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MINI-REVIEW

Pneumococcal vaccines in China

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ABSTRACT

Invasive pneumococcal disease (IPD) is a serious global public health problem and the leading cause of morbidity and mortality in children and adults in China. Thus, developing and administering pneumococcal vaccines are important for disease prevention. The PPV23 and PCV13 vaccines are available in the Chinese market and are primarily produced by domestic manufacturers. The potential risk of increased IPD caused by non-vaccine serotypes should be considered. Here, we review the current status of IPD, pneumococcal vaccines, and their quality control in China. We also address the challenges and future directions for making progress in controlling IPD, emphasizing the need for further evaluation of the disease burden and monitoring the effectiveness of vaccination efforts.

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Introduction

Streptococcus pneumoniae (*Spn*), also known as pneumococcus, causes pneumonia, meningitis, bacteremia, and other serious diseases.[1] *Spn* transmission primarily occurs directly through respiratory droplets or infections caused by bacterial colonization of the respiratory tract, and *Spn* infections are a serious public health problem.[1–3] Approximately 14.5 million serious cases of pneumococcal diseases occur annually, and approximately 290,000 infants aged <5 years die of *Spn* infections worldwide each year, mainly in developing and underdeveloped countries with poor medical and health resources.[1,3] In addition, *Spn* infection is an important cause of morbidity and mortality among infants and older adults in China.[4] Due to the large Chinese population, it ranks second among the 10 countries with the highest number of invasive pneumococcal disease (IPD) cases in children aged under 5 years, and the burden of IPD is extremely heavy.[1,5] Vaccination is generally accepted as the most economical and effective means of preventing *Spn* infection. Currently, 23-valent pneumococcal polysaccharide vaccines (PPVs) (covering serotypes 1–5, 6B, 7F, 8, 9 N, 9 V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), as well as pneumococcal polysaccharide conjugate vaccines (PCVs), such as PCV7 (covering serotypes 4, 6B, 9 V, 14, 18C, 19F, and 23F), PCV10 (covering PCV7 serotypes plus serotypes 1, 5, and 7F), and PCV13 (covering PCV10 serotypes plus serotypes 3, 6A, and 19A) are used in the immunization programs of many countries. In its classification of vaccine-preventable diseases, the World Health Organization (WHO) classifies IPD as a high-priority disease.[6] To further understand the potential risks of increased IPD associated with non-vaccine serotypes, examine the development of current pneumococcal vaccines and identify areas that require strengthening in the prevention and control of IPD, in this review we briefly describe the epidemiological characteristics of IPD and summarize the development and quality control assessments of various pneumococcal vaccines in China. New challenges for enhancing the control of IPD are discussed.

Pneumococcal disease in China

As *Spn* infections are not included from the list of notifiable infectious diseases in China, the epidemiological characteristics of IPD and the distribution of serotypes have not been systematically investigated at the national level. The available epidemiological data are primarily derived from specific provinces or regions, and comprehensive national data on IPD remain limited.[5] In 2015, over 210,000 severe cases of IPD were estimated to have occurred in children under 5 years of age in China, resulting in approximately 7,000 deaths. Among those cases, approximately 200,000 were attributed to *Spn*, which had a fatality rate of 1% and a mortality rate of 6.43 per 100,000 people.[5,7]

A retrospective study of the clinical information from 5,960 hospitalized children in Chongqing, China between 2009 and 2016 revealed *Spn* culture-positive rates of 13.9% in children under 12 months, 20.4% in those aged 13–36 months, and 18.9% in the 37–59 month age groups.[8] Furthermore, 8.79% of the bacterial isolates (4,011/45,631) were *Spn*, making it the third most frequent bacterial agent in a 7-year hospital-based investigation in Beijing from 2015 to 2021. Further investigation demonstrated that most *Spn* strains were isolated from patients aged under 5 years (77.1%).[9] Taken together, these results indicate that *Spn* is one of the most commonly

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detected pathogens in hospitals, especially in children <5 years old, highlighting the importance of prevention for at-risk population groups. Furthermore, a prospective study was performed with 3,052 samples from elder patients from 2010 to 2012 in Hainan, of which 7.4% (225/3052) were identified as *Spn* strains. Pathogens were identified in 324/610 adult patients (53.1%) with community-acquired pneumonia at 12 centers in seven Chinese cities in 1 year, of which 10.3% (63) were *Spn*,[10] providing further evidence that *Spn* is a major cause of pneumonia in the older population.

Capsular polysaccharides of *Spn* play a crucial role in IPD pathogenesis, and at least 100 serotypes have been identified based on genetic differences in the capsule synthesis locus.[2] Serotypes 14, 19A, and 19F were the most common serotypes in children <5 years old in China with pneumonia or meningitis, where PCV7 represented approximately 79.5% of the serotypes.[11] Overall, 300 *Spn* isolates from 13 provinces in China were collected between 2010 and 2015, and the most common serotypes were 23F, 19A, 19F, 3, and 14. The coverage rates were 42.3% for PCV7, 45.3% for PCV10, 73.3% for PCV13, and 79.3% for PPV23.[12] Recent findings from a study of *Spn* isolated from patients of all ages in southwest China from 2018 to 2022 showed that the most common pneumococcal serotypes were 19F (17.87%), 19A (11.41%), 3 (8.75%), 23F (6.46%), and 6A (5.70%). The coverage rates for PCV10, PCV13, PCV15, PCV20, and PCV24 were 36.12, 61.98, 61.98, 63.12, and 64.26%, respectively.[13] Consistent with these findings, a recent systematic review and meta-analysis reported that the top 10 serotypes with the highest proportion during 2019–2023 were serogroups 19F, 6A, 19A, 6A/B, 23F, 14, 6B, 15A, 3, and 9 V. Notably, the non-PCV13 and non-PSV23 vaccine serotype 15A ranked eighth, accounting for 5.3% of isolates during this period.[14] The high coverage rates of PCV13 and PPV23 suggest that vaccine-targeted serotypes continue to predominate in the Chinese population; however, there is an increasing trend in the prevalence of non-vaccine serotypes.

According to antimicrobial-resistance surveillance reports published in 2021, the resistance rate of *Spn* to erythromycin was expected to reach 96.4% in 2021. Furthermore, most (79.85%) *Spn* isolates were reported to be resistant to tetracycline, and high resistance is presumably associated with the heavy use of tetracycline in agriculture and livestock in China.[13] The results of many studies have demonstrated that PPVs and PCVs can control the prevalence of pneumococcal diseases, which reduces transmission, thereby alleviating its resistance to antibiotics and reducing the emergence of drug-resistant strains.[5,12] Therefore, vaccination is one of the most effective means for reducing *Spn* drug resistance.

Pneumococcal vaccines in China

The earliest recorded use of pneumococcal vaccines dates back to 1911[15,16] when Wright invented a whole-bacteria vaccine to prevent *Spn* infections (1). The currently available pneumococcal vaccines are PPV and PCV, which are primarily based on capsular polysaccharides from the most common serotypes that cause IPD. Over the past two decades, increased investment from the Chinese government and multinational pharmaceutical companies has created a stronger environment for vaccine research and development in China.[17] Furthermore, a new administration law was enacted in China in 2019,[18] introducing more robust regulations for new drug approval and registration. These regulatory changes aim to improve transparency and efficiency, potentially paving the way for the development of more innovative vaccines in the long term.[17,19]

Polysaccharide vaccines

Research on pneumococcal polysaccharide vaccines began in 1945, and two forms of hexavalent PPV were developed in 1947.[16] The rapid development of antibiotics limited the development and application of *Spn* vaccines. With the emergence of drug-resistant strains, vaccine development has returned to the focus.[16] In 1978, a 14-valent PPV was licensed for use in the USA,[20] followed by the approval of PPV23 (which covers 90% of resistant strains in the USA and 85–90% of the prevalent strains) in 1983.[21]

In China, vaccine strains representing 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9 V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) were used to produce PPV23. In 2007, PPV23 was successfully developed by the Chengdu Institute of Biological Products (Figure 1). The seropositive conversion rate was 86.4% after immunization with the PPV23 test vaccine. Only two subjects (0.23%) showed moderate erythema, and most of the systemic reactions were mild.[22] In 2012 and 2013, a phase III trial was conducted by other Chinese manufacturers to evaluate the immunogenicity and safety of PPV23.[23] A greater fold-increase in the geometric mean of anti-pneumococcal antibodies was observed in the treatment group, with the 2-fold increase rate for the 23 serotypes ranging from 62.47% to 97.01%, compared with 51.49% to 95.77% in the control group. Most adverse events were mild to moderate in intensity. Taken together, these results suggest that PPV23 is well tolerated and immunologically effective in the Chinese population, over 2 years of age.[22] The proportion of imported PPV23 in the total PPV23 supply ranged from 2.8% to 61.8% during 2013–2023, with the ratios being 13.9% in 2022 and 18.6% in 2023. To date, five versions of PPV23 have been produced by four local manufacturers and one foreign manufacturer in the Chinese market, and approximately 8.7 million doses of vaccines were expected to be released in 2023 for use in humans (Figure 2).

As pneumococcal capsular polysaccharides represent a thymus-independent antigen, the induced antibody response primarily depends on the linear epitope consisting of its repetitive units. In the absence of auxiliary T lymphocytes, the induced antibody subtypes are mainly IgM and IgG2, which are not maintained at sufficient levels over time, preventing the induction of immune memory.[24] These characteristics of PPV23 lead to poor immunogenicity for key pneumococcal serotypes in infants, and PPV23 is currently recommended for use in older individuals and those with a high risk for infection.[5,25]

Protein – polysaccharide conjugate vaccines

The development of thymus immune function in infants aged under 2 years is not fully mature, resulting in a poor immune response to capsular polysaccharides.[24] However, the

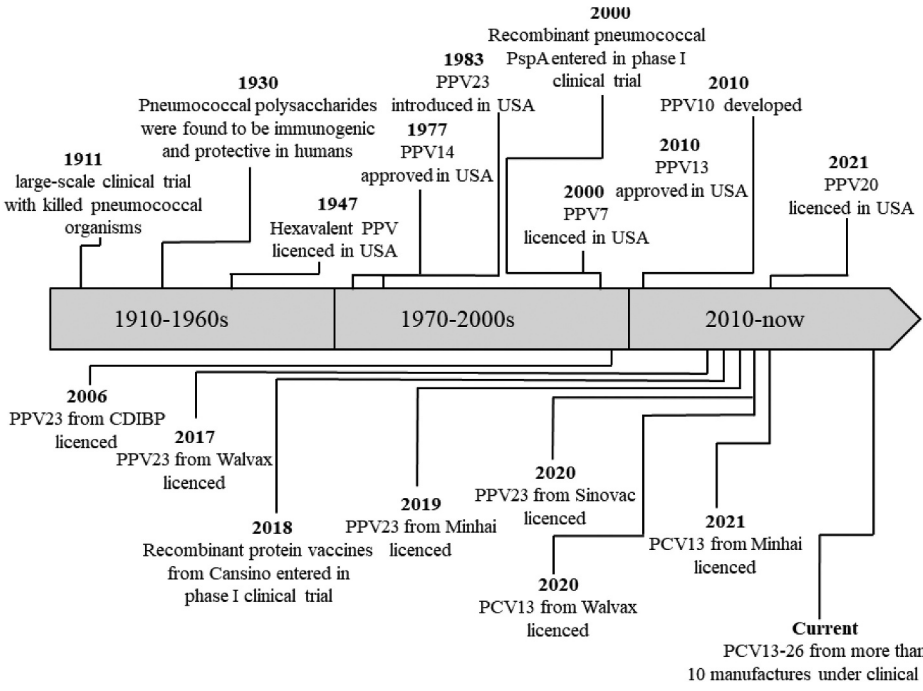

Figure 1. Development history of pneumococcal vaccines in China. The upper section presents key milestones in the history of global vaccine development. The lower section provides detailed information for pneumococcal vaccines from Chinese domestic manufacturers that are licensed or in clinical trials.

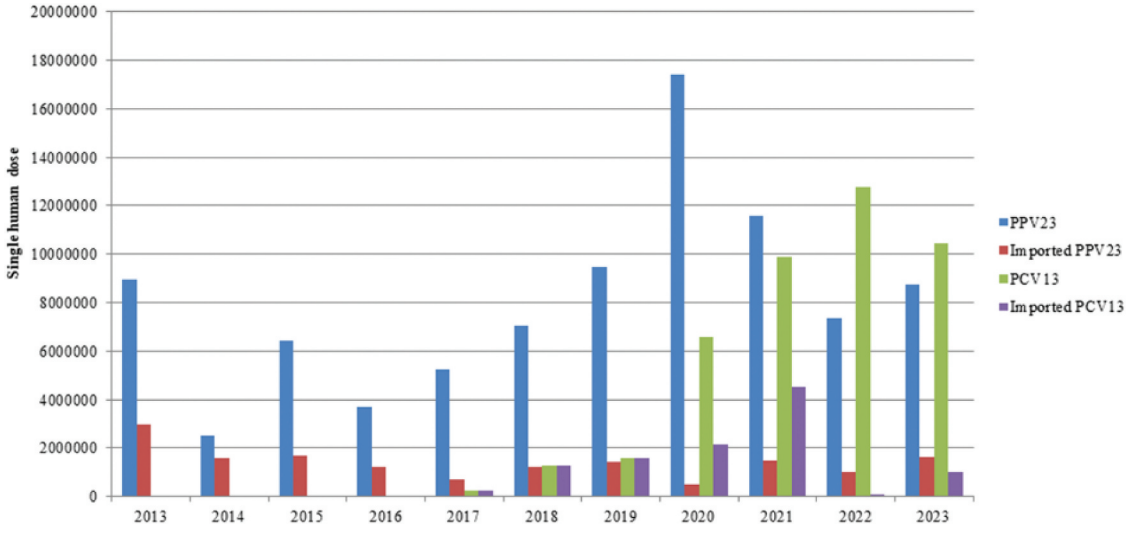

Figure 2. Number of lot releases of different types of pneumococcal vaccines in China, 2013–2023. The proportion of imported PPV23 in the total PPV23 supply ranged from 2.8% to 61.8% during 2013–2023, with the ratio being 13.9% in 2022 and 18.6% in 2023. For PCV13, the proportion of imported products decreased from 100% in 2017 to 9.72% in 2023.

incidence of IPD in infants and young children in that age group is very high.[1,3] Capsular polysaccharides conjugated with carrier proteins elicit a T cell-dependent immune response, characterized by increased antibody concentrations, the induction of memory cells, and a booster response upon subsequent exposure, which provides good protection for infants and young children.[23]

The first PCV7 was marketed in 2000 and is recommended for use in infants in the USA. The results of many clinical trials demonstrated that immunization with heptavalent conjugate vaccines was highly effective in preventing invasive disease.[25] Since the introduction of PCV7, a substantial increase in invasive diseases has been observed among non-vaccine strains, leading to the development of higher-valency conjugate vaccines.[26] PCV10 was developed by GlaxoSmithKline and approved by the European Union. PCV13 was developed by Pfizer (formerly Wyeth) in 2010 and has been approved for use in the USA. Over 100 countries have included PCV in their national immunization programs (NIPs), and the global third-dose coverage was predicted to reach 65% by the end of 2023, whereas it was only predicted to reach 26% in the WHO Western Pacific Region.[27]

In China, imported PCV 7 have been introduced in 2008, and replaced with imported PCV13 in 2016. DomesticPCV13

was developed successfully and approved in 2020[5]. This vaccine contains 4.4 μg pneumococcal polysaccharide serotype 6 and 2.2 μg of the remaining 12 serotypes, conjugated to a tetanus toxoid carrier protein and adsorbed on aluminum phosphate.[28] After three vaccine doses were administered at 3, 4, and 5 months of age, along with a booster dose between 12 and 15 months, the results of a clinical trial demonstrated that all seven common serotypes in PCV13 were non-inferior to those in PCV7 in terms of serotype-specific IgG production. In addition, opsonophagocytic activity (OPA) antibody titers ≥ 1:8 reached 89.25% or higher in the PCV13 group.[30] In 2021, a new PCV13 strain with two carriers (i.e., tetanus and diphtheria toxoids) was licensed for use in China. Immunogenicity analysis showed that the IgG and OPA indicators in the PCV13 groups were generally superior to those in the control groups, and no PCV13-associated serious adverse events (SAEs) occurred during the study period of phase III clinical trial,[31] and further data on long-term immunity persistence revealed that 11 serotypes except for 3 and 4, seropositive rates were 100% and IgG GMCs against 13 serotypes ranged from 0.73 to 15.16 μg/mL in the subject aged 2 months with PCV13 primary vaccination after 5 years. For other groups aged 7–11 months, 12–23 months, and 2–5 years, IgG GMCs were 0.75–11.03 μg/mL, 0.82–13.11 μg/mL and 0.68–12.28 μg/mL, respectively.[32] The good immune persistence offered more extensive evidence of long-term efficacy for domestic PCV13.

Currently, three PCV13 vaccine products from one imported and two domestic manufacturers are on the market in China, and PCV13, PCV15, PCV20, PCV24, and PCV26 from over 10 domestic manufacturers are in different stages of clinical trials (http://www.chinadrugtrials.org.cn/). Approximately 12.7 and 10.4 million doses of PCV13 were administered to humans in 2022 and 2023, respectively. For imported PCV13 products, the market share decreased from 100% in 2017 to 9.72% in 2023 (Figure 2), indicating that the majority of PCV13 used in the Chinese market now comes from domestic manufacturers. As PCV is not included in the NIP, immunization should be paid for by the children's families.

Recombinant vaccines

Over 100 *Spn* serotypes are known, and the current multivalent PCV only targets a subset of possible clinical strains; more complex PCVs are expected in the future.[33] However, a physical limit exists regarding the number of serotypes that can be formulated into a vaccine because of competition for specific T cells that can recognize the protein components. An increase in the number of serotypes can diminish the antibody response to each individual serotype.[25,33] Therefore, considerable attention has been paid to developing vaccines based on pneumococcal protein antigens that are common to all serotypes. Highly conserved pneumococcal proteins have been used as vaccine antigens to provide broader protection against IPD than PPVs or PCVs.[25,34] Various candidate pneumococcal protein antigens have been reported, including the pneumococcal surface protein A (PspA), PspC, pneumolysin, lipoproteins (PlyLD), pneumococcal histidine triad, and sortase-dependent surface proteins.[25,34–38]

Several new vaccines comprising different pneumococcal protein-containing formulations have been evaluated in clinical trials.[36,39] Investigational formulations containing pneumolysin toxoid alone (10 or 30 μg) or in combination with histidine-triad protein D (10 or 30 μg), with or without polysaccharide conjugates from the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, were assessed in a phase I/II clinical study. The results showed that the formulations were immunogenic for the targeted antigens and generally well tolerated, with unsolicited adverse events thought to be related to vaccination.[39] In China, protein-based pneumococcal vaccines containing four candidate protein antigens have completed preclinical studies and were approved for phase I trials in 2018. The immunogenicity results demonstrated a significant increase in antibodies against all components, including PspA-RX1, PspA-3296, PspA-5668, and PlyLD, in serum. The candidate PBPV was shown to be safe and well-tolerated across all experimental groups, with no vaccine-related SAEs observed following the administration of three doses to a total of 118 participants.[40] Other possible pneumococcal protein vaccines are currently undergoing preclinical evaluations.

Additionally, next-generation whole-cell pneumococcal vaccines are under development, utilizing several methods such as attenuation, chemical treatment, and preparation of whole-cell crude extracts to reduce or inactivate a pathogen's virulence.[41–43]

Quality control of pneumococcal vaccines in China

As vaccines are used in healthy populations, ensuring a consistent quality of each vaccine lot released to the market is essential. The WHO recommends that lot release for pneumococcal vaccines should involve independent testing and a careful review of the manufacturing and quality-control data before market approval.[19,44] In China, selection tests primarily focus on identifying effective components and sterility testing for each batch of pneumococcal vaccines. In addition, a polysaccharide-content test is required for 25% of the pneumococcal vaccine products. The data review emphasizes the consistency of critical raw materials and manufacturing processes with approved parameters, as well as compliance of bulk vaccines and final products with current national pharmaceutical standards.[19]

Polysaccharide-content tests represent the most important quality-control parameters for PPVs and PCVs. The Chinese National Regulatory Authority (NRA) recommends that the polysaccharide-content test results for the manufacturer's final vaccine product be subjected to trend analysis in terms of key quality-control parameters. Any significant deviations detected through this analysis trigger actions from both the NRA and manufacturer, with results falling outside of the ±2 standard deviation (SD) and ±3 SD ranges serving as warning and actions limits, respectively.[44]

Quality-control assessment of PPV23 relies mainly on various physical and chemical tests and animal experiments

involving vaccine safety. The pneumococcal polysaccharide monovalent bulk is a critical intermediate product during vaccine production that is used to prepare the final products.[45] To ensure the consistency and efficacy of vaccine products, key considerations for quality control include identifying and purifying polysaccharide antigens, which impact immunogenicity and protection. The composition of pneumococcal polysaccharides can be defined in various ways depending on the methodology employed, and each specification used should be approved by the NRA in China (Table 1).

The results of many studies involving humans and animals have demonstrated that a reduction in the molecular mass of polysaccharides below a minimum threshold can decrease immunogenicity.[45,46] The molecular-size distribution of polysaccharides is an important parameter for monitoring vaccine potency and stability. The molecular size is typically determined by gel filtration with Sepharose CL-4B or Sepharose CL-2B columns, depending on the different polysaccharides involved. The advantages of traditional agarose gel chromatography include a simple operation and relatively inexpensive instrumentation. Recently, new methods for determining the molecular size, such as high-performance size-exclusion chromatography with multi-angle laser light scattering and refractive index detection, have been established.[47] Furthermore, safety indicators that typically include endotoxins should be investigated. Unlike the bulk material, quality control for PPV23 involves a content test of each polysaccharide included in the final product, with scattering rate nephelometry recommended for quantitative immunochemical determinations of pneumococcal polysaccharides.[29]

In contrast to PPVs, developing PCVs is more complex and involves fermentation engineering, large-scale and efficient purification processes, protein chemistry, polysaccharide chemistry, analytical chemistry, organic synthesis, immunology, and other multidisciplinary technical fields. Considering polysaccharide modification strategies; selection and modification of carrier proteins; and the application of conjugation, quality control, and evaluation methods for conjugates is important.[48] After selecting an appropriate carrier protein, a certain degree of derivatization is required. The processed polysaccharides and carrier proteins are chemically coupled and combined at a certain ratio to prepare a conjugate. The polysaccharide chain length, molecular size, specific groups, polysaccharide activation degree, carrier protein ratio, binding rate, cross-linking degree, and free polysaccharide content can all influence the immune effects of the conjugate. To avoid excessive crosslinking and ensure proper sterilization and filtration, the sizes of the polysaccharide and conjugated molecules should be controlled to a certain extent.[29,48]

Quality-control assessment of PCV13 involves testing both the polysaccharide bulk and the conjugated bulks due to differing production processes. For the conjugated bulks, testing to evaluate the identity, content of bound polysaccharides, free polysaccharides, proteins, polysaccharide/protein ratio, molecular size distribution, residual reagents, and sterility is required. In contrast to PPV23, a new capsular polysaccharide (6A) was included in PCV13. Although PCV13 was not included in the 2020 edition of the Chinese Pharmacopoeia,[29] a data review for PCV13 has been completed, and PCV13 will be included in the next edition of the Chinese Pharmacopoeia. The monovalent conjugate bulks may be individually adsorbed onto the aluminum adjuvant before mixing to formulate the final vaccine. In addition to testing the pneumococcal polysaccharide contents, the adjuvant contents should be determined in the final products of PCV13.[29] In contrast, a high-field proton nuclear magnetic resonance (NMR) method has been widely used for identifying

Table 1. Specifications of relevant test items for the monovalent pneumococcal polysaccharide bulk.

Serotype	Protein (%)	Nucleic acid (%)	Total nitrogen (%)	Phosphorus (%)	Molecular size (KD) CL-4B	Molecular size (KD) CL-2B	Uronic acid (%)	Hexosamines (%)	Methyl pentose (%)	O-acetyl group (%)
1	≤2	≤2	3.5–6.0	0–1.5	≤0.15	N/A	≥45	N/A	N/A	≥1.8
2	≤2	≤2	0–1.0	0–1.0	≤0.15	N/A	≥15	N/A	≥38	N/A
3	≤5	≤2	0–1.0	0–1.0	≤0.15	N/A	≥40	N/A	N/A	N/A
4	≤3	≤2	4.0–6.0	0–1.5	≤0.15	N/A	N/A	≥40	N/A	N/A
5	≤7.5	≤2	2.5–6.0	≤2.0	N/A	≤0.60	≥12	≥20	N/A	N/A
6B	≤2	≤2	0–2.0	2.5–5.0	N/A	≤0.50	N/A	N/A	≥15	N/A
7F	≤5	≤2	1.5–4.0	0–1.0	≤0.20	N/A	N/A	N/A	≥13	NN/AA
8	≤2	≤2	0–1.0	0–1.0	≤0.15	N/A	≥25	N/A	N/A	N/A
9N	≤2	≤1	2.2–4.0	0–1.0	≤0.20	N/A	≥20	≥28	N/A	N/A
9 V	≤2	≤2	0.5–3.0	0–1.0	N/A	≤0.45	≥15	≥13	N/A	N/A
10A	≤7	≤2	0.5–3.5	1.5–3.5	N/A	≤0.65	N/A	≥12	N/A	N/A
11A	≤3	≤2	0–2.5	2.0–5.0	N/A	≤0.40	N/A	N/A	N/A	≥9
12F	≤3	≤2	3.0–5.0	0–1.0	≤0.25	N/A	N/A	≥25	N/A	N/A
14	≤5	≤2	1.5–4.0	0–1.0	≤0.30	N/A	N/A	≥20	N/A	N/A
15B	≤3	≤2	1.0–3.0	2.0–4.5	N/A	≤0.55	N/A	≥15	N/A	N/A
17F	≤2	≤2	0–1.5	0–3.5	N/A	≤0.45	N/A	N/A	≥20	N/A
18C	≤3	≤2	0–1.0	2.4–4.9	≤0.15	N/A	N/A	N/A	≥14	N/A
19A	≤2	≤2	0.6–3.5	3.0–7.0	≤0.45	N/A	N/A	≥12	≥20	N/A
19F	≤3	≤2	1.4–3.5	3.0–5.5	≤0.20	N/A	N/A	≥12.5	≥20	N/A
20	≤2	≤2	0.5–2.5	1.5–4.0	N/A	≤0.60	N/A	≥12	N/A	N/A
22F	≤2	≤2	0–2.0	0–1.0	N/A	≤0.55	≥15	N/A	≥25	N/A
23F	≤2	≤2	0–1.0	3.0–4.5	≤0.15	N/A	N/A	N/A	≥37	N/A
33F	≤2.5	≤2	0–2.0	0–1.0	N/A	≤0.50	N/A	N/A	N/A	N/A

All data are from the Chinese Pharmacopoeia (2020 version) 3rd Part. N/A: not applicable.

polysaccharides in many manufactures from other countries and is also recommended by WHO for the quality control of PPV and PCV.[49] The specificity and reproducibility of the NMR-based identity assay are superior to those of colorimetric assays. Recently, an antibody-enhanced high-performance liquid chromatography assay was developed for serotype-specific quantitation of the polysaccharide contents in PCVs.[50] It is suggested that appropriate specifications be assigned for these tests as manufacturers obtain more control test data. These advanced and innovative approaches are expected to strengthen the quality control of pneumococcal vaccines. Furthermore, with the development of more 20-valent PCVs, it is a significant challenge to identify potential immunological correlates of protection and develop *in vitro* assays to measure immune parameters against the new serotype polysaccharide included in these vaccines. Although serologic antibody concentrations alone or in combination with OPA antibody titers were used to evaluate PCV13[30, 31], potential protective roles of cell – mediated and mucosal immunity in PCVs should also be investigated.

Conclusion

Remarkable progress has been made in controlling IPD in China, although new challenges continue to arise. To further evaluate the disease burden and monitor the effectiveness of vaccination, the WHO suggests that countries conduct appropriate pneumococcal disease surveillance.[46] All serotypes included in marketed PPVs and PCVs are based on epidemiological data from developed Western countries, and further steps are needed to improve vaccine introduction and development in developing countries. The epidemiological characteristics of IPD and the distribution of pathogenic serotypes in China are key factors in shaping vaccine-immunization strategies. Because of variations in methodology, population figures, and the inclusion of limited studies from China, the true burden of pneumococcal pneumonia may be underestimated. In particular, the recent increase in non-vaccine serotypes, such as 15A, should not be overlooked. With the gradual expansion of PCV use, serotype shifts are expected to become more pronounced in China.[4,14,51] It is therefore recommended that China establish a national IPD surveillance system to monitor disease incidence and conduct related research. Such efforts should include accurately tracking IPD cases, performing serotyping, determining vaccination rates, detecting antibiotic resistance, and measuring carrier-infection rates in healthy populations. These measures would provide more precise estimates of the IPD burden in China. Additionally, environmental factors significantly impact the effectiveness of pneumococcal vaccination. These factors include personal conditions (e.g., age groups ranging from infants to older adults and conditions such as chronic diseases or immunocompromised states), geographic and ethnic factors (e.g., population density, ethnicity, poverty), and social risks (e.g., closed settings, occupation). These variables should be considered when assessing the burden of pneumococcal disease.[52] To better alleviate the burden of IPD, other public health interventions should be extensively promoted. These include improving sanitation facilities, maintaining personal hygiene habits, strengthening public health education, and increasing public health awareness among the population.

Three PCV13 products from different manufacturers are available in China, resulting in the potential problem of replacement vaccination with a different PCV13 formulation, perhaps with a higher valency. In principle, full vaccination should be completed using a vaccine from the same manufacturer. If completing the entire immunization procedure using a vaccine from the same manufacturer is not possible, then determining whether substitution is permitted according to the relevant local or national regulations is necessary. If a vaccine can be replaced, then scientifically informing the child's parents or recipients of the possible health benefits and risks is necessary.[5] Furthermore, all three current PCV13 products licensed in China are recommended for children aged 6 weeks to 5 years. PCV13 was also effective in preventing vaccine-type IPD among adults and was approved for use in people aged more than 6 years in many countries.[53–55] Notably, PCV20 has been approved for active immunization of IPD caused by *Spn* in adults since June 2021 in the USA and February 2022 in the EU.[56] More age groups with indications for immunization should be investigated in future clinical trials of PCV13 and PCVs with other valencies in China.

A high vaccination rate is required to maximize the performance of a vaccine product.[5] Although PPV23 was included in the provincial immunization program for older adults in China, the vaccination rate remains low compared with other vaccines in the NIP.[5,28] Improving the vaccination rate with PPV23 has been challenging. Most importantly, PCV13 has not been introduced into the Chinese NIP and is, therefore, not available to much of the population because of its high cost (approximately US $68–100 per dose), although three PCV13 products are available in the Chinese market. Numerous studies have demonstrated that PCV13 is highly cost-effective in various countries.[57,58] For instance, cost-effectiveness evidence from the first 5 years of routine PCV use in the USA indicated that 109,000 cases of IPD were averted, with a cost of $7,500 per life-year saved.[58] A cost-effectiveness analysis of domestic PCV13 for children under 5 years of age in mainland China estimated the cost of obtaining one quality-adjusted life year as $2,417, $4,445, $9,292, and $15,394 for one to four doses of the vaccine compared with a non-vaccination strategy.[59] Similarly, based on comprehensive modeled estimates of subnational morbidity and mortality of IPD in China, incorporating provincial PCV coverage, it was found that introducing PCV13 into the NIP could prevent approximately 4,807 pneumococcal deaths (a 66% reduction) and 1,057,650 pneumococcal cases (a 17% reduction) in the first 5 years of the 2019 birth cohort. Under the assumed base case price of US $25 per dose in the NIP, PCV13 was cost-effective nationally, with incremental cost-effectiveness ratios of US $5,222 per quality-adjusted life year gained. It was cost-effective in 17 provinces and cost-saving in 4 of the 31 provinces compared to the *status quo*, suggesting a 98% probability of cost-effectiveness nationally.[59,60] These findings highlighted that incorporating PCV13 into the NIP in China would be a cost-effective approach to saving lives and reducing disability in

most provinces. As recommended by the WHO, by the end of 2023, 159 WHO member countries had included childhood vaccination against pneumococcus in their NIPs.[28]

Although PCVs greatly contribute to controlling IPD, several issues remain unresolved. First, PCV is only protective against *Spn* infection because it expresses the polysaccharide capsule contained in vaccines. Disease substitution by non-vaccine serotypes may diminish the overall benefit observed in reducing vaccine serotypes.[25] Furthermore, with the increased production of non-vaccine serotypes, the development of PCVs with higher valencies is required. Currently, several PCVs with valencies higher than 20 have entered clinical trials in some countries, including China, and many similar products from different manufacturers are concentrated on preclinical studies.[60–62] In 2024, the USA Food and Drug Administration approved a 21-valent PCV with eight new serotypes for adults aged ≥18 years.[14]

The complexity of vaccine production means that only a few companies can produce vaccines, which raises their prices. To address this challenge, pneumococcal proteins universally expressed among all serotypes are being explored as potential alternatives for developing broad-spectrum universal pneumococcal vaccines. These highly conserved commons are not restricted by serotype and can be effective against all strains. In addition, pneumococcal protein vaccines can induce immune memory and provide long-lasting protection across different age groups. Importantly, the relatively low production cost of protein vaccines makes them suitable for large-scale use in developing countries.

In conclusion, with the gradual increase in the use of PCVs, serotype shifts are expected to become more pronounced in the future and should not be overlooked in China. A national pneumococcal disease surveillance system should be established to evaluate the true disease burden and monitor the effectiveness of vaccination programs. Importantly, based on the significantly reduced mortality and high cost-effectiveness, it is recommended that PCV13 should be incorporated into the NIP in China.

Disclosure statement

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Author contributions

Conceptualization, Yinghua Xu and Chune Wang; methodology and analysis, Shanshan Wang, Bin Li, Qiong Chen, Bin Wang, Qiang Ye; writing – original draft preparation, Shanshan Wang and Chune Wang; writing – review and editing, Yinghua Xu and Chune Wang; supervision, Yinghua Xu. All authors have read and agreed to the published version of the manuscript, and they have no competing interests.

The statement of ethical approval

This study was performed in accordance with the principles of the Declaration of Helsinki of 1964. The paper belongs to the reviews, and all data are from published literatures. The ethical approval does not apply to this study.

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