Scientific Research Publishing

World Journal of Vaccines, 2025, 15(1), 1-19
https://www.scirp.org/journal/wjv
ISSN Online: 2160-5823
ISSN Print: 2160-5815

The Evolution of Pneumococcal Vaccine and Vaccine Schedule in the USA: A Narrative Review of the Last Two Decades (2003-2023)

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How to cite this paper: Ekpa, Q.L., Oranu, K.P., Okobi, O.E. and Adekoya, O. (2025) The Evolution of Pneumococcal Vaccine and Vaccine Schedule in the USA: A Narrative Review of the Last Two Decades (2003-2023). *World Journal of Vaccines*, **15**, 1-19.
https://doi.org/10.4236/wjv.2025.151001

Received: December 8, 2024
Accepted: February 10, 2025
Published: February 13, 2025

Abstract

Streptococcus pneumoniae is a known notorious cause of invasive pneumococcal diseases as well as asymptomatic host carriage. Efforts have been made to curb this infectious organism through various vaccine strategies. However, its several strains and serotypes have necessitated various vaccine schedules and updates in the USA and globally. The evolution in pneumococcal vaccine schedules is not without challenges, such as cost, vaccine hesitancy, uptake and global disparities. This narrative review synopsizes the history of the Pneumococcal Vaccine and changes in its schedules in the last two decades based on published data. We focused on the impact of pneumococcal vaccination on invasive pneumococcal diseases, historical limitations, current challenges and future directions. Despite advancements in vaccination against *S. pneumoniae* infections, some pertinent issues exist that need to be swiftly fixed, to reduce national and thus global burden of pneumococcal diseases.

Keywords

Pneumococcal, Vaccines, PCVs, PPVs, Invasive Pneumococcal Diseases, *S. pneumoniae,* Evolution

1. Introduction/Background

Pneumococcal disease is a huge contributor to the global burden of disease. It is caused by the *Streptococcus pneumoniae* bacterium; responsible for pneumococcal pneumonia and invasive pneumococcal diseases (IPDs) like meningitis, osteomyelitis, septic arthritis, bacteremia and endocarditis [1] [2]. The organism is

commonly isolated from the respiratory tract, especially the nasopharynx. However, isolating the organism from a normally sterile body site or fluid like blood, aids in a definitive diagnosis of pneumococcal infection [1] [3]. It is a gram-positive organism occurring in short chains. It is encapsulated with a polysaccharide surface which is antigenic, a basis for the development of the pneumococcal vaccines [1]. These capsular polysaccharides are also used to classify the organism into more than 100 identified serotypes, as different pneumococci have chemically different capsular polysaccharides [1] [4]. The pneumococcal vaccine is an inactivated polysaccharide conjugate vaccine which proffers a long-lasting active immunity [5]. This chemical conjugation of the polysaccharide antigen to a protein, offers a better immunogenicity against pneumococcal infections in groups where a polysaccharide vaccine alone provides little or temporary protection such as in children below two years old, who are at highest risk of the infection [4] [5]. There are two preparations of pneumococcal vaccines: the conjugate and the polysaccharide vaccines [6]. **Figure 1** below illustrates the bacterial structure.

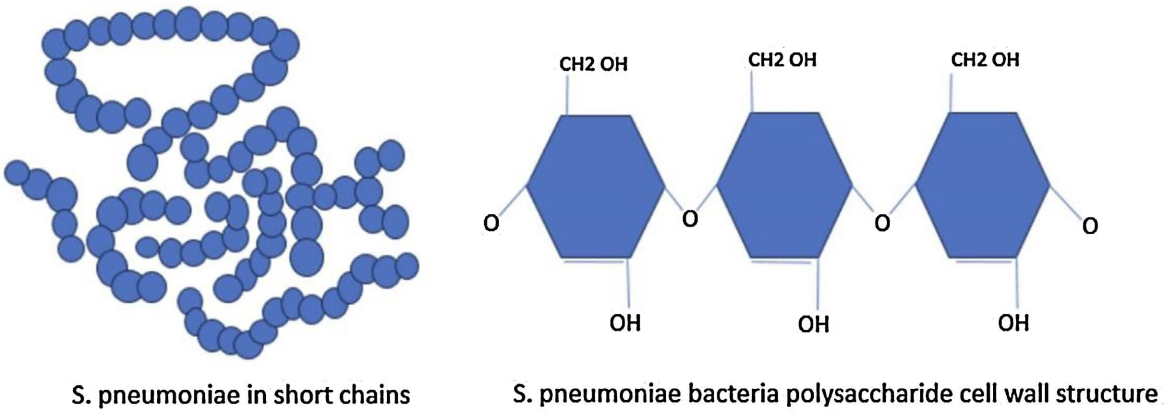

Figure 1. *S. pneumoniae* bacterial cell structure.

Epidemiology and Risk Factors

In first-world countries, younger children, older adults, and people with chronic illnesses are most vulnerable to Pneumococcal infections [2]. More than 50% of deaths following IPDs occurred in adults who had a need for the polysaccharide vaccine, and a sizable proportion of hospitalized individuals due to severe Pneumococcal disease are yet to receive the vaccine [1]. Prior to the scheduled vaccination of children with PCV in 2000, there were about 200 pediatric deaths annually, and a mean annual incidence of 167/100,000 in under-twos before 2006 from IPDs in the USA [1] [3]. Acute otitis media (AOM) was responsible for an estimated 200 million deaths in children under five annually [1].

Data from the Active Bacterial Core surveillance (ABCs) system showed that PCVs reduced the overall incidence of IPDs between pneumococcal serotypes (PCV7 and PCV13) by an average of 94.5% [1]. CDC report in 2008 revealed results from the United States (US) studies demonstrating a 77% reduction in IPDs in under-five and 39% in pneumonia-related hospital admissions in under-two

children, respectively [7]. Another study showed a huge reduction in serotype 19A and subsequent emergence of mutually reversible 15B/C as the most common serotype in Massachusetts following the initial introduction of PCV13 in the state [8]. 19A, 15B/C, and 6C serotypes were responsible for 50% of pneumococcal carriage isolated in the examined samples collected between 2009-2011 in children 3 months - 7 years [8].

Vaccination rates have also increased in the past decade. 91.6% of children born between 2016-2017 received 3 doses of PCV while an estimated 81.7% received up to 4 doses by two years of age [1]. Apart from children and the elderly, people with chronic conditions and those requiring frequent clinic visits are at increased risk for pneumococcal infection [1] [4].

2. Scope and Objective of the Research

The goal of this paper is to provide a narrative synopsis of the literature on the changes in pneumococcal vaccine guidelines in the USA over the last two decades. The goal was not to conduct a systematic review or meta-analysis of the epidemiology of pneumococcal vaccines. Our perspective is that considering the prevalence and risk factors for IPDs discussed above, the history and the evolvement of vaccines against IPDs, it would be more beneficial to explore the changes in vaccine schedules over the years and the reasons for these changes. Based on the literature, we pivot on the impact of vaccination against pneumococcal bacteria, as well as historical limitations, with regard to issues of public health concerns and provision of public health services. In addition, these areas have not been extensively reviewed in the past. We conclude with some prospects for future directions and areas of research in this area.

3. Pneumococcal Vaccines

3.1. First-Generation Pneumococcal Vaccines: Composition, Efficacy, Limitations, and Drawbacks

Whole Killed Pneumococcal vaccines: First-generation vaccines are live attenuated whole organisms or inactivated toxins, able to provoke innate immunity [9]. They are cheap, easy to produce, and induce long-term protection. More than a century ago, cases of Pneumococcal infection from Pneumococcus types 1, 2, and 3 were successfully challenged by inoculation with doses of killed Pneumococcal vaccines [4]. This followed an earlier study in 1891 when repeated inoculation with killed pneumococci, provided immunity against future attacks, using animal specimens, based on humoral immunity. In the USA, in 1917, varying doses of killed pneumococci were inoculated from infected subjects. Pneumococcal agglutination, protection from serum vaccines, and their adverse effects were studied. In 1944, polysaccharides from types 1, 2, 5, and 7 Pneumococcus were used in a clinical trial and showed significant reduction in types 2 and 7 pneumococcal infection [4].

Limitations and drawbacks: Efficacy from killed, whole pneumococci could

have been from other bacterial cell components apart from the polysaccharide antigen. Also, the incidence of non-vaccine type pneumonia was unchanged [4].

3.2. Introduction to Pneumococcal Conjugate Vaccines (PCVs): Composition, Efficacy, Limitations, and Drawbacks

In 1911, attempts to develop pneumococcal vaccines that would be efficacious against *Strep. Pneumoniae* began [1]. Despite antibiotic treatment with penicillin in the 1940s, patients still died within 4 days of treatment from pneumonia caused by this bacterium [1] [4]. By the 1960s, further attempts were made to develop a polyvalent vaccine against pneumococcal pneumonia [1]. The first pneumococcal vaccine and the first pneumococcal conjugate vaccine (PCV) were first licensed in the United States for use in 1977 and 2000, respectively. The first pneumococcal vaccine is no longer produced; however, it was a 14-valent capsular polysaccharide purified from fourteen distinct types of pneumococci. This vaccine was replaced by a 23-valent polysaccharide vaccine (PPSV23), also called Pneumovax 23, in 1983, made from serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F [1].

The introduction of pneumococcal conjugate vaccine7 (PCV7) also called Prevnar7, the first PCV, in the US immunization schedule in 2000, saw a reduction in *S. Pneumoniae* antibiotic resistance, which further declined in children following the invention of PCV13 in 2010 [1] [8]. PCV7 also exhibited herd immunity in unvaccinated adults [10]. Before it replaced PCV7, serotypes of PCV13 (Prevnar13) were discovered to cause 61% of severe disease in under-fives, compared to 2% from PCV7 serotypes [1]. PCV7 and PCV13 have both caused a decline in invasive pneumococcal serotype infections in the pediatric population by 99% and 90%, respectively. PCV13 contains serotypes of PCV7 (7F), 1, 3, 5, 6A, 6B, 7F, 9V, 14, 18C,19A, 19F and 23F. PPSV23 is administered intramuscularly or subcutaneously by injection, while PCV13 is administered intramuscularly [1]. PCV15 and 20 are newly introduced vaccines in 2021, both sterile suspensions of polysaccharides from 15 and 20 serotypes respectively [2] [6] [11]. Both PCV15 and PCV20 are conjugated to CRM_{197} [6] [10] [12] [13].

3.3. Second-Generation Pneumococcal Vaccines

This generation of vaccines is made of the pathogen's subunit elements, recombinant proteins, non-protein antigens such as glycans, and the pathogen's expressed immunogens [9]. These immunogens include several antigenic determinants and molecules of the different strains of the organism. Examples of second-generation vaccines are subunit, conjugated, and recombinant vaccines [9], which includes all PCVs and the PPSV.

Composition and efficacy: The pneumococcal vaccines are conjugate subunit vaccines [5]. They are made from the chemical bonding of polysaccharides from the surface of the Pneumococcal bacteria to a protein molecule. This initiates a host B-cell response autonomous from T-helper cells, stimulating host immunity

[5]. The average efficacy of PPSV is 84% [4]. Both PCV and PPSV vaccines do not contain any antibiotic, however, PPSV23 contains phenol as a preservative, and PCV13 has no preservatives. Whereas PCV13 has aluminum phosphate adjuvant and succinate buffer, PPSV23 has no adjuvant [4] [14]. It is an aseptic mixture of 13 capsular polysaccharides of *S. pneumoniae,* available in a single-dose injection [14]. PCV13 is chemically conjugated to a nontoxic variant of diphtheria toxin (CRM_{197}) [1] [4] [14]. The PPSV did not produce an immune response in children less than 2 years old [4] [15]. This poor immunogenicity was overcome by PCV7 through conjugation technology. PCV7 and 13 both provide herd immunity and similar adverse events records, however, PCV13 produces a better immune response in adults at one month post-vaccination and no difference after 12 months of vaccination respectively, in contrast to PPSV23 [4] [10] [15]. PCV13 has further shown cost-effectiveness in vaccine-preventable Pneumococcal disease in HIV-specific populations and in the general populations of adults over 50 years [4].

In 2008, the World Health Organization (WHO) recommended the inclusion of PCVs in national immunization programs for those under five and above 65 years of age, as well as those with positive infection for human immunodeficiency virus (HIV) [7]. PCV7 was the only vaccine licensed for use and introduced into the US infant immunization schedule in 2000 before PCV10 and PCV13 were formulated, yet it was not quickly implemented in other countries due to its inflated cost [2] [7]. Before its first use in 2000, the incidence of IPDs was highest in under 2 years of age [8]. These IPDs included bacteremia, meningitis, community-acquired pneumonia, otitis media, and pneumonia with *S. pneumoniae* as the leading culprit, [1] [12] an annual incidence of 165 cases/100,000 children < 12 months of age and 203 cases/100,000 children 12 - 23 months of age [15]. It is estimated that worldwide use of PCVs will avoid 5.4 - 7.7 million deaths in children by 2030 [7].

Prior to 2004, a surveillance study done in Massachusetts showed a significant increase in IPD due to serotype 19A [16]. It was also shown that serotype 19A was the most common cause of refractory acute otitis media in Rochester, New York, and acute mastoiditis and chronic sinusitis in hospitalized children at Texas Children's Hospital in Houston [17]. These prompted the need to develop a second-generation PCV, a 13-valent vaccine contains capsular polysaccharides antigens of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F. It was licensed and recommended for universal immunization of children less than two years and through age five years in 2010, due to its safety profile and immunogenicity [16] [17]. The simultaneous increase in non-vaccine serotypes (NVTs) did not affect the decline in IPDs covered by PCV13 serotypes [1].

Limitations and drawbacks: Contemporary research has shown a decrease in efficacy of PPSV23 due to perseverance of serotypes (such as 3 & 19A) for which it does not offer good protection; decrease in PCV13 strains; and resulting evolution of strains (types 15A, 23B, 35 and 38) not covered by PPSV23 [4]. Thus, PPSV failed to immunize toddlers and infants, leading to production of conjugated

pneumococcal vaccines. Following the introduction of PCVs, specifically PCV7, there was an increase in NVT pneumococcal infection, which were also resistant to antibiotics (for example, serotype 19A). This led to the introduction of PCV13 a second-generation PCV in 2010, to curb infections by serotypes not covered by PCV7 [1] [8]. PCVs do not protect against infections caused by NVTs and unencapsulated organisms [18]. PCV13 also does not cover serotypes of *S. pneumoniae* disease not in the vaccine [19]. **Table 1** below summarizes pneumococcal vaccines and **Table 2** summarizes PCV13 recommendations by the Advisory Committee Immunization Practices (ACIP).

Table 1. Summary of the History of Pneumococcal Vaccines [1] [2] [11] [13].

Vaccine Type	Date of Licence/ Approval in the USA	Composition	Efficacy
Pneumococcal vaccine	1977 (no longer produced)	14-valent capsular polysaccharide	14 serotypes
PCV7/Prevnar7	2000	Purified capsular polysaccharide	7 serotypes and 99% reduction in pediatric IPDs and nasopharyngeal carriage
PCV13/Prevnar13	2010	PCV7 + 1, 3, 5, 6A, 7F, and 19A, conjugated to CRM_{197}	13 serotypes and 90% reduction in pediatric IPDs
PPSV23	1983	23-valent purified polysaccharide	23 serotypes and 84% against pneumococcal diseases
PCV15	(adults) (children 6 - 17 years)	Purified capsular polysaccharides of PCV13 + 22F and 33F, conjugated to CRM_{197}	15 serotypes, produced Abs levels comparable to PCV13 immunogenicity
PCV20	2021 (adults) 2023 (children 6 - 17 years)	PCV13 + 10A, 11A, 12F, 15B, 22F, and 33F, conjugated to CRM_{197}	20 serotypes, produced Abs levels comparable to PCV13 immunogenicity

Note: Abs = antibodies.

Table 2. Advisory Committee Immunization Practices (ACIP) Recommendations on PCV13 (Prevnar13)

	ACIP Recommendations for PCV13 [9] [18] [19]
1.	PCV13 for all children 2 - 59 months and 60 - 71 months with underlying conditions that increase their risk of IPD
2.	Use of PCV13 and the immunization schedules for infants and toddlers 2 - 59 months without prior PCV7 or PCV13 doses remain the same as earlier recommendations for PCV7; PCV13 replaced PCV7 for all doses
3.	Infants below 24 months should receive 1 or more doses PCV13 depending on the doses of PCV7 received to date and the age of the child; Toddlers 24 - 59 months should receive 1 dose of PCV13
4.	High-risk children 24 - 71 months who have received less than 3 doses of PCV7, should receive two doses of PCV; high risk children 24 - 71 months who have received 3 or more doses of PCV 7, should receive a single dose of PCV13
5.	All children 14 - 59 months who have received 4 doses of PCV7 should receive a single dose of PCV13; for all high-risk children 14 - 71 months, a single dose is recommended
6.	Children 6 - 18 years at increased risk of IPDs due to SCD, HIV-infection or other immunocompromising condition, cochlear implant or CSF leaks may receive a single dose of PCV13, regardless of whether they have previously received PCV7 or PPSV23

Note: IPDs = invasive pneumococcal disease, SCD = sickle cell disease, CSF = cerebrospinal fluid, HIV = human immunodeficiency virus.

3.4. Protein-Based Pneumococcal Vaccines

Protein-based pneumococcal vaccines are purified protein vaccines (PPVs) that use select conserved proteins shared by all strains of pneumococcal bacteria regardless of their capsular glycans [20]-[22]. Most PPVs target surface proteins which anchor the bacteria to the human epithelial cells, providing wider protection not covered by PCVs, and to overcome the prevailing obstacles with serotype-dependent PCVs [20] [21] [23] [24]. Natural immunity to IPD is determined by production of antibodies against protein antigens when compared to capsular antigens [20]. PPVs such as pneumococcal histidine triad protein D (PhtD), pneumococcal choline-binding protein A (PcpA) and pneumolysin detoxified derivative (PlyD1) provide protection against AOM [20] [24]. Other widely studied PPVs include pneumococcal surface protein A (PspA), pneumococcal surface protein C (PspC), pneumococcal surface antigen A (PsaA), pneumococcal iron uptake A (PiuA) and pneumococcal iron acquisition A (PiaA) [21].

The Pneumolysin (PLY) is a cholesterol-dependent cytolysin, which activates the classical pathway of the complement system, inflammation and causes direct cell toxicity [21] [23]. There are several PLY derivatives tested to provide protection against pneumococcal bacteria. PspA and PspC are choline-binding surface proteins on *S. pneumoniae.* It is widely expressed by capsular serotypes and is a critical virulence factor in pneumococci-host reactions. PspA-fusion protein and PspA-based trivalent vaccines have demonstrated efficacy against a wide range of pneumococcal strains in mice [21] [23]. Pht is a group of *S. pneumoniae* surface proteins with versatile immunogenicity with potential for non-serotype-dependent activity against pneumococcal infections, also involved in iron regulation [21] [24]. PhtD protects against pneumococcal sepsis [23]. PsaA is also surface lipoprotein with a strong immune response, that also reduces nasopharyngeal colonization. PiuA and PiaA are surface iron transport proteins that provide systemic protection against *S. pneumoniae* (*i.e.* in both serum and respiratory fluids) [21]. However, PPVs require adjuvants for lasting immunity, are largely variable in heterogenicity and need to be studied in depth [20] [21] [23]. Non-repeating sequences in protein antigens makes it difficult to mount a defensive antibody-antigen mediated immunity, especially against surface bacterial pathogens [23].

3.5. Pneumococcal Vaccines and Respiratory Diseases

There is demonstrable evidence of the role of Pneumococcal vaccines in reducing respiratory disease burdens and curbing exacerbations of chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis and asthma. There is an established co-adjuvant relationship between S. *Pneumoniae* and respiratory viruses such as the influenza virus [25]. This pneumococcal-viral interaction, including bacterial host carriage, which alters host defenses, is also implicated in the pathogenicity of COVID-19. PCVs reduce pneumococcal colonization of the respiratory tract and thus reduce secondary viral infections, as well as the risk of coronavirus respiratory diseases, including COVID-19 [25].

4. Updates to the Vaccine Schedule

PCV7 first introduced in the United States in 2000, was recommended by the WHO recommended to be included in the national immunization schedule. Prevenar (PCV 13) is currently being used in the United States and given via the 3 + 1 dosing schedules *i.e.*, 3 doses plus 1 booster dose [26]. In addition, PCV15 containing serotypes 22F and 33F plus PCV13 serotypes, and PCV20 containing serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F were recommended by the Advisory Committee on Immunization Practices Pediatrics ACIP in 2022 for use in adults 19 - 64, and 65 years and above [6] [11]-[13]. Three PCV doses have been licensed for use and made commercially available: PCV 7- first licensed in 2000 using a 4-dose schedule (3 primary doses plus 1 booster *i.e.* 3+1); PCV10- licensed in 2010 using 3 + 1 in the European Union and 2 + 1 in other countries; and PCV 13- same schedule as PCV 10, however PCV10 was never registered in the US [2] [27]. PSSV23 is given as a booster dose and is not a routine childhood pneumococcal vaccination [27] [28]. It contains 12 serotypes of PCV13 plus 11 additional serotypes [28]. A summary of vaccine schedules and the year of introduction is illustrated in **Table 3** below.

Table 3. Vaccine schedule and year of introduction [1] [2] [27] [28].

Vaccine	Year Introduced	Schedule + comments
PCV 7	2000	3 doses +1 booster (withdrawn)
PCV 13	2010	3 doses (at 2, 4, 6 months) + booster (between 12 - 15 months) as routine in under-two aged children; PCV13 + PPSV23 for adults with immunocompromising conditions, CSF leaks, or cochlear implants; and adults 65+ years without immunocompromise, CSF leak, or cochlear implant based on shared clinical decision-making
PCV 15	2021	PCV naive individuals or unknown vaccination history aged 19 - 64 and 65+, plus a dose of PPSV23 after 1 year or more
PCV 20	2021	Used alone in PCV naive individuals or unknown vaccination history aged 19 - 64 and 65+ years
PPSV23	1983	Booster dose after 9 months old for kids 2 - 18 years with high-risk medical conditions such as DM, HIV, and immunocompromised states after receiving PCV13; 1 dose for all adults above 65 yrs, at risk groups at 2 yrs and 7 years

Note: CSF = cerebrospinal fluid, DM = diabetes mellitus, HIV = human immunodeficiency virus.

The PCV vaccine schedules have seen changes over the years. The vaccine series has been defined as

- Primary series: consists of 2 or 3 doses received before 7 months of age
- Booster Dose: A dose of PCV or PPSV23 received after completing a primary series and after 9 months of age
- Complete series: A primary series alone in cases where a booster was not

planned or a primary series plus booster in cases where a booster was planned [27]

According to the American Association of Pediatricians, The Heptavalent Pneumococcal Conjugate Vaccine (PCV 7) is recommended at 2, 4, 6,12, and 15 months for children below 23 months while only 2 doses are given for children 7 months and above who have not been earlier vaccinated and are at increased risk of invasive pneumococcal infection [29].

4.1. Impact of the Pneumococcal Vaccine Schedule on Pneumococcal/Respiratory Disease

Reductions in disease burden: In preventing pneumococcal disease, different vaccine schedules have proven to reduce the disease incidence in children. This also translates to reduced use of antibiotics and lower treatment costs from an economic perspective. Studies have pointed PCV-7's 50% - 60% reduction in disease burden due to the pneumococcal serotypes included in the vaccine [30]. In 2000, when the PCV-7 was introduced in the United States for children below 2yrs with a vaccine catch-up program for children up to 5 years old, this led to a decrease in the annual incidence of IPDs from about 16,000 - 18,000 cases between 1997-1997 to less than 5000 cases annually between 2002 and 2019. The number of healthcare visits for children with otitis media caused by *S. pneumoniae* was reduced by 50% between 1997 and 2019 [15].

Changes in pneumococcal serotypes and impact on antibiotic resistance: The *S. pneumoniae* cell wall is composed of peptidoglycan and teichoic acid [31]. Teichoic acid has a significant component, the C-polysaccharide which is present in all wild strains of *S. pneumoniae,* and this is important in differentiating the serotypes. The serotypes can be grouped based on the antigenic component of their capsules [31]. These capsules are also important in developing antibiotic resistance. Many serotypes use capsular gene cassette transformation to enhance a change in capsule specificity and cause antibiotic resistance [31]. *S. pneumoniae* antibiotic resistance steadily increased between 1998-2021, thus posing a serious health threat [32]. Since pneumococcal vaccines target streptococcal serotypes, they protect against many antibiotic-resistant IPDs [32] [33]. Pneumococcal vaccines have been found in a study to reduce any type of antibiotic use, a number of people receiving antibiotics, the number of prescriptions, and the days of antibiotic use [33]. The serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F were known to cause the highest burden of antibiotic-resistant *S. pneumoniae* before 2000 however after the introduction of PCV7 in 2000 there was a decrease in infection rates by all these serotypes except 19A [32]. PCV13 which was introduced in 2010 contained the 19A serotype effectively reducing its disease burden [32].

Effectiveness of vaccine strategies: The introduction of pneumococcal vaccines caused a significant reduction in pneumococcal disease burden, and helped establish herd immunity further reducing disease incidence. With the development of each new vaccine a stronger and wider disease coverage was received with each

new vaccine. For example, PCV7 has led to a 50% - 60% reduction in disease burden for serotypes included in the vaccine, and PCV13 which hassled to a 90% decrease in invasive pneumococcal serotype infections since their introduction. Although the PPSV23 had a decreased efficacy towards providing immunity for children and infants due to the perseverance of serotypes, the evolution of PCV7 and PCV13 help counter those limitations. However, distribution and supply shortage has limited the availability of the pneumococcal vaccines to remote areas. Break in cold chain vaccine transport is also a challenge that the WHO is combating. Vaccine hesitancy and behavioural factors also reduces the response to vaccination and immunity.

4.2. Comparison of Pneumococcal Vaccine Schedules in Canada and the United Kingdom

In Canada, IPDs are prevalent in the very young and elderly (65 years+); the vaccine schedule has been updated to include the use of PCV 15 and 20, rather than the previously used PCV13 [34]. In children 2 months - less than 18 years, without medical or environmental IPD risk factors, routine immunization with PCV15 (Pneu-C-15) or PCV20 (Pneu-C-20) follows a 3-dose schedule (2, 4 and 12 months of age) or 4-dose schedule (2, 4 and 6 months, and at 12 - 15 months of age). All adults 65 years + should receive one dose of PCV20 regardless of previous status with PCV13 or PPSV23 and given at a minimum of one-year interval from the last PCV13 or PPSV23 dose in previously vaccinated seniors [34]. They can also be offered PCV15 followed by PPSV23 as an alternative, with an interval of 8 weeks between PCV15 as the first dose. Children at increased of IPD who have completed recommended PCV13 or PCV15 schedules and adults 18 - 64 years with IPD specific risk factors are offered one dose of PCV20 with minimum of one-year interval from the last PCV dose received. No additional doses of PCV20 or PPSV23 are required for children with completed vaccine series for age which included at least one dose of PCV20 [34].

In the UK, infant PCV schedule was introduced since 2006 with PCV7, later replaced with PCV13 by 2010 [35]. The PCV13 immunization schedule is used and has achieved herd immunity [35]. The Joint Committee of Vaccination and Immunisation (JVCI) concluded that since the maximum effect of the PCV13 has been achieved in the UK reducing disease or asymptomatic carriage to the barest minimum, doses of PCV13 will be administered as 1 + 1 schedule, shifting from the previous 2 + 1 schedule, offered at 12 weeks and one year of age [35]. Children born on or after January 1, 2020, are offered a single dose of PCV13 at 12 weeks old, along with routine vaccinations, followed by PCV13 booster doses at their first birthday, in a 1 + 1 PCV13 schedule. Whereas infants born on or before December 31, 2019, continue to receive two doses of PCV13 at 8 and 16 weeks old, followed by a booster dose at their first birthday, in 2 + 1 schedule. Additional doses of PCV13 are recommended for immunosuppression, asplenia or severe splenic dysfunction like in the US. Other clinical risk groups follow the regular

national schedule. This new schedule reduces how much vaccines are given during clinic visits and allows opportunity to introduce new future vaccines [35].

4.3. Global Disparities in Pneumococcal Vaccine Coverage

Pediatric pneumococcal disease exacts a substantial burden on global health, much of which is vaccine preventable. Despite this considerable burden and the demonstrably high efficacy of PCVs, the overall level of PCV uptake remains concerningly low, especially compared with that of other childhood-recommended vaccines, such as tuberculosis and polio. A wide array of plausible expositions exists for this low uptake, including logistical challenges, psychosocial factors, and cost-effectiveness. Although decisions regarding PCV introduction and recommendation vary by country, an increasing number of both high- and low-income countries now incorporate PCV into their national immunization programs (NIPs). As of March 2019, 147 countries had introduced one or more PCVs into their NIPs (including 136 universal, five subnational, and three special risk programs), and 15 countries had announced plans to introduce a PCV [26]. These 147 countries include 60 low-income countries eligible for international assistance in procuring vaccines that introduced PCV after 2009 (the year in which funding from Gavi, the Vaccine Alliance, became available for PCVs) [36]. **Figure 2** shows global PCV coverage by countries.

Reductions in the worldwide burden of childhood pneumococcal diseases reflect the widespread adoption of pneumococcal vaccines over the past two decades. Within the past 10 years, the total number of countries that have introduced PCVs (in at least one population and at least one region) has more than quadrupled. Despite these recent progress and relative growth in vaccine coverage, the

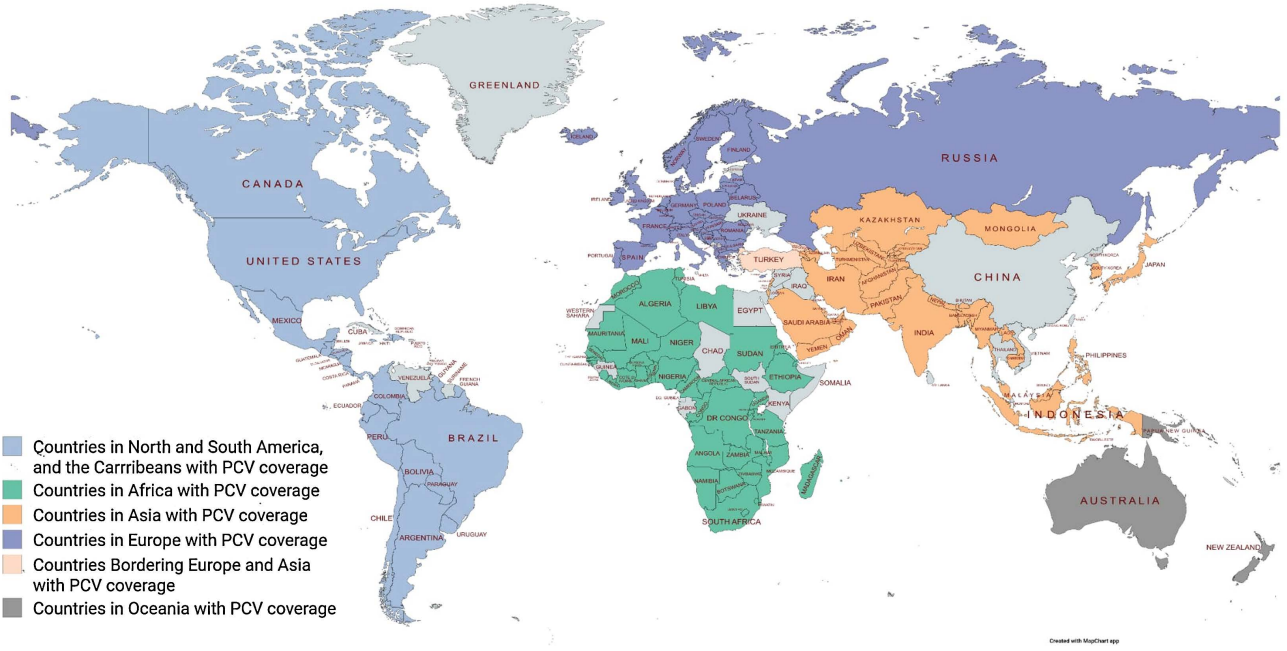

Figure 2. Vaccine coverage map [26]. Countries in grey represent areas without PCV coverage.

universal acceptance level of PCV is still subpar. The World Health Organization (WHO) estimates that global coverage of the third dose of PCV, while notably greater than in 2014, still only reached 48% of its target population in 2018 [37]. Table 4 below describes the percentage of the global population in the last 10 years who were vaccinated annually, and Figure 3 illustrates the trend in annual vaccination during the same period.

Table 4. Global vaccine coverage in the last 10 years according to World Health Organization (WHO) [37].

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
% population	26	32	38	41	45	48	51	51	51	60	65

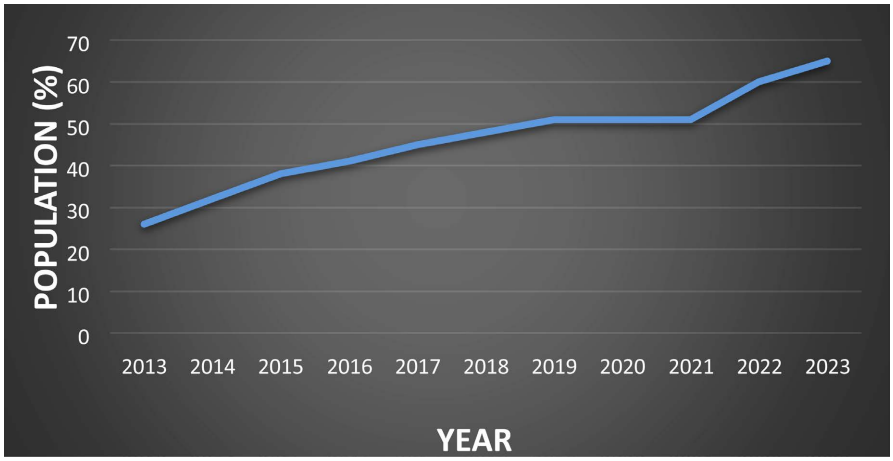

Figure 3. Trends in global vaccine coverage over the last decade [37].

Many barriers and obstacles can impede PCV uptake. From a logistical standpoint, sustaining high coverage rates requires a dependable supply chain network, which has become increasingly challenging due to widening varieties of available vaccines, increasing supply costs, and tightening infrastructure standards. Many existing immunization and supply chain logistics (ISCL) systems are not keeping pace with the changing vaccine landscape, often resulting in stock shortages, inventory unpredictability, the potential administration of ineffective vaccines and avoidable wastage. The WHO estimates that in 2011, cold-chain failures in five countries resulted in the loss of 2.8 million vaccine doses [38].

Even when existing ISCL systems are running smoothly and efficiently for the areas that they serve, accessibility often remains an especially important consideration for uptake in developing and rural areas. In underserviced areas, limitations such as travel opportunity costs, direct costs, and safety concerns may play a larger role in vaccination decisions. Children born to families living farther away from a road or clinic are at demonstrably greater risk of not being fully vaccinated, even where vaccines are reliably available and reimbursed [36]. Accessibility shortcomings and insufficient ISCL system funding both have far-reaching implications for vaccine coverage, uptake, and—in cases of noncompletion—efficacy [38].

Behavioral and psychosocial considerations are also key determinants of vaccination uptake [36]. Vaccine hesitancy is one leading impediment to sustaining high coverage rates and is common worldwide: more than 90% of countries reported some level of vaccine hesitancy [39]. The top three reasons cited for vaccine hesitancy globally in 2016 were 1) risk-benefit concerns (such as vaccine safety concerns, 23% of responses); 2) lack of knowledge and awareness of vaccination and its importance (10%); and 3) religion, culture, gender, and socioeconomic issues regarding vaccines (12%) [39]. The spread of misinformation through anti-vaccination lobbies and the media exerts a powerful influence on parents' vaccination decisions and perceptions of vaccine safety. Another basis of low pediatric PCV uptake is affordability. PCVs are more expensive than earlier generations of vaccines, and their prices have been rising in the United States and globally [40] [41].

One other plausible major and systemic cause of low uptake is economists' and policymakers' tendency to undervalue vaccination in general, particularly PCVs, by adopting a narrow health sector perspective when performing economic evaluations of vaccines. The conventional health sector perspective focuses on two benefit categories of vaccination: healthcare cost savings (stemming from reductions in visits to healthcare professionals, inpatient stays, and prescription drugs) and health gains (the value of reduced morbidity, mortality, and suffering from pneumococcal diseases). These two benefit measures alone are inadequate to establish a panoramic assessment of the value of PCVs, as they do not capture a much broader set of socioeconomic benefits to society [37].

4.4. Challenges and Future Directions for Pneumococcal Vaccination

Despite the increase in vaccination rates with the pneumococcal vaccines, there are still missed opportunities for vaccination, such as at the time of hospital discharge or clinic visits, [1] as well as vaccine hesitancy. Other avenues to offer pneumococcal vaccination include nursing homes and long-term care facilities. Early identification through screening and vaccination of at-risk groups especially in hospitalized populations would remarkably reduce morbidity and mortality from pneumococcal diseases [1]. The lack of a vaccine that can protect against all pneumococcal serotypes as well as the spread of resistant serotypes pose significant challenges for both pneumococcal vaccines and antibiotic-resistant pneumococcus [37]. The CDC recommends that expanding vaccine use can prevent future infections, slow, and even reverse emerging antibiotic resistance [37]. According to Dunne *et al.*, the knowledge gap between host responses, viral and pneumococcal respiratory infections, and the role of PCVs need to be explored further [25]. Cai et all surmised that newer vaccines that target all strains, can reduce disease burden as well as asymptomatic carriage [42]. A non-dependent-serotype protein vaccine is also an advantageous and more affordable pneumococcal vaccine option for children in third world countries, providing extensive coverage against

geographical serotypes against IPDs and other pneumococcal infections, thus curbing the global impact of pneumococcal diseases [23] [24].

Active surveillance will continue to identify populations with vaccine hesitancy, low vaccine uptake, and poor vaccine education as well as growing antibiotic resistance. Constant public reminders such as vaccine education and advocacy on the unparalleled importance of vaccination and herd immunity, will promote active vaccine acceptance and uptake and reduce cost association with antibiotic resistance and treatment of pneumococcal infection.

4.5. Actionable Plans to Improve Pneumococcal Vaccine Coverage

Prioritization of vaccination scheme: this involves initiatives such as pharmacist-led distribution programs, standing orders for nurses to administer vaccines and appropriate protocols for distribution, improved protocols for eligibility (e.g. notification within electronic medical record when accessing a patient's chart, standardized checklist guidelines), and routine vaccination guidelines on a national level. A study by Patel *et al.* showed that pharmacy-led teams in the United States increased national immunizations by an estimated 3.5 million doses per year [43] [44].

Removing practical barriers to immunization such as access: Limited access to vaccination is one of the leading causes to reduced coverage (e.g. limited opening hours, distance to health centers, inconvenient booking system). Improving on the booking system such that individuals can book and receive vaccination same day would increase the rate of vaccination. In addition, the creation of mobile vaccination units will reduce the distance between individuals and vaccination sites [45].

Use of immunization information system: Immunization information systems (IIS) are confidential, computerized, population-based systems that collect and consolidate vaccination data from vaccination providers and provide important tools for designing and sustaining effective immunization strategies at the provider and immunization program levels. These tools include clinical decision support, vaccination coverage reports, interoperability with electronic health record systems, vaccine inventory management, and the ability to generate reminder and recall messages. Patient recall and reminder systems such as sending text messages or phone calls to individuals to remind them of their upcoming vaccination appointment or pending vaccination booking have shown to be an effective way to increase coverage [46] [47].

5. Recommendations

There is great need to increase pneumococcal vaccine uptake in the US and globally. Initiatives to increase vaccine uptake should be prioritized and promoted. For instance, opportunities for vaccinations such as at a clinic visit, hospital discharge, long-term care facilities, nursing homes and general public health promotion should be maximized. Issues of vaccine hesitancy need to be addressed at all levels

of health care services, especially at the primary care level which serves as the patients' medical home and the bridge between community and health care services. Addressing behavioral and psychosocial issues such as health-seeking behaviors; vaccine safety concerns; lack of knowledge and awareness of vaccination and its importance; religion, culture, gender, and socioeconomic issues regarding vaccines; and misinformation are key to solving vaccine uptake barriers such as vaccine hesitancy and nescience.

Despite ongoing research efforts to provide a single vaccine that can cover all serotypes or antigens, policies need to be set in place by health care policymakers to improve vaccination rates. Factors such as barriers to vaccine access; ability to schedule and attend appointments; ability to pay for uninsured vaccine services, limited opening clinic hours are important considerations for policymakers. These are especially important in resource poor communities and populations facing social and health inequities.

6. Conclusion

Though there have been great strides in the evolution of pneumococcal vaccines and its effect on IPDs, there is still much to be done. Vaccine uptake in more developed countries like the US is unsatisfactory, as the prevalence of pneumococcal diseases persists. This is of great public health concern. Areas for future research in pneumococcal vaccines include coverage for all serotypes and NVTs. We believe that public health policies surrounding vaccine advocacy need more attention to encourage PCV accessibility and embrace, while also addressing the issue of its costs.

7. Strength and Limitations of the Study

This study uses moderate quality evidence derived from multiple publications including those from the CDC and WHO, providing a general overview and a practical, comprehensive and pertinent synthesis of diverse literature. It is believed that as research evolves, new serotypes of the pneumococcal disease may develop, and existing serotypes may mutate which would affect the development of new vaccines and the use of existing vaccines. Our study observes gaps in vaccine schedules and coverage, and sets the stage for future research. The study design also includes observational studies based on the effect of the vaccines observed over the years. However, our study lacks methodology, and an exhaustive and systematic review of the data.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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