Review

Development and Clinical Application of Pneumococcal Vaccines

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Review

Development and Clinical Application of Pneumococcal Vaccines

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Abstract

Streptococcus pneumoniae remains a leading global cause of morbidity and mortality, particularly affecting young children and older adults. While vaccination against pneumococcus has markedly reduced the disease burden worldwide, challenges such as serotype replacement, antibiotic resistance, and limited vaccine uptake persist. To address these issues, this review summarizes the mechanisms of vaccine-induced immunity, the development of diverse vaccine platforms—including polysaccharide, conjugate, and protein-based vaccines—as well as recent innovations such as mRNA and mucosal vaccines. Clinical and epidemiological data are integrated to evaluate the effectiveness of current strategies and the growing requirement for personalized, region-specific, and cost-effective vaccination approaches. We further highlight the ongoing challenges, including vaccine design optimization, low coverage rates in vulnerable populations, and market competition, emphasizing the critical need for enhanced surveillance and policy support to advance global pneumococcal disease prevention efforts.

Keywords: pneumococcal vaccines; vaccine development; clinical application; immunity; global health

1. Introduction

Pneumococcal vaccines represent a cornerstone strategy for reducing the global disease burden caused by *Streptococcus pneumoniae (S. pneumoniae)*. By activating the immune response of host, pneumococcal vaccines have demonstrated significant preventive efficacy across diverse populations and offer a critical intervention for improving survival, particularly among high-risk individuals[1-3]. Advancements in pneumococcal conjugate vaccine (PCV), pneumococcal polysaccharide vaccine (PPSV), and other techniques (such as recombinant antigen design and mucosal delivery platform) have significantly expanded the serotype coverage and enhanced immunogenicity[4-6]. Furthermore, strategies such as co-administration of PPSV23 with PCV, alongside process optimizations, have improved cost-effectiveness, thereby providing critical support for global implementation[7]. Nevertheless, there are still persistent barriers to global implementation, including serotype replacement, suboptimal vaccination coverage, and the absence of personalized vaccination regimens[8-10]. This review provides a summary of pneumococcal vaccine development by synthesizing recent insights from immunological studies, clinical trials, and epidemiological research. Specifically, we elucidate the underlying immune mechanisms, highlight key translational challenges, and evaluate innovative platforms shaping the next generation vaccine design, while underscoring

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the importance of sustained serotype surveillance and tailored immunization strategies for effective pneumococcal disease control.

1.1. Burden of Pneumococcal Diseases

Pneumococcal diseases, particularly community-acquired pneumonia, remains a significant global health issue in people of all ages, posing a serious threat to children younger than 5 and adults aged 65 and above[11]. Despite increasing PCV coverage worldwide, a high disease burden still exists in low - and middle - income countries (LMICs). Recent global epidemiological surveillance estimated that pneumococcal pneumonia caused approximately 826,000 deaths in 2019 (including 225,000 children under five), with the majority concentrated in these settings[12]. In LMICs with insufficient and unevenly distributed medical resources, the severity of pneumonia becomes particularly pronounced, where its high mortality rates and complication risks show significant correlations with urban-rural and regional resource disparities[13,14].

1.2. Streptococcus Pneumoniae

S. pneumonia is a Gram-positive diplococcus[15] and facultative anaerobe[16] that primarily colonizes the human upper respiratory tract and propagates through respiratory droplets[17]. The bacteria's pathogenicity is attributed to its polysaccharide capsule[18], and to date, more than 100 serotypes have been discovered[19]. Pneumococcal serotypes demonstrate marked heterogeneity concerning invasive potential, geographic distribution, and antibiotic resistance[20-22]. For example, serotypes 19F and 23F predominate in invasive pneumococcal diseases[8], while 6A/B are more frequently found in carriers[23]. These serotype-specific pathogenicity facilitate *S. pneumoniae* as a leading global cause of community-acquired pneumonia, with the capacity to induce severe conditions including meningitis and sepsis across all age groups[24]. Regional investigations have showed distinct epidemiological patterns. In Iran, serotypes 23F and 19F are the main causes of invasive pneumococcal diseases, accounting for 16.4% and 15.2% respectively[23]. In China, the predominant carriage strains in children are 19F, 19A, and 23F, and the PCV13 vaccine coverage is about 74.8%[8]. Antimicrobial resistance is emerging globally, mediated through multiple mechanisms, including altering the structure and affinity of penicillin-binding proteins[26], altering cell wall permeability[27], and utilizing efflux pumps[28]. Resistance rates reach alarming levels in some regions, with Tunisia reporting 75.3% penicillin resistance and 71.4% erythromycin resistance [25], while Ethiopia found that 17.5% penicillin resistance and 33.3% multi-drug resistance[29]. These findings collectively underscore the dual challenges posed by serotype diversity and antibiotic resistance, and emphasize the critical need for effective vaccination strategies to mitigate these issues.

1.3. Rationale for Vaccination

Vaccination represents the most cost-effective strategy for pneumococcal disease prevention[30,31]. PPSV and PCV exert protective effects by inducing serotype-specific antibodies, which reduce the risk of pathogen colonization and invasive infections[32]. The pneumonia vaccination program has rolled out phased immunization plans for infants, adolescents, and adults. For instance, the inclusion of PCV in childhood immunization schedules has significantly reduced pneumonia-related mortality[33]. As evidenced by numerous studies, PCV introduction has led to a reduction in pneumonia-related mortality, with impacts ranging from 10% to 78%[34]. Moreover, antibiotic resistance is a significant issue in treating pneumococcal disease[35]. Using PCV vaccines can lower antibiotic use and slow antibiotic resistance development. This is achieved by reducing pneumococcal infection rates and cutting back on unnecessary antibiotic use.

Vaccines currently in use have shown effectiveness in lowering the *S. pneumoniae* infection rate and alleviating post-infection symptoms. Pneumococcal vaccines, particularly the PCV13, have been widely used globally to reduce the burden of pneumococcal disease[36]. PCV13 is an extension of the PCV7, providing protection against six additional serotypes that are closely associated with invasive pneumococcal disease (IPD)[37]. Global evidence demonstrates the remarkable effectiveness of PCV13 vaccination: in United States, PCV13 vaccination successfully prevented 216,303 pneumonia hospitalizations caused by vaccine-covered serotypes from 2019 to 2021 [38]; in Mongolia, after

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implementation in 2016, vaccine-serotype carriage rates decreased by 44% with a concurrent significant reduction in pneumonia cases[39]. Among Portuguese children aged 0-6, PCV13 introduction led to a significant drop in vaccine-covered serotype carriage (from 47.6% to 10.7%) via herd immunity. However, unvaccinated kids and those aged 4-6 still had 2.5 - fold and 2.9 - fold higher risks of carrying PCV13 serotypes[40]. As PCV13 coverage expands, serotypes not included in the vaccine have become major causes of invasive pneumococcal disease, either by the rise of new resistant strains like the 24F type common in France, or by previously existing strains changing their serotype, as seen in the transition from 23F to 35B/D in some bacterial populations[41,42]. Geographically, large-scale PCV13 immunization in both Portugal and Mongolia has induced serotype replacement phenomena[39,40]. These evolving epidemiological trends pose new challenges for pneumococcal disease prevention and control.

2. Pneumococcal Vaccines: Production and Immunity

The development and production of pneumococcal vaccines have significantly advanced over the years, with highly diverse processes that can be broadly classified into three main categories based on the antigenic components and preparation methodology: polysaccharide vaccines, conjugate vaccines, and protein-based vaccines. Each category has its unique characteristics, advantages, and limitations, and necessitating thorough understanding of their production processes and mechanisms to optimize vaccine strategies in global public health initiatives.

2.1. Polysaccharide Vaccines

Polysaccharide vaccines, such as the PPSV23, are manufactured through extraction and purification of capsular polysaccharides from *S. pneumoniae*[43]. As a pivotal virulence factor, capsular polysaccharides can elicit specific immune responses; however, their inability to effectively activate T cells constrains immunogenicity, with these vaccines directly stimulating B cells to produce IgM antibodies that lack immune memory and confer protection lasting approximately 5-10 years[44,45]. Current polysaccharide vaccines typically target 23 serotypes (e.g., 1, 3, 19A), encompassing most pneumococcal strains associated with pneumonia[46]. These vaccines are effective in preventing pneumococcal pneumonia among elderly individuals with chronic respiratory conditions and may also help lower the risk of cardiovascular events in older adults[1,47]. Their primary target populations include high-risk individuals aged ≥2 years, particularly the elderly (≥65 years)[1], those with chronic conditions (diabetes[48], chronic obstructive pulmonary disease[3]), and immunocompromised patients[49], while infants under 2 years remain non-responsive due to immature immune systems. Despite this limitation, their broad serotype coverage, cost-effectiveness, and well-established manufacturing processes have secured their position as a cornerstone in aging populations immunization programs endorsed by authoritative bodies and incorporated into multiple national immunization programs[50-52].

Recent studies on the PPSV23 highlight progress in three key domains. Prior evidence confirms the vaccine's efficacy in preventing IPD and pneumococcal pneumonia caused by vaccine-covered serotypes[53]. A longitudinal study conducted in Denmark involving individuals over 65 years of age showed that PPSV23 offered protection against overall IPD and IPD linked to specific serotypes, with effectiveness rates of 32% for all-type IPD and 41% for serotypes included in PPSV23[50]. Nonetheless, its protective effect tends to diminish among adults over 75 years old, people with specific underlying health conditions, and those who received the vaccine more than five years prior to disease onset[53]. Furthermore, a phase III clinical trial evaluated the safety, immunogenicity, and tolerability of PCV21 in comparison with PPSV23 among adults aged 50 and above. The study found that the PCV21 was non-inferior to PPSV23 for all 12 common serotypes and superior for nine serotypes unique to the PCV[54]. This suggests that newer conjugate vaccines may offer broader protection while maintaining a similar safety profile to PPSV23. While PPSV23 remains a cornerstone in pneumococcal disease prevention, its limitations—such as limited serotype coverage, waning immunity in older adults, and short-lived immunity—highlight the need for next-generation vaccines with broader serotype coverage and enhanced immunogenicity, particularly for high-risk populations.

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2.2. Conjugate Vaccines

To address the shortcomings of polysaccharide-based vaccines, conjugate vaccines were engineered by covalently attaching pneumococcal polysaccharide antigens to protein carriers such as cross reactive material 197 (CRM197), a non-toxic derivative of diphtheria toxin[55,56]. This conjugation process—involving polysaccharide activation, protein modification, and purification—enhances T-cell activation, resulting in stronger immune responses and immunological memory, especially in infants[55]. For instance, PCV13 conjugates polysaccharides from 13 serotypes to CRM197, providing robust protection[57]. Following conjugation, the vaccines undergo additional purification and formulation steps to produce the final product, ensuring that the polysaccharide antigens can trigger a strong immune response upon administration.

In 2000, the U.S. Food and Drug Administration approved the PCV7, which targeted serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, marking it as the first pneumococcal vaccine specifically designed for use in infants and young children[58]. Its introduction led to a notable decline in IPD rates. Nevertheless, the broad use of PCV7 was followed by a rise in infections caused by non-vaccine serotypes, prompting the development of vaccines with expanded serotype coverage[59-61]. In response, the PCV13 was approved in 2010, building on PCV7 by adding six more clinically significant serotypes: 1, 3, 5, 6A, 7F, and 19A[62]. With broader serotype coverage, more flexible immunization schedules, and cost-effectiveness in large-scale production, PCV13 demonstrated superior public health utility, becoming the preferred choice in most countries[63-66]. Currently, the 15-valent vaccine (PCV15, also known as V114) covering additional serotypes 22F and 33F has completed clinical trials in healthy infants, showing comparable or superior immunogenicity to PCV13[67]. Meanwhile, to address the evolving epidemiology of pneumococcal disease, the development of higher-valent PCVs such as the PCV20 and PCV21 formulations aims to provide broader serotype coverage[4,68]. In addition, the U.S. Centers for Disease Control and Prevention updated its recommendations in 2024 for the use of PCV21 in adults, extending its application to all individuals aged 18 and older, including those with chronic diseases or immunocompromised conditions[69].

With successive iterations, PCVs have shown improved immunogenicity and safety profiles, leading to their adoption in many national immunization programs worldwide. Despite the successful implementation of PCVs, several challenges have emerged—most notably, the growing issue of serotype replacement, where non-vaccine serotypes become more prevalent following widespread vaccine use. For instance, after New Zealand switched from PCV13 to PCV10 in 2017, the incidence of IPD caused by non-vaccine serotype 19A surged, accompanied by a sharp rise in penicillin resistance rates (from 39% to 84%)[70]. In Taiwan, although the implementation of PCV13 led to a decline in the overall incidence of IPD, non-vaccine serotypes such as 15A and 23A continued to rise in prevalence, highlighting the importance of ongoing monitoring of serotype patterns and antimicrobial resistance trends[71]. Furthermore, widespread PCV adoption remains constrained by multiple factors: the spread of non-vaccine serotypes may undermine long-term prevention efficacy, necessitating the development of broad-spectrum or rapidly adaptable vaccine technologies[71,72]; elevated manufacturing costs hinder accessibility in low- and middle-income nations, indicating the need for cost-reduction strategies such as technology transfer or global cooperation[73]; and complex multi-dose regimens complicate management, suggesting that simplified formulations or combination vaccines could improve compliance[74]. A comparison of the key characteristics of the major pneumococcal vaccines discussed (PPSV23, PCV13, PCV20, and PCV21) is provided in Table 1 and Table 2.

Table 1. Valency, Serotype Coverage, and Target Groups of Key Pneumococcal Vaccines

Vaccine Type	Valency	Target Serotypes	Mechanism	Key Target Populations
PPSV23	23	2, 3, 4, 5...[A]	T-cell-independent	Adults ≥65 years

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PCV13	13	PCV7[B] + 1, 2, 5, 6A, 7F, 19A	T-cell-dependent	Infants, high-risk
PCV20	20	PCV13 + 8, 10A, 11A, 12F, 15B, 22F, 33F	T-cell-dependent	Adults, children
PCV21	21	PCV20 + 23B	T-cell-dependent	Adults (≥18 years)

[A] PPSV23 includes 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F
[B] PCV7 includes 4, 6B, 9V, 14, 18C, 19F, and 23F.

Table 2. Timeline, Advantages, and Challenges of Key Pneumococcal Vaccines.

Vaccine Type	Year	Use Status	Advantages	Challenges
PPSV23	1983	In use	Low cost; Established manufacturing; WHO-recommended for elderly	Low immunogenicity; No immune memory; Less effective in young children and immunocompromised individuals
Vaccine Type	**Year**	**Use Status**	**Advantages**	**Challenges**
PCV10/PCV13	2009-2010	In use	Broader coverage than PCV7	Waning efficacy in individuals over 75 years old; Serotype replacement; Multi-dose regimens
PCV15/PCV20	2021-2022	Recently introduced	Broader serotype coverage; Single dose sufficient for some populations	Higher cost compared to PPSV23
PCV21	2024	Recently introduced	Potential for expanded protection against pneumococcal disease	Still under evaluation; Regulatory approval pending; Limited data available on long-term efficacy and safety

2.3. Emerging Vaccine Technologies

Recent advances in pneumococcal vaccine development encompass a range of innovative approaches:

- Novel antigen combinations, such as vaccines incorporating pneumococcal surface protein A (PspA) and detoxified pneumolysin, have demonstrated favorable safety and immunogenicity profiles in adults, particularly at intermediate doses[75]. Newly identified antigens like LafB have shown the ability to induce broad Th17-mediated mucosal immunity, remaining effective even under influenza-induced immunosuppression[5].
- Technological innovations have also played a crucial role. For instance, protein glycan coupling technology has enabled the development of recombinant conjugate vaccines that show protective efficacy comparable to Prevnar-13 at reduced production costs[76]. Innovative immunization strategies, including the use of attenuated influenza vectors carrying chimeric pneumococcal proteins, have enhanced protection against viral-bacterial co-infections[77].
- Mucosal vaccine platforms, such as probiotic surface expression systems[6] and Lactobacillus-based intranasal sprays[78], represent another major advancement, capable of eliciting both protective mucosal and systemic immune responses without requiring adjuvants. In parallel, significant progress has been made in addressing manufacturing challenges throughimproved antigen production techniques and rational vaccine design.

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- Efforts to improve antigen production and apply rational vaccine design have addressed key manufacturing challenges. Optimized processes for producing critical components like PspA4Pro[79] and recombinant Ply have enhanced vaccine feasibility[80], while computational immunoinformatics has facilitated the development of epitope-based candidates, such as the PspA (1–5c+p)[81] vaccine, which induces strong cross-reactive and functional antibody responses.
- Genetic engineering and proteomics have opened new avenues for vaccine development. Recombinant protein vaccines, such as protein-based pneumococcal vaccines, utilize conserved antigens like PspA to achieve broader serotype coverage while simplifying manufacturing and ensuring product consistency. Phase I clinical trials have demonstrated favorable safety profiles and robust antibody responses in both adults and the elderly[75].

These colletive breakthroughs—from enhanced traditional methods to cutting-edge platforms—are paving the way for the next generation of pneumococcal vaccines that promise greater efficacy, broader protection, and improved accessibility to address pressing public health needs.

3. Challenges

3.1. Serotype Epidemiology and Vaccine Design Optimization

The epidemiology of *S.pneumoniae* serotypes presents significant challenges for vaccine development, with significant geographic variability requiring region-specific surveillance to inform effective vaccine strategies. Post-vaccination serotype replacement has been well documented, as evidenced by the emergence of non-vaccine serotypes 6C, 15B, 16F, and 15A following PCV13 introduction in China[8], and the predominance of serotypes 35B, 11A, and 3 in adult community-acquired pneumococcal pneumonia cases in Goto City, Japan [82].

These findings underscore the importance of tailoring vaccine formulations to local epidemiological patterns. While next-generation vaccines like PCV20 offer broader serotype coverage, their actual protective efficacy must be evaluated within the context of regional serotype prevalence. For instance, in the Japanese study, PCV20 covered approximately 43.7% of the identified serotypes, suggesting that even higher-valency vaccines may not fully address the regional serotype landscape[9]. Continuous molecular epidemiological surveillance, including whole-genome sequencing of isolates, is crucial for monitoring serotype dynamics and the emergence of new clones. A genomic analysis of invasive pneumococcal isolates collected in Norway over a 40-year period revealed that different lineages responded variably to vaccination, emphasizing the importance of whole-genome sequencing in guiding timely vaccine revisions and public health strategies[83].

3.2. Clinical Challenges and Strategic Responses

The clinical management of pneumococcal infections faces mounting challenges due to escalating antimicrobial resistance, making vaccination an increasingly vital preventive strategy. Recent studies have documented an increase in resistance among pediatric *S. pneumoniae* isolates, particularly to penicillin, third-generation cephalosporins, fluoroquinolones, and carbapenems. This pattern is primarily driven by the emergence of non-PCV13 serotypes following vaccine introduction[84]. Vaccination remains a critical strategy in mitigating the spread of resistant strains; however, the effectiveness of current vaccines depends on their coverage of prevalent serotypes. In South and Southeast Asia, serotypes such as 6A, 6B, 14, 15B/15C, 19F, and 23F are commonly associated with disease and are included in existing vaccines[20]. Nevertheless, the dynamic nature of serotype distribution necessitates continuous evaluation to ensure that vaccine formulations remain relevant.

Despite vaccine availability, suboptimal immunization coverage persists as a major barrier to disease control, especially among high-risk groups like the elderly. In Germany, data indicate that only 26% PCV23 coverage among older adults with IPD , with decreasing effectiveness over time[10]. Similar challenges exist in China, where vaccination rates among the elderly remain low due to barriers such as limited awareness, concerns about vaccine efficacy, and financial constraints, even in with subsidized programs[85]. To address these barriers and improve vaccination coverage, a range of evidence-based interventions have been identified as effective. A scoping review encompassing over 2.4 million participants identified strategies such as periodic health examinations, electronic

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medical record reminders, inpatient vaccination protocols, and multimodal educational initiatives as effective in increasing vaccination rates among older adults[86].

3.3. Market Competition and the Role of Policy

The pneumococcal vaccine market is experiencing dynamic shifts globally, driven by increased competition and evolving policy frameworks aimed at enhancing vaccine accessibility. China's vaccine landscape exemplifies this shift, where domestic manufacturers such as Walvax and CanSino have successfully challenged the market dominance of imported PCV13, resulting in substantial price reductions that enhance affordability[87]. In Europe, countries such as the Netherlands have conducted cost-effectiveness analyses to inform vaccination strategies for older adults. These studies have considered the indirect benefits of childhood vaccination programs and the emergence of higher-valency vaccines like PCV20 and PCV21. Findings suggest that incorporating these vaccines into adult immunization schedules could be cost-effective, particularly when accounting for serotype replacement and herd immunity dynamics[88]. These examples underscore the critical role of policy support in shaping the pneumococcal vaccine market. Strategic decisions regarding vaccine procurement, pricing negotiations, and inclusion in public health programs are essential to enhance vaccine uptake and reduce the burden of pneumococcal diseases across diverse populations.

4. Conclusions

Pneumococcal vaccines have revolutionized infectious disease prevention, achieving remarkable reductions in *S. pneumoniae*-related morbidity and mortality. While the development of higher-valency conjugate vaccines and innovative platforms like mucosal and mRNA-based vaccines marks a new frontier, persistent issues such as serotype replacement, vaccine hesitancy, and inequitable access limit their full potential. To maximize public health benefits, future multifaceted strategies should focus on region-specific vaccine design, improved surveillance of serotype dynamics and antimicrobial resistance, and policies that promote widespread and equitable vaccine uptake. Integration of real-world data, artificial intelligence-driven vaccine design, and global cooperation will be essential to overcoming the next wave of pneumococcal challenges.

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Abbreviations

The following abbreviations are used in this manuscript:

CRM197	Cross reactive material 197
LMICs	Low - and middle - income countries
S. pneumoniae	*Streptococcus pneumoniae*
PPSV	Pneumococcal polysaccharide vaccine
PCV	Pneumococcal conjugate vaccine
IPD	Invasive pneumococcal disease
PspA	Pneumococcal surface protein A

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