require readjustment in each new vaccine formulation.[102]

Alternative approaches

In light of the above-mentioned drawbacks, novel vaccines based on a non-serotype-independent approach targeting

Table 5. Properties of different *S. pneumoniae* proteins investigated as vaccine candidates.

Protein		Properties	References
Ply		(1) Highly conserved (2) Immune evasion (3) Triggers inflammation (4) Cell death	9,29,170,171
CBPs	PspA	(1) Highly conserved (2) Immune evasion (3) Pneumococcal adhesion (4) Binds lactoferrin for critical iron uptake	29,165,172
	PspC	(1) Highly immunogenic (2) Highly conserved (3) Immune evasion (4) Pneumococcal adhesion	9,29,173
	PcpA	(1) Pneumococcal adhesion (2) Biofilm formation	165,174
	LytA	(1) Immunogenic (2) Highly conserved (3) Facilitates the release of cytotoxin Ply (4) Inhibits complement	165,175
	LytB	(1) Biofilm formation (2) Attachment to host epithelial cells (3) Immune evasion (4) Well-conserved	165
	CbpG	(1) Pneumococcal adhesion (2) Secreted form can cleave host ECM	165
	CbpM	(1) Binds fibronectin	165
PsaA		(1) Oxidative stress resistance (2) Bacterial adhesion (3) Manganese and zinc acquisition (4) Highly conserved	9,176
PHTs	PhtA	(1) Highly conserved (2) Immune system evasion (3) Bacterial dissemination in the lungs	177,178
	PhtB	(1) Conserved protein (2) Immunogenic	179
	PhtD	(1) Highly conserved (2) Adherence to nasopharyngeal and epithelial cell lines (3) Inhibits complement (4) Zinc acquisition	165,179–183
	PhtE	(1) Highly conserved protein (2) Adherence to nasopharyngeal and epithelial cell lines (3) Inhibits complement	165,179,180
PiuA and PiaA		(1) Iron uptake (2) Highly conserved (3) Highly immunogenic	9
PsrP		(1) Biofilm formation (2) Lung adhesion and infection	165
Ef-Tu		(1) Highly conserved protein (2) Enhances pathogenicity through complement inhibition and degradation of ECM	184

Abbreviations: Ply: Pneumolysin; CBPs: Choline-binding proteins; PspA: Pneumococcal surface protein A; PspC: Pneumococcal surface protein C; PcpA: Pneumococcal choline binding protein A; LytA: N-acetylmuramoyl-L-alanine amidase; LytB: N-acetylglucosaminidase; CbpG: Choline-binding protein G; ECM: Extracellular matrix; CbpM: Choline-binding protein M; PsaA: Pneumococcal surface antigen A; PHTs: Pneumococcal histidine triad proteins; PhtA: Pneumococcal histidine triad protein A; PhtB: Pneumococcal histidine triad protein B; PhtD: Pneumococcal histidine triad protein D; PhtE: Pneumococcal histidine triad protein E; PiuA: Pneumococcal iron uptake A; PiaA: Pneumococcal iron acquisition A; PsrP: Pneumococcal serine-rich repeat protein; Ef-Tu: Elongation factor Tu.

conserved antigens are warranted and have been extensively investigated.[10,38,102,112,140,162,165] An ideal pneumococcal vaccine with broader coverage, the ability to induce mucosal and systemic immunity, and the ability to prevent primary intranasal colonization and invasive disease is highly desirable.[12] Several protein-based vaccines and whole-cell (live-attenuated and inactivated) vaccines are being evaluated in preclinical and clinical studies.[10] Protein vaccines targeting the highly conserved virulence proteins can confer broad serotype coverage.[29] Different types of protein vaccines that are investigated include recombinant proteins (individual or in combination), fusion or hybrid proteins, nanoparticle-packaged fusion or hybrid proteins, recombinant protein-boosted PCVs, and capsular polysaccharide-conjugated recombinant protein carrier.[162,167] Protein-based vaccines offer several advantages, such as the production of opsonophagocytic antibodies, providing respiratory tract protection, preventing invasion of the pathogen in different organs, neutralizing pneumolysin cytotoxicity, cross-protection against additional childhood pathogens, and blunting complications arising out of disseminated bacterial infections.[38,162] It can also serve as a cheaper option for children in developing countries, provide coverage for a wide range of serotypes responsible for IPD, and offer an alternative option to prevent recurrent infections.[140] With respect to manufacturing, there are less hindrances associated with structural differences and variations, a drawback that is commonly observed with conjugate vaccines.[140] On the flip side, protein antigens have numerous limitations. They contain non-repeating conformational epitopes for antibody binding as compared to capsular polysaccharides that have repeating and conformationally less-restricted antigenic

Table 6. Results of protein-based vaccines investigated in animal models.

Protein		Results	References
Ply		• Intramuscular immunization with recombinant PlyD1 protected mice against lethal intranasal challenge with pneumococci and lung injury mediated through Ply challenge. Protection was associated with PlyD1-specific IgG titers and *in vitro* neutralization titers.	185
		• CaP-ΔA146PLY[1] nanoparticles induced efficient humoral and cellular immune responses in mice that protected them from both pneumonia and sepsis.	186
		• Intramuscular immunization with dPly protected mice against lethal intranasal challenge with Ply. Also, intranasal immunization in mice inhibited nasopharyngeal colonization after intranasal challenge with homologous or heterologous pneumococcal strain.	187
		• Mice immunized subcutaneously with ΔA146Ply-SP0148[2] elicited high levels of anti-ΔA146Ply and anti-SP0148 IgG antibodies. Mice had a high survival rate when challenged with a lethal dose of *S. pneumoniae*.	188
		• Subcutaneous immunization of mice with ΔA146 Ply[3] generated high titers of anti-Ply IgGs and protected them from intraperitoneal challenge with TIGR4 *S. pneumoniae*.	189
		• Intramuscular immunization of mice with PLY-D[4] conferred significant protection post-intranasal challenge with different *S. pneumoniae* serotypes and strains.	190
		• Vaccination with a monovalent formulation of recombinant PlyD1 led to bacterial reductions in both infant and adult mice after a lethal-dose intranasal challenge with serotype 6A.	191
CBPs	CbpG	• Intramuscular immunization of mice with recombinant CbpG provided significant protection against colonization and substantial protection against systemic infection by wild-type TIGR4 cells.	192
		• Subcutaneous immunization with recombinant CbpG protected mice against intraperitoneal challenge with serotype 19F pneumococcal strain.	193
	CbpM	• Subcutaneous immunization with recombinant CbpM protected mice against intraperitoneal challenge with serotype 19F pneumococcal strain.	193
	LytA	• Purified recombinant LytA administered intranasally elicited IgG and IgA antibodies in mice. These mice also showed significantly higher survival rates and lower bacterial carriage in response to *S. pneumoniae* infection.	194
	LytB	• Intraperitoneal immunization with LytB enhanced *S. pneumoniae* recognition by complement components C1q and C3b, demonstrating that anti-LytB antibodies activated the classical pathway. Vaccination with LytB protected mice against pneumococcal sepsis and invasive pneumonia caused by clinical isolates of serotypes 3 or 23F.	195
	PspC/ CbpA	• Intranasal immunization with PspC using cholera toxin subunit B as an adjuvant protected mice against intranasal challenge with pneumolysin mutant of D39 or serotype 6B strain BG7322.	196
		• Intraperitoneal immunization of PspC protected mice from intraperitoneal challenge with virulent capsular type 2 pneumococcal strain D39.	197
		• Intranasal immunization with PspC induced high levels of anti-PspC antibodies in mice. The hyperimmune sera significantly inhibited the adhesion of *S. pneumoniae* to A549 cells.	198
		• Nasal immunization with *L. casei* expressing PspC primed the immune system of mice that prompted faster immune responses, resulting in a decrease in pneumococcal colonization.	199
		• Subcutaneous immunization with purified PspC protected mice against sepsis. The protection was mediated by antibodies cross-reactive with PspA.	200
		• Subcutaneous or intranasal immunization of PspC vaccines did not protect mice against an invasive intranasal challenge with pneumococcal strain ATCC 6303.	201
	PcpA	• Vaccination with a monovalent formulation of recombinant PcpA led to bacterial reductions in both infant and adult mice after a lethal-dose intranasal challenge with serotype 6A.	191
	PspA	• Antibodies generated post-immunization with recombinant family 1 PspA in humans in a phase 1 trial offered passive protection in mice against a pneumococcal challenge from serotypes 3, 6A, or 6B.	202
		• Transcutaneous immunization with PspA + cholera toxin B induced antigen-specific mucosal and systemic immune responses in mice. It significantly reduced the CFU numbers in nasal washes and passages when they were challenged with *S. pneumoniae* strain EF3030 via the nasal route.	203
		• Intranasal immunization with a nanogel-based PspA nasal vaccine provided protective immunity in mice against intranasal lethal challenge with *S. pneumoniae* Xen10. It reduced the bacterial colonization and invasion and induced high levels of PspA-specific IgG and nasal and bronchial IgA responses.	204
		• Mucosal immunization with various nanoparticle PspA formulations protected mice against lethal intranasal challenge *S. pneumoniae* strain ATCC6303.	205
		• Intranasal immunization with PspA delivered by BLPs enhanced PspA-specific antibody responses in mice and provided significant protection against intranasal challenge with pneumococci of two different clades of both homologous and heterologous PspA families.	206
		• Intranasal immunization with PspA-BLP vaccine[5] conferred protection in mice against fatal intranasal challenge with both PspA family 1 and 2 pneumococcal strains regardless of serotype.	207
		• Intramuscular immunization with polymer particles entrapping PspA elicited robust IgG responses both in mice and in rats. Antigen load in microparticles correlated with the antibody titers.	208
		• Mucosal immunization with NP/NCMP PspA4Pro[6] provided partial protection against intranasal lethal pneumococcal challenge with a serotype 3 strain expressing PspA from clade 5.	209
		• Intranasal vaccination with PspA and cationic liposomes conferred protective immunity against lethal *S. pneumoniae* inhalation and improved the survival rate of infected mice. It also induced the production of PspA-specific IgA and IgG by both mucosal and systemic compartments as well as elicited PspA-specific Th17 responses.	210
		• Subcutaneous immunization of mice with PspA-based polyanhydride nanovaccine had significantly higher survival rates upon intravenous challenge with *S. pneumoniae* strain A66.1 clad 2 of family 1.	211
		• Nasal vaccination with PspA-nanogel[7] effectively induced PspA-specific serum IgG with protective activity and mucosal SIgA antibody responses in cynomolgus macaques.	212
		• Mice vaccinated orally with a RASV strain delivering PspA decreased pulmonary inflammation. It provided effective protection against secondary pneumococcal pneumonia that was established in mice by intratracheal challenge with influenza PR8 and *S. pneumoniae* WU2 strains.	213
		• Subcutaneous immunization of mice with fusion proteins containing family 1 and family 2 PspA fragments increased complement deposition and provided protection against pneumococcal infection with strains bearing PspA fragments from both families.	214

(*Continued*)

Table 6. (Continued).

Protein		Results	References
		• Nasal vaccination of macaques with cCHP-trivalent PspA generated PspA-specific IgGs that protected from pneumococcal intratracheal challenge through inhibition of lung inflammation and a reduction in the numbers of bacteria in the lungs.	215
		• Subcutaneous immunization with PspA3+2[8] provided significant protection against intranasal challenge by five pneumococcal strains with different clades in mice.	216
		• Nasal immunization of mice with a combination of PspA5 and wP[9] or wP_{low}[10] conferred protection against intranasal respiratory lethal challenge with *S. pneumoniae* ATCC6303 or A66.1 strain. Both PspA5-wP and PspA5-wP_{low} vaccines induced high levels of systemic and mucosal antibodies against PspA5.	217
PsaA		• Subcutaneous immunization of mice with PsaA using either complete Freund's or TiterMax adjuvants significantly protected against challenge from type 3 pneumococcal strain WU2.	218
		• Intranasal or oral administration of full-length PsaA in mice demonstrated significant reduction in colonization of nasopharyngeal tissues after intranasal challenge with *S. pneumoniae* strains compared to controls.	219
		• Intraperitoneal immunization with PsaA admixed with BlyS exhibited only modest elevations in PsaA-specific responses. Mice sera obtained post-immunization exhibited high titers of IgG1, IgG2a, IgG2b, and IgG3, but no IgA.	220
		• Intranasal immunization with chitosan-PsaA[11] generated mucosal and systemic immune responses in mice, and fewer pneumococci were recovered from the immunized mice following intranasal challenge with ATCC 6303 (serotype 3).	221
		• Intranasal immunization with chitosan-PsaA generated mucosal and systemic immune responses in mice. Immunized mice had increased protection against AOM following middle ear challenge with pneumococcus serotype 14 and improved survival following intraperitoneal challenge with pneumococcus serotype 3 or serotype 14.	222
PHTs	PhtA	• Subcutaneous immunization with full-length PhtA generated antibodies that protected mice against lethal sepsis challenge with serotype 6A or 6B.	178
		• Immunization with either N-terminal or C-terminal portion of PhtA also protected mice against serotype 6B challenge.	
		• N-terminal half of PhtA induced a protective response against serotype 6A challenge.	
	PhtB	• Subcutaneous immunization with full-length PhtB generated high levels of antibody titers and protected mice against challenge with serotype 6B.	178
	PhtD	• Subcutaneous immunization with recombinant PhtD induced antibodies that protected mice against sepsis challenge with serotype 6A and 6B and highly virulent capsular type 4 strain or with the capsular type 3 strain WU2.	178
		• Subcutaneous immunization of PhtD and its C-terminal fragment provided protection against pneumococcal sepsis in mice.	223
		• Mice immunized intraperitoneally with PhtD and its C-terminal with OMVs and alum as adjuvants survived after intraperitoneal challenge with *S. pneumoniae* ATCC6303.	224
		• Vaccination with a monovalent formulation of recombinant PhtD led to bacterial reductions in both infant and adult mice after a lethal-dose intranasal challenge with serotype 6A.	191
		• Intranasal administration of PhtD in mice conferred protection against pneumococcal colonization through robust serum antibodies and CD4 Th1-biased immune memory.	225
	PhtE	• Intranasal administration of PhtE in mice conferred protection against pneumococcal colonization through robust serum antibodies and CD4 Th1-biased immune memory.	225
		• Subcutaneous immunization of mice with recombinant PhtE elicits protective immunity against experimental sepsis and pneumonia.	226
PsrP		• Antibodies directed against SRR1 and BR regions of recombinant PsrP neutralized bacterial adhesion to lung cells *in vitro*.	227
		• Passive immunization of mice with PsrP antiserum conferred protection against pneumococcal challenge.	
Ef-Tu		• Subcutaneous immunization with recombinant EF-Tu induced the production of inflammatory cytokines and IgG1 and IgG2a antibodies in mice.	184
		• Significantly and non-specifically protected mice against lethal intraperitoneal challenge with *S. pneumoniae* serotypes 2 and 15A.	
Pneumococcal proteins explored as carrier proteins			
PLD[12]		• Mice immunized subcutaneously with 19F polysaccharide conjugated with PLD as a carrier protein elicited high antibody titers against the polysaccharide and the carrier protein. Immunized mice effectively cleared the bacteria and had a significantly better survival rate when they were challenged intraperitoneally with type 19F pneumococci.	228
PLD		• Subcutaneous immunization of mice with both monovalent and tetravalent conjugate formulations (serotypes 6B, 14, 19F, and 23F) conjugated to PLD as a carrier protein generated high levels of polysaccharide-specific IgGs that demonstrated opsonophagocytic activity for serotypes tested, viz., 6B, 14, 19F, and 23F.	229
Ply		• Intraperitoneal immunization of 18C polysaccharide conjugated to recombinant Ply conferred significant protection in mice challenged with type 18C pneumococci.	230
PsaA		• Intraperitoneal immunization with Hib polysaccharide vaccine conjugated with recombinant PsaA protein carrier in mice generated anti-PsaA and anti-Hib immune responses. It was able to offer effective protection against AOM caused by pneumococcus.	231
Proteins explored in combination			
PhtD-dPly		• Intranasal immunization with PhtD-dPly vaccine protected rhesus macaques from mortality induced by *S. pneumoniae* challenge.	232
PlyD6[13], PspA, PsaA, PiuA, RrgB, RrgA, Hsp 60, and Hsp 70		• Intramuscular vaccination of rabbits with a multiantigen vaccine comprising PlyD6, PspA, PsaA, PiuA, RrgB, RrgA, Hsp 60, and Hsp 70 demonstrated the killing of vaccine strain TIGR4 in an opsonophagocytic killing assay and heterologous strains 6B, 19F, and 15B.	233
Ply, PspC, and PspA		• In the intraperitoneal infection sepsis model, mice immunized intraperitoneally or subcutaneously with H70+YLN[14] provided significant protection against challenge with three different strains (serotypes 1, 2, and 6A).	234
PspA and PsaA		• Intranasal immunization with a combination of PspA and PsaA offered the best protection against nasopharyngeal carriage.	235
PsaA and PspA		• Subcutaneous immunization of mice with a vaccine containing the fusion protein PsaA-PspA23 and a single protein, PspA4, significantly increased anti-PspA IgG levels. Mice challenged intranasally with *S. pneumoniae* from PspA clades 1 to 5 were protected as demonstrated by a decrease in the bacterial load in the lungs and blood along with an increase in survival rates.	236

(*Continued*)

Table 6. (Continued).

Protein	Results	References
PspA and PdT	• Subcutaneous immunization with rPspA-FL-PdT[15] and rPspA-RL-PdT[16] protected mice against intranasal challenge with *S. pneumoniae* strain A66.1.	237
CbpA and Pneumolysoid	• Passive and active immunization with CbpA peptide–L460D fusion protein[17] protected mice from pneumococcal carriage, otitis media, pneumonia, bacteremia, meningitis, and meningococcal sepsis.	238
PdB, PspA, and PspC	• Intraperitoneal immunization of mice with a combination of PdB, PspA, and PspC offered the best protection after they were challenged intraperitoneally with virulent type 2 and 6A.	239
PcpA, PhtD, and PlyD1	• Immunization with trivalent PPrV containing PcpA, PhtD, and PlyD1 conferred protection in infant mice from lethal pneumonia challenge using serotypes 6A and 3.	240
	• Intramuscular vaccination with trivalent PPrV containing PcpA, PhtD, and PlyD1 enhanced the serum and lung antibody levels to the three components, reduced *S. pneumoniae* lethality, enhanced the clearance of the pathogen via phagocytosis, and reduced lung inflammation and tissue damage.	241
	• Intramuscular immunization with trivalent PPrV containing PcpA, PhtD, and PlyD1 protected mice against AOM caused by *S. pneumoniae*. It reduced the bacterial burden and cytokine inflammatory response in middle ears during AOM induced by *S. pneumoniae*.	242
	• Immunization with PPrV comprising PhtD, PcpA, and PlyD1 induced anti-PhtD and anti-PcpA antibodies in mice that protected against *S. pneumoniae* through complement- and macrophage-dependent opsonophagocytosis.	243
PsaA and PspA	• Subcutaneous immunization of mice with PsaA-PspA fusion protein reduced *S. pneumoniae* levels in the blood and lungs after intranasal infection. It also protected mice against a fatal challenge with pneumococcal strains expressing different PspAs irrespective of the challenge route.	244
PcsB, StkP, PsaA, and PspA	• Subcutaneous immunization of mice with a quadrivalent vaccine formulation containing PcsB, StkP, PsaA, and PspA with adjuvant significantly reduced bacteremia and lung infection when challenged intranasally with *S. pneumoniae* serotype 1.	245
PiuA and PiaA	• Two booster vaccinations consisting of recombinant PiuA and PiaA administered intraperitoneally induced stronger antibody responses (majorly IgG1) in mice than a single or no booster vaccinations.	246
	• Intraperitoneal immunization of mice with purified recombinant PiuA and PiaA proteins elicited antibody responses. It also provided a high degree of protection against intraperitoneal challenge with *S. pneumoniae*.	247
	• Intranasal vaccination of mice with PiuA and PiaA generated specific antibody responses in serum and respiratory secretions and protected against intranasal challenge with *S. pneumoniae*.	248

[1]CaP-ΔA146PLY: Calcium phosphate binding domains fused with attenuated pneumolysin mutant, viz., ΔA146PLY.
[2]ΔA146Ply-SP0148: Fusion protein composed of noncytotoxic mutant of Ply, viz., ΔA146Ply and conserved lipoprotein with high immunogenicity produced by *S. pneumoniae*, viz., SP0148.
[3]ΔA146 Ply: Ply mutant with one single-amino acid deletion.
[4]PLY-D: Genetic toxoid constructed with two amino acid changes to attenuate PLY toxicity.
[5]PspA-BLP vaccine: PspA proteins from two different families, PspA2 from family 1 and PspA4 from family 2, and formulated with a BLP adjuvant also acting as a carrier.
[6]NP/NCMP PspA4Pro: Poly(glycerol adipate-co-ω-pentadecalactone) polymeric nanoparticles adsorbed with PspA from clade 4 within L-leucine microcarriers.
[7]PspA-nanogel: cCHP nanogel containing PspA.
[8]PspA3+2: Recombinant PspA protein comprising PspA families 1 and 2.
[9]wP: *B. pertussis* vaccine.
[10]wP_{low}: Vaccine containing low levels of *B. pertussis* LPS.
[11]Chitosan-PsaA: Chitosan-DNA nanoparticles expressing PsaA.
[12]PLD: Genetic derivative of Ply.
[13]PlyD6: Nontoxic Ply.
[14]H70+YLN: L460D [Ply toxoid with the L460D substitution] fused with protective peptide epitopes from PspC + PspA proline-rich region and SM1 region.
[15]rPspA-FL-PdT: Proteins joined by flexible linker.
[16]rPspA-RL-PdT: Proteins joined by rigid helix-forming linker.
[17]CbpA peptide–L460D fusion protein: Biologically active peptides derived from CbpA of pneumococcus genetically fused to L460D pneumolysoid.
Abbreviations: Ply: Pneumolysin; PlyD1/dPly/PdT: Detoxified pneumolysin; *S. pneumoniae*: *Streptococcus pneumoniae*; IgG: Immunoglobulin G; CBPs: Choline-binding proteins; CbpG: Choline-binding protein G; CbpM: Choline-binding protein M; LytA: N-acetylmuramoyl-L-alanine amidase; LytB: N-acetylglucosaminidase; PspC/CbpA: Pneumococcal surface protein C/Choline-binding protein A; *L. casei*: *Lactobacillus casei*; PspA: Pneumococcal surface protein A; PcpA: Pneumococcal choline binding protein A; CFU: Colony-forming unit; IgA: Immunoglobulin A; BLPs: Bacterium-like particles; SIgA: Secretory immunoglobulin A; RASV: Recombinant attenuated Salmonella vaccine; cCHP: Cationic cholesteryl pullulan; *B. pertussis*: *Bordetella pertussis*; LPS: Lipopolysaccharide; PsaA: Pneumococcal surface antigen A; BlyS: B lymphocyte stimulator; IgG1: Immunoglobulin G1; IgG2a: Immunoglobulin G2a; IgG2b: Immunoglobulin G2b; IgG3: Immunoglobulin G3; AOM: Acute otitis media; PHTs: Pneumococcal histidine triad proteins; PhtA: Pneumococcal histidine triad protein A; PhtB: Pneumococcal histidine triad protein B; PhtD: Pneumococcal histidine triad protein D; OMVs: Outer membrane vesicles; PhtE: Pneumococcal histidine triad protein E; PsrP: Pneumococcal serine-rich repeat protein; SRR1: Short serine-rich repeat region; BR: Basic region; Ef-Tu: Elongation factor Tu; PLD: Pneumolysoid; HiB: *Haemophilus influenzae* type b; PiuA: Pneumococcal iron uptake A; Hsp 60: Heat shock protein 60; Hsp 70: Heat shock protein 70;PdB: Pneumolysin toxoid; PPrV: Pneumococcal protein vaccine; PcsB: Putative murine hydrolase; StkP: Serine/threonine kinase protein; PiaA: Pneumococcal iron acquisition A.

determinants.[140] This poses challenges to mounting a protective antibody-mediated immune response as well as explains the difficulty in developing protein-based vaccines.[140] Also, they may not be present in all clinical isolates and may be poorly conserved due to significant sequence heterogeneity.[140] Another drawback of protein antigens is their accessibility to opsonic antibodies.[140] WCVs present a wide range of antigens in their native form and can confer broader protection against *S. pneumoniae*.[29,102] These vaccines can serve as an economical alternative to PCVs in developing countries because of their low manufacturing costs.[29,102] WCVs can be developed from killed or live-attenuated whole-cell or by using genetically modified strains of pneumococcus for ensuring safety and retaining immunogenicity.[9] Inactivated WCVs offer the advantage of carrying several types of antigens, which are common to all serotypes.[10] These vaccines are relatively safe as the organism is completely inactivated.[10] Live-attenuated vaccines enhance humoral and mucosal immune responses after a single-dose, as compared to inactivated ones.[168] Other merits and demerits of these vaccine technologies are described in detail by Kumraj et al.[169] Table 5 highlights the properties of *S. pneumoniae* proteins that are investigated as vaccine candidates. Tables 6 and 7

Table 7. Results of WCVs investigated in animal models.

Sr. No.	Vaccine candidate	Results	References
Inactivated WCVs			
1.	*S. pneumoniae* strain RX1mutated by deletingLytA and killed using ethanol	• Intranasal administration using cholera toxin as an adjuvant conferred protection against nasopharyngeal colonization by serotype 6B in mice as well as conferred protection against illness and death in rats with serotype 3 strains. • In murine models, intranasal administration significantly decreased nasopharyngeal and middle ear colonization by serotypes 6B, 14, and 23F.	249
2.	RM200 (Rx1E PdT Δ*lytA*): Constructed by replacing the entire LytA gene with a kanamycin resistance gene in strain RX1E and inactivated using beta-propiolactone	• Intramuscular immunization in mice offered strong protection against nasopharyngeal colonization with serotype 6B and activated IL-17A priming.	250,251
3.	SPY1: Developed from strain D39 and killed using ethanol	• Intranasal immunization with killed SPY1 using cholera toxin as an adjuvant elicited effective protection against colonization with pneumococcal strains 19F and 4 as well as lethal infection with pneumococcal serotypes 2, 3, 14, and 6B.	252
Live-attenuated WCVs			
1.	*S. pneumoniae* D39 attenuated by removing pep27 gene	• Intranasal immunization in mice exhibited high levels of IgG and serotype-independent protection against lethal intranasal challenge.	253
2.	Δpep27ΔcomD: Constructed by deleting comD gene	• Immunization in mice significantly increased survival time after heterologous challenge and diminished colonization levels independent of serotype.	254
3.	TIGR4Δ*lgt*: Constructed by removing Lgt gene in the encapsulated pneumococcal strain TIGR4	• Colonized mouse nasopharynx long enough to induce strong mucosal IgA and IgG2b-dominant systemic antibody responses, exhibiting cross-reactivity to heterologous pneumococcal serotypes. • Intranasal immunization in mice demonstrated serotype-independent protection against pneumococcal challenge.	168
4.	cpsE-endA double mutant strain: Constructed by knocking out cpsE and endA genes in *S. pneumoniae* D39	• Intranasal immunization in mice showed the highest survival rate and longest survival time after a lethal dose intranasal challenge with wild-type *S. pneumoniae* D39 infection compared to the single-gene knockout strains.	255
5.	Δcps/piaA and Δcps/proABC: Strains containing cps locus deletions along with *S. pneumoniae* virulence factors PsaA or proABC	• Previous colonization with these strains in mice protected them against septicemic pneumonia but could not prevent recolonization with the wild-type strain.	256

Abbreviations: WCVs: Whole-cell vaccines; LytA: N-acetylmuramoyl-L-alanine amidase; IL-17A: Interleukin-17A; IgG: Immunoglobulin G; Lgt: Prolipoprotein diacylglyceryl transferase; IgA: Immunoglobulin A; IgG2b: Immunoglobulin G2b; PsaA: Pneumococcal surface antigen A.

Table 8. Results of protein-based vaccines and WCVs (inactivated and live-attenuated) evaluated in clinical trials.

Proteins	Phase	Identifier	Status	Results	References
Protein-based candidates in clinical trials					
PlyD1[1]	1	NCT01444352	Completed	• Vaccine was immunogenic and safe. • Anti-PlyD1 antibodies produced were shown to be functional in an *in vitro* assay by neutralizing wild-type Ply activity.	257
PnuBioVax (PlyD6[2] + PspA + PsaA + PiuA + RrgB + RrgA + Hsp60 + Hsp70)	1	NCT02572635	Completed	• The vaccine was safe and immunogenic.	233,258
dPly-PhtD ± PHiD-CV[3]	2	NCT00985751	Completed	• The vaccine formulations were safe and immunogenic.	259
PhtD	1	NCT01444001	Completed	• The vaccine was safe and immunogenic at various doses evaluated.	260
PhtD, PhtD + PcpA	1	NCT01444339	Completed	• The vaccine candidates were immunogenic and had promising safety profiles.	261
PcpA + PhtD + PlyD1	1	U1111–1117–7316	Completed	• The vaccine was safe and immunogenic.	262
PcpA + PhtD + PlyD1	1	NCT01446926	Completed	NA	263
PhtD	1	NCT01767402	Completed	• The formulations had an acceptable reactogenicity profile, without safety concerns. • Vaccination with PhtD elicited both CD4 T cell and memory B cell responses in adults.	264
dPly, PhtD-dPly ± PHiD-CV	1	NCT00707798[4]	Completed	• Vaccine formulations were well-tolerated and immunogenic when given as standalone proteins or combined with PhiD-CV conjugates.	265
PhtD-dPly ± PCV 8	1	NCT00756067	Completed	• Vaccine formulations containing free or conjugated PhtD and dPly had acceptable reactogenicity and safety profiles.	266
PhtD-dPly + PhiD	2	NA	Completed	• The vaccine was well-tolerated and immunogenic.	267

(*Continued*)

Table 8. (Continued).

Proteins	Phase	Identifier	Status	Results	References
PhtD-dPly + PHiD	2	NCT01262872	Completed	• PhtD-dPly + PHiD had no impact on pneumococcal nasopharyngeal carriage. • dPly and PhtD proteins did not alter the immune response to PHiD-CV antigens. • PhtD-dPly + PHiD did not alter the immunogenicity of co-administered routine vaccines.	268,269
PhtD- dPly + PCV13[5]	2b	NCT01545375	Completed	• The dPly-PhtD vaccine was immunogenic and well-tolerated.	270
dPLY+PsaA +24CPS[6]	1	NCT04525599	Completed	• The vaccine had an acceptable safety and tolerability profile. • Immune responses were elicited (IgG concentrations and OPA titers) against 13 common and 10 of the 11 unique *S. pneumoniae* serotypes.	271
dPLY+PsaA +24CPS	1/2	NCT03803202	Completed	• The vaccine was immunogenic, well-tolerated, and had a safety profile comparable to PCV13.	272
PspA	1	NCT01033409	Completed	NA	273,274
PsaA + StkP + PcsB	1	NCT00873431	Completed	• The vaccine was safe and immunogenic. • It induced protective antibodies against all three proteins.	275,276
SP_2108 + SP_0148 + SP_1912 (GEN-004)	1	NCT01995617	Completed	• The vaccine was safe and immunogenic. • Rise in antigen- specific IgG response was observed.	263,277
SP_2108 + SP_0148 + SP_1912 (GEN-004)	2	NCT02116998	Completed	• Reduced colonization rate by 22–25%.	263,277
WCVs in clinical trials					
Inactivated					
SPWCV developed from strain RM200 (RX1E PdT ΔlytA) using alum as an adjuvant	1	NCT01537185	Completed	• The vaccine was safe, well-tolerated, and elicited a significant rise in IgG responses to PspA and Ply. • An increase in T cell cytokine responses, including IL-17A, was also observed.	278
SPWCV developed from strain RM200 (RX1E PdT ΔlytA) using alum as an adjuvant	1/2	NCT02097472	Completed	NA	29,279,280
SPWCV developed from strain RM200 (RX1E PdT ΔlytA) using alum as an adjuvant	1/2	NCT02543892	Completed	NA	281

[1]PlyD1: Detoxified form of Ply.
[2]PlyD6: Non-toxic Ply.
[3]PHiD-CV: 10-valent pneumococcal non-typeable *H. influenzae* protein D conjugate vaccine, viz., Synflorix (GSK).
[4]Two groups primed with a formulation containing dPly and PhtD (10 or 30 µg each) continued to the follow-up phase II study (NCT00896064), in which they received a booster dose at 5–9 months after primary vaccination. The study has been completed.[282]
[5]PCV13 refers to Pfizer's Prevnar 13.
[6]dPLY+PsaA +24CPS refers to AFX3772.
Abbreviations: Ply: Pneumolysin; PspA: Pneumococcal surface protein A; PsaA: Pneumococcal surface antigen A; PiuA: Pneumococcal iron uptake A; Hsp 60: Heat shock protein 60; Hsp 70: Heat shock protein 70; dPly: Pneumolysin toxoid; PhtD: Pneumococcal histidine triad protein D; PcpA: Pneumococcal choline binding protein A; CPS: Capsular polysaccharides; IgG: Immunoglobulin G; OPA: Opsonophagocytic activity; *S. pneumoniae*: *Streptococcus pneumoniae*; StkP: Serine/threonine kinase protein; PcsB: Putative murine hydrolase; WCVs: Whole-cell vaccines; SPWCV: *S. pneumoniae* whole-cell vaccine; IL-17A: Interleukin-17A; *H. influenzae*: *Haemophilus influenzae*; GSK: GlaxoSmithKline.

highlight the results of protein-based vaccines and WCVs (inactivated and live-attenuated) investigated in suitable animal models, respectively. Table 8 highlights the results of protein-based vaccines and WCVs (inactivated and live-attenuated) evaluated in clinical trials.

From Tables 6–8, it is evident that there are numerous *S. pneumoniae* proteins, such as pneumolysin (Ply), pneumococcal surface protein A (PspA), pneumococcal surface protein C (PspC), pneumococcal histidine triad protein D (PhtD), pneumococcal surface antigen A (PsaA), etc. that are investigated as vaccine candidates either alone or in combination with other proteins using suitable adjuvants and delivery systems. Some of these proteins have also been explored as carrier proteins to conjugate vaccines. Many of these candidates have shown promising results in animal studies, while some have demonstrated their safety and efficacy in clinical trials. Similarly, many WCVs (inactivated and live-attenuated) have shown promising results in animal studies and clinical trials. However, further studies are warranted to demonstrate the efficacy and safety of these protein vaccines and WCVs.

Some of the vaccine technologies, such as mRNA vaccines, deoxyribonucleic acid (DNA) vaccines, non-replicating viral vaccines, etc., grabbed the limelight during the coronavirus disease 2019 (COVID-19) pandemic. There exists a possibility that the next generation of pneumococcal vaccines may be developed using such technologies.[102]

Recommendations for future vaccine design and development for LMICs of South Asia

(1) LMICs should have a robust surveillance system to monitor the pneumococcal serotype prevalence and distribution, the emergence of NVTs, the burden of IPD, and the impact of PCVs. This will give a better and in-depth understanding of the evolving epidemiology of *S. pneumoniae*, aid in formulating and

Table 9. Plausible serotypes that can be incorporated in the existing PCV formulations.

Region	*Plausible serotypes
South Asia	2, 8, 13, 20, 29, 31, 34, 38, 39, 45, 10A, 10F, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 18B, 19B, 22F, 23B, 28A, 28F, 33F, 35B, 35F, 6C, 6D, 7B, 9 L, 9N

1) *These serotypes have been implicated in IPD, non-IPD, and drug resistance as shown in Table 2.

Abbreviations: IPD: Invasive pneumococcal disease; Non-IPD: Non-invasive pneumococcal disease.

implementing vaccination policies, and guide the development of next-generation pneumococcal vaccines.

(2) These countries should have access to high-end and quality diagnostics to understand the AMR pattern of *S. pneumoniae*. Antibiotic stewardship programs and national AMR plans should be religiously implemented. Data from the AMR pattern can play a decisive role in selecting the appropriate serotypes for PCV development.

(3) Pharmaceutical/Biotech companies should customize or tailor PCVs as per the region-specific prevalence and disease-causing potential of pneumococcal serotypes based on robust surveillance data as well as taking into consideration the pros and cons of adding additional serotypes. For example, companies can develop or modify the existing PCV formulations and incorporate serotypes as shown in Table 9.

(4) Serotype replacement due to PCVs and regional differences in the dominant serotypes warrant the inclusion of additional serotypes in the existing vaccines. Adding a new serotype will increase the complexity and the cost. This in turn can affect affordability and accessibility in countries with high pneumococcal disease burden and lack of robust healthcare infrastructure. To mitigate this risk, a non-serotype-based approach, such as a protein-based vaccine, a live-attenuated vaccine, or an inactivated vaccine, would be an ideal one. Such vaccines target the highly conserved proteins across all *S. pneumoniae* serotypes and can provide broader protection as compared to the existing PCVs. However, large, robust studies in different geographies are warranted to demonstrate its efficacy and safety in clinical trials as well as the real-world effectiveness of these vaccine candidates.

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Notes on contributor

Syed Ahmed is the director and chief executive officer of TechInvention Lifecare Private Limited, an innovation-driven biotech company focused on vaccines, diagnostics, and biotherapeutics for infectious diseases. He is also the board member and vice president of Emerging Biopharmaceutical Manufacturers Network (EBPMN), a not-for-profit pan global association supporting access and manufacturing of biopharmaceuticals across low- and middle-income countries (LMICs). Syed is also the co-founder of another not-for-profit organization in its inception stage, namely Association for Veterinary Vaccine Manufacturers (AVVM), with a focus on enabling access and equity of veterinary vaccines in LMICs. Syed is the co-inventor and has 15+ patents filed in the field of discovery and development of immunobiologicals. He's also the corresponding author of four manuscripts in the arena of vaccines and biotherapeutics published in global journals of repute. He's also leading quite a few 'One Health' initiatives and focused on interventions in the domain of infectious diseases that can impact climate change and sustainability.

Author contributions

Conceptualization, P.D., S.S., K.S., and S.A.; writing – original draft preparation, P.D., S.S., K.S., V.K., A.B., S.D., P.S. S.A.; writing – review and editing, P.D., S.S., D.S., and S.A. All authors have read and agreed to the published version of the manuscript.

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