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REVIEW

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Pneumococcal conjugate vaccines in older adults and immunocompromised individuals

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ABSTRACT

Introduction: Pneumococcal disease leads to high morbidity and mortality, particularly in older adults and immunocompromised individuals. Many pneumococcal conjugated vaccines (PCVs) have become available. However, the immunogenicity, efficacy, and effectiveness data of these vaccines in older adults and immunocompromised individuals are limited.

Areas covered: This review aims to critically examine the immune responses, immune correlations, efficacy, real-world effectiveness, and cost-effectiveness of pneumococcal conjugated vaccines (PCVs) in older adults and immunocompromised individuals.

Expert opinion: A single dose of 20-valent or 21-valent PCV is recommended for older adults and immunocompromised individuals. Immune correlates of protection vary by serotype and race. An IgG level of 0.35 µg/mL is associated with protection, though this threshold is serotype-dependent. Opsonophagocytic assays, with a threshold of 1:8, remain the most reliable functional correlate of protection against invasive pneumococcal disease. Standardized immunological assays are essential for evaluating immune responses. High-valent PCVs have shown noninferior immunogenicity compared to PCV13, though geometric mean fold rises (GMFRs) for shared serotypes are slightly lower. Real-world effectiveness data are still needed, particularly in regions with differing serotype prevalence. Serotype surveillance is crucial when introducing PCV programs. Due to the high cost of higher-valent PCVs, many countries continue using PCV13 or PCV15 followed by PPSV23 for high-risk groups.

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1. Introduction

Incidence of invasive pneumococcal disease (IPD) varies with time, countries, and regions, as the surveillance strategies vary and are heterogeneous. IPD was 18.7 per 100,000 adults aged 65 years and above in 2018 [1]. The distribution of serotypes varied with age. The five most common serotypes in the age group of more than 45 years are shown in Table 1. Overall, the case-fatality rate for invasive pneumococcal disease was reported to be high (26.1%) [2]. A study from Singapore reported characteristics of 496 pneumococcal cases identified during 2015–2017. Nearly 19% of pneumococcal cases were IPD, which had a high ICU admission rate of about 20% and an inpatient mortality of more than 25% [2]. Various risk factors for case fatality rates (CFRs) have been demonstrated in the population-based study, including age over 80 years (10.6%) and underlying comorbidities, especially hematological neoplasia (10.3%) and severe renal disease (10.1%) [3] HIV infection, prior all-cause pneumonia, and a history of prior IPD have been shown to have high hazard ratios (HRs) of 5.16, 3.96, and 2.56, respectively, [3].

After vaccine implementation in 2000, the global annual incidence of IPD decreased from 800,000 to 541,000 cases in 2008 [4]. After the introduction of PCV13 , the incidence of IPD, pneumonia, and mortality in adults aged <65 years was reduced by about 14% (IRR 0.86, 95% CI 0.81–0.91). The 30-day overall mortality from pneumonia was reduced by 46% after vaccine introduction (IRR 0.54, 95% CI 0.42–0.69). However, there was a significant increase in non-vaccine-type IPDs among adults, especially in those over 65 years [5,6].

Furthermore, the serotype distribution of IPD and noninvasive pneumococcal diseases varies greatly depending on factors such as region and vaccination policies. This highlights the critical need for surveillance data at both the regional-specific level and for special groups to inform vaccine policies.

Patients with immunocompromised conditions, including those with organ transplants and HIV infection, are at a higher risk for invasive pneumococcal disease (IPD) compared with the general population. A systematic review and meta-analysis revealed that the pooled IPD incidence among healthy individuals was 10 per 100,000 person-years, compared with 331 and 318 per 100,000 person-years in individuals with HIV receiving advanced antiretroviral therapy (ART) in non-African and African countries, respectively. The pooled incidence rates were 696 and 812 per 100,000 person-years in patients undergoing autologous and allogeneic stem cell transplantation, respectively; 414 per 100,000 in patients with solid organ transplantation; and 65 per 100,000 in patients with chronic inflammatory diseases [7].

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Article highlights

- A single dose of either 20-valent (PCV20), 21-valent (PCV21), or 15-valent PCV (PCV15) is recommended for older adults and immunocompromised individuals; if 15-valent PCV is given, follow with PPSV23 after ≥1 year.
- PCV20 or PCV21 is preferred as the vaccine of choice for older adults and immunocompromised individuals.
- IgG anti-capsular antibody measured by an enzyme-linked immunosorbent assay was shown to be correlated with efficacy/protection (CoP). However, opsonophagocytic assays (OPAs) have been shown to be the best functional correlate of protection.
- The immune responses and correlates of protection (CoPs) for PCVs vary by serotypes.
- The immune responses stimulated by high-valent PCVs have been demonstrated to be noninferior to those of PCV13 and/or PCV15.
- The immune responses of high-valent PCVs were slightly lower than those of PCV13 for shared serotypes.
- The immune responses were reduced in immunocompromised conditions; however, few studies have shown that PCVs are effective in this population.

Table 1. Proportions of the five most frequent serotypes of *S. pneumoniae* from confirmed cases of invasive pneumococcal disease, by age group.

Age group (years)	45–64	>65
Five most common serotypes by age group (% of all cases per age group)	8 (21.5%)	3 (14.7%)
	3 (14.6%)	8 (14.0%)
	19A (7.2%)	19A (7.6%)
	12F (7.1%)	22F (7.4%)
	22F (6.4%)	9N (5.4%)

Modified from www.ecdc.europa.eu/sites/default/files/documents/AER_for_2018_IPD.pdf accessed on 26 March 2025 [1].
*Number of cases for which information on serotype and age was available: 45–64 years: n = 3,481; ≥65 years: n = 8,864.

Unfortunately, the immunogenicity of pneumococcal vaccines is impaired in patients with immunosuppressive treatment compared to healthy controls. A systematic review and meta-analysis focusing on the effect of immunosuppressive agents on the immune response to pneumococcal vaccination reported an impaired humoral immune response to PCV and PPSV in autoimmune disease patients on immunosuppressive therapy compared to control cohorts [8]. In addition, an impaired response was more profound after PCV than after PPSV.

Furthermore, vaccine effectiveness tended to be lower in groups with underlying medical conditions and immunocompromising conditions. The subgroup analysis of immunocompromised adults showed lower PCV13 vaccine efficacies when compared with immunocompetent adults; vaccine efficacy for the first episode of VT-IPD – Modified Intention-to-Treat Population was 75.00 (41.43, 90.78) in the immunocompetent adult subgroup compared to 66.67 (−315.14, 99.37) in the immunocompromised adult group [9].

Therefore, this review focuses on immunogenicity, efficacy/real world effectiveness, and cost-effectiveness of the currently available pneumococcal vaccine, PCV13, PCV15, PCV20, and the current evidence of the 21- and 24-valent conjugated pneumococcal vaccine in elderly and immunocompromised hosts. The challenging issues of immune correlates of protection (CoPs) and antibiotic resistance are also included.

2. Pneumococcal vaccines and serotype coverage

There are almost a hundred capsular serotypes of *S. pneumoniae*. Pneumococcal vaccines are categorized by pneumococcal serotype coverage (Table 2). First pneumococcal vaccine, a 23-valent pneumococcal polysaccharide vaccine (PPSV23), was introduced in the early 1980s. In 2000, first 7-valent conjugate pneumococcal vaccine (PCV7) was developed and implemented in a childhood immunization program; it was substituted by 10-valent conjugate pneumococcal vaccine (PCV10) or 13-valent conjugate pneumococcal vaccine (PCV13) in 2010, depending on individual countries/regions [11]. The higher valency of vaccines primarily aims to broaden serotype coverage. However, adding more serotypes did not guarantee the immunogenicity [12]. Most countries in North America and Europe implemented PCV13 in the national immunization program for children, but South America region mostly used PCV10 instead. This is because of the epidemiological data regarding serotypes and vaccine cost-effectiveness in such countries.

For IPD, the efficacy of PPSV23 or PCV13 for preventing IPD in the first episode is about 73% and 76%, respectively [9,13,14]. Meanwhile, the efficacy of the pneumococcal vaccine against pneumonia ranges from 43% to 64% [9,13,14].

After the conjugate vaccine introduction (PCV7 and PCV13) for children since 2000 and 2010, respectively, IPD trends have declined not only among children but also in adults [15,16]. Among adults more than 65 years old, the overall IPD incidence gradually declined from 61 cases per 100,000 in 1998 to 24 cases per 100,000 in 2016 [17,18]. However, these effects were observed only in PCV13 serotype diseases.

There was a report on the decline in the incidence of IPD after the introduction of PCV13 in children. PCV13 reduced the risk of IPD, with the incident risk ratio (IRR) of 0.87 in adults aged 50–64 years and 0.86 in those aged ≥65 years, respectively. The 30-day overall reduction in mortality from pneumonia was significant with the IRR of 0.54 [6]. However, there was a significant increase in non-vaccine-type IPDs among adults, especially in those over 65 years [19].

3. Immune correlates of protection for PCV

From the data of the meta-analysis of three efficacy trials of seven serotypes in children, a level of 0.35 µg/ml of IgG anti-capsular antibody (measured by enzyme-linked immunosorbent assay) was shown to be correlated with efficacy/protection (CoP) [20]. However, the protective level is very much dependent on the serotype. Serotype 3 is the most resistant, followed by serotypes 1, 7F, 19A, and 19F, which require high antibody levels, while serotypes 6A, 6B, 18C, and 23F are less resistant [21]. CoP is referred only to protection against IPD and not to other clinical outcomes such as acute otitis media, nonbacteremic pneumonia, or nasopharyngeal carriage. Furthermore, protective correlates were 2.15 times higher in low/lower middle-income countries than in high/upper middle-income countries [22]. Thus, the efficacy of pneumococcal conjugated polysaccharide vaccines will vary with the composition of serotypes and the sites of infections, and this has to be evaluated for each serotype [23]. However, WHO guidance

Table 2. Serotype components in the currently evaluated pneumococcal polysaccharide vaccines.

	Product					
Serotype	PCV13	PCV15	PCV20	PCV21	PPSV23	PCV24
1	☆	☆	☆		☆	☆
4	☆	☆	☆		☆	☆
5	☆	☆	☆		☆	☆
6B	☆	☆	☆		☆	☆
7F	☆	☆	☆	☆	☆	☆
9V	☆	☆	☆		☆	☆
14	☆	☆	☆		☆	☆
18C	☆	☆	☆		☆	☆
19F	☆	☆	☆		☆	☆
23F	☆	☆	☆		☆	☆
3	☆	☆	☆	☆	☆	☆
6A	☆	☆	☆	☆		☆
19A	☆	☆	☆	☆	☆	☆
22F		☆	☆	☆	☆	☆
33F		☆	☆	☆	☆	☆
8			☆	☆	☆	☆
10A			☆	☆	☆	☆
11A			☆	☆	☆	☆
12F			☆	☆	☆	☆
15B			☆	☆	☆	☆
2					☆	☆
9N				☆	☆	☆
17F				☆	☆	☆
20					☆	
20A				☆		
20B						☆
15A				☆		
16F				☆		
23A				☆		
23B				☆		
24F				☆		
31				☆		
35B				☆		

Adapted from https://www.cdc.gov/mmwr/volumes/72/rr/rr7203a1.htm [10].

states that meeting either the predefined noninferiority criteria for IgG response rates or GMCs should be adequate for approval [24].

The functional assay, opsonophagocytic assay (OPA), is a bioassay measuring the capacity of antibodies to opsonize pneumococci, which is known to correlate well with protection against pneumococcal disease [24]. OPA titers, particularly with a threshold of ≥8, have been shown to be better predictors of vaccine effectiveness against invasive pneumococcal disease than ELISA antibody concentrations, especially for certain serotypes [25]. It is noted that OPA geometric mean fold rises (GMFRs) from baseline to 1 month after vaccination 1 for the 13 serotypes contained in both PCV20 and PCV13 were lower for PCV20 compared with PCV13, ranging from 6.0 to 58.6 in the PCV20 group and from 7.1 to 68.6 in the PCV13 group, depending on the serotype [26,27].

4. Pneumococcal conjugated vaccines in elderly

4.1. PCV13

The indirect effect of the pediatric PCV13 vaccination program on adult IPD was evaluated using Canadian data to assess changes in community-acquired pneumonia (CAP) incidence before and after the introduction of the PCV13 program. The study found that the PCV13 infant program was not associated with a declining CAP incidence among adults aged 50–64 years (adjusted incidence rate ratio (aIRR) 1.07; 95% CI: 1.04–1.11), aged 65 years (1.05; 95% CI: 1.02–1.08) [28]. Conversely, the study conducted in Japan comparing two phases of the multicenter prospective study before and after inclusion of PCV13 in the pediatric program showed that the proportion of VT-CAP notably declined following the vaccine introduction [29].

The efficacy results of the 13-valent pneumococcal conjugate vaccine (PCV13) in preventing vaccine-type strains and pneumococcal community-acquired pneumonia (CAP) have been shown in older adults. The CAPiTA trial reported PCV13 efficacy rates of 45.6% against vaccine-type pneumococcal CAP, 45.0% against nonbacteremic/noninvasive pneumococcal CAP, and 75.0% against invasive pneumococcal disease in older adults aged ≥65 years. Post-licensure studies corroborate these findings, indicating effectiveness rates of 47–59% for PCV13-type invasive pneumococcal disease (IPD), 38–70% for noninvasive PCV13-type pneumonia , and 6–11% for all-cause pneumonia [9]. PCV13 also demonstrated modest effectiveness against all-cause medically attended lower respiratory tract infections (9.5%) and pneumonia (8.8%) in older adults. Previously, the Advisory Committee on Immunization Practices (ACIP) recommended PCV13 in combination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults aged 65 and older to provide comprehensive protection against pneumococcal diseases.

The vaccine effectiveness was similar among the elderly regardless of age. The trial of PCV13 conducted in the Netherlands showed a decline in vaccine efficacy with age;

the efficacy in preventing CAP and IPD declined from 65% to 40% for subjects aged 65 and 75 years in a post hoc analysis [30]. However, the retrospective cohort in the U.S.A. found that the vaccine effectiveness against PCV13 serotypes was approximately the same among those who were ≥75 years (VE = 63.6%; CI: 42.2–77.1%) and those who were 65 to <75 years (VE = 55.6%; CI: −6.7–81.5%) [31].

4.2. PCV15

In clinical studies, PCV15 displayed acceptable safety profiles and induced serotype-specific immune responses comparable to PCV13 in healthy adults ≥50 years [32]. The systematic review and meta-analysis revealed superior immunogenicity of PCV15 compared to PCV13 in older adults [33].

The clinical studies of the 15-valent pneumococcal conjugate vaccine (PCV15) have been evaluated in several studies. Greenberg et al. evaluated the safety and immunogenicity of PCV15 in healthy infants [34]. The study demonstrated that PCV15 had a comparable safety profile to PCV13 and induced similar immunogenic responses for most shared serotypes. Additionally, PCV15 induced higher antibody levels for serotypes 3, 22F, and 33F compared to PCV13. In adults, PCV15 induced comparable levels of serotype-specific IgG and opsonophagocytic activity (OPA) as PCV13 and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for shared serotypes [35]. PCV15 also induced higher antibody responses for the unique serotypes 22F and 33F [35]. The cost-effectiveness was also reported. A study by Prasad et al. assessed the public health impact and cost-effectiveness of replacing the 13-valent pneumococcal conjugate vaccine (PCV13) with PCV15 in the routine infant immunization program in the United States. The study found that replacing PCV13 with PCV15 could prevent an additional 92,290 pneumococcal disease events and 22 associated deaths while also saving $147 million in costs.

These studies collectively indicate that PCV15 is clinically effective in both pediatric and adult populations, providing broader protection against additional pneumococcal serotypes compared to PCV13.

4.3. PCV20

The 20-valent pneumococcal conjugate vaccine (PCV20) has demonstrated significant efficacy in older adults through various clinical trials. In a pivotal phase 3 randomized clinical trial, PCV20 was shown to be safe, well tolerated, and immunogenic in adults aged ≥60 years [36]. The study found that immune responses to PCV20 were noninferior to those elicited by the 13-valent pneumococcal conjugate vaccine (PCV13) for the 13 shared serotypes and to the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for six of the seven additional serotypes [36].

Another phase 3 study conducted in Japan, South Korea, and Taiwan confirmed these findings, demonstrating that PCV20 generated robust immune responses to all 20 vaccine serotypes in adults aged ≥60 years. The safety profile of PCV20 was similar to that of PCV13, with no significant safety concerns identified [37]. Furthermore, in the phase 3 study, PCV20 was shown to be well tolerated and immunogenic in adults aged 60–64 years, with substantial opsonophagocytic activity responses against all 20 serotypes [26]. Another study confirmed that PCV20 was well tolerated and induced strong opsonophagocytic antibody responses in adults aged ≥65 years, regardless of their prior pneumococcal vaccination history [38].The summary of clinical effectiveness of PCV13, 15, and 20 was shown in Table 3.

Additionally, a study evaluating the cost-effectiveness of PCV20 in older adults in England found that PCV20 averted more cases of invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP) compared to PCV15 and PPSV23, suggesting that PCV20 could provide broader protection against pneumococcal disease in this population [39]. The cost-effectiveness study in the U.S. reported that PCV20 alone improved health outcomes compared with PCV15 in series with PPSV23; however, PCV15 in series with PPSV23 increased quality-adjusted life years (QALYs) [40]. Other cost-effectiveness studies of PCV20 in the elderly are summarized in Table 4.

The latest observational study on the elderly (age ≥65) in the UK reported that vaccinating newly admitted older adults in care homes could significantly lessen the impact of

Table 3. Summary of clinical effectiveness of PCV13, 15, and 20 in older adults.

Author	Study vaccine	Study design	Study population	Outcome	Finding
Vila-Córcoles et al. [41]	PCV13	Cohort	Spain, age ≥50, 2015–6	Hospitalization from pneumococcal or all-cause pneumonia	VE −52% (−97 to −17) Pneumococcal vaccination with either PCV13 or PPSV23 showed no clinical benefit against pneumonia in the context of widespread childhood PCV immunization.
Lewnard et al. [42]	PCV13	Open cohort	U.S.A. (PCV13 coverage 43–49%), age ≥65, 2016–9	Medically attended pneumonia, Pneumonia	VE was 9.5% (2.2% to 16.3%) against all-cause medically attended LRTI VE 8.8% (−2% to 17.0%) against all-cause medically attended pneumonia
Prato et al. [17]	PCV13	Test-negative design case-control	Italy, CAP hospitalization, age ≥65, 2013–5	VT-CAP and pneumococcal CAP	VE 33.2% (−106.6% to 82%) against PCAP irrespective of serotype VE 38.1% (−131.9% to 89%) against VT-CAP
McLaughlin et al. [43]	PCV13	Test-negative design case-control	U.S.A. (PCV13 coverage 18%), CAP hospitalization age ≥65, 2015–6	Hospitalized VT-CAP	Adjusted VE range, 71.1%-73.3%

VE = vaccine effectiveness; CAP = community-acquired pneumonia; VT-CAP = vaccine-type community-acquired pneumonia.

Table 4. Summary of cost-effectiveness of PCV13, 15, and 20 in older adults.

Author	Study vaccine	Study population	Finding
Ngamprasertchai et al. [46]	PCV13 vs PPSV23	Thailand, age ≥65	PCV13 is a cost-effective vaccination option for older adults compared to PPSV23 or no vaccination.
Rosenthal et al. [40]	PCV15 vs PCV20	U.S.A., age ≥65, 2017–8	PCV20 alone was cost-saving, while the sequential use of PCV15 followed by PPSV23 resulted in increased QALYs.
Danelian et al. [39]	PCV15, PCV20, PPSV23	UK, age ≥65, 2017–8	Both PCV20 and PPSV23 were found to be cost-effective, with PCV15 being less cost-effective than PCV20. Vaccination at age 75 proved to be more cost-effective than vaccination at age 65.
de Boer et al. [47]	PCV15, PCV20, PCV21, PPSV23	Netherland, age ≥65, 2021	When PCV10, PCV13, or PCV15 was used in children, PCV20 was more effective and less costly for older adults compared to PPSV23 and PCV15. With PCV20 implemented in childhood immunization, its cost-effectiveness for older adults was no longer observed. Indirect effects had minimal influence on the cost-effectiveness of PCV21
Malene et al. [48]	PCV20 vs. PPSV23	Norway, age 18–99, 2019	PCV20 was linked to a greater QALY gain (7,966 more) and lower overall costs compared to PPSV23.
Kang et al. [49]	PCV20 vs. PPSV23	Korea, age ≥65	PCV13 is a cost-effective vaccination option for older adults compared to PPSV23 or no vaccination.
Nakamura et al [50]	PCV20 vs. PPSV23	Japan, age ≥65 and high-risk adults age 60–64, 2022	PCV20 alone was cost-saving, while the sequential use of PCV15 followed by PPSV23 resulted in increased QALYs.

QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio.

pneumococcal disease in this high-risk group [44]. The PCV20 vaccine is expected to offer greater protection than PPSV23.

Overall, PCV20 has been shown to be safe, well-tolerated, and immunogenic in older adults, with the potential to expand protection against pneumococcal disease beyond that provided by PCV13 and PPSV23. In October 2024, the ACIP recommended one dose of PCV21, PCV20, or PCV15 for PCV-naïve adults who are either aged ≥65 years or aged 19–64 years with certain underlying conditions, and PCV15 should be followed by PPSV23, typically ≥1 year later. PCV20 simplifies the schedule by giving broad protection with a single dose without requiring a follow-up dose of PPSV23. A recent study on the real-world vaccine effectiveness against IPD and acute community-acquired pneumonia (ACP) among adults >65 years old has confirmed by the prevention of 25.6% of IPD cases and 15.2% of ACP cases [45].

5. Pneumococcal conjugated vaccines in immunocompromised individuals

While there is robust evidence supporting the use of pneumococcal conjugate vaccines (PCVs) in children and an increasing number of studies in older adults, data on immunogenicity, clinical effectiveness, and cost-effectiveness of PCVs in immunocompromised populations remain significantly limited. The heterogeneity among immunocompromised subgroups such as differences in underlying conditions, immune status, and treatment regimens adds further complexity and limits the generalizability of existing study results. While immunogenicity data are better studied across various types of immunocompromised hosts, clinical efficacy, and effectiveness data remain limited. This critical gap highlights the need for well-designed, subgroup-specific studies in immunocompromised populations to address the effectiveness of PCV, especially the use of higher-valent PCVs in this population.

5.1. PCV13

A review by Chilson et al. summarized immunogenicity data from 30 publications involving 2406 immunocompromised individuals [51]. The study showed that although antibody responses to PCV13 in these individuals were variable and generally lower compared to healthy controls, the vaccine was still immunogenic and well tolerated. The effectiveness and the cost-effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) in immunocompromised patients have been evaluated in a few studies (Tables 5 and 6).

M. B. Roberts demonstrated the superior clinical effectiveness of PCV13 over PPSV23 in preventing infection following hematologic stem cell transplantation (HSCT) [18]. In this retrospective analysis of HSCT recipients from 2004 to 2015, they evaluated the vaccination uptake and compared IPD rates in patients receiving PPV (pre-2010 group) and PCV (post-2010 group). The IPD rate was significantly reduced from 38.5/1000 unique HSCTs pre-2010 to 4.0/1000 unique HSCTs post-2010 ($p < .001$). A significant reduction was seen in both auto-HSCTs (from 29.4 to 3.1/1000 unique auto-HSCTs; $p = .011$) and allo-HSCTs (from 58.3 to 5.6/1000 unique allo-HSCTs; $p = .011$).

In HIV-infected adults, Glesby et al. reported that PCV13 induced significant increases in anticapsular immunoglobulin G concentrations and opsonophagocytic antibody titers, especially among those previously vaccinated with the 23-valent

Table 5. Summary of clinical effectiveness of PCV in immunocompromised individuals.

Author	Study vaccine	Study design	Study population	Outcome	Finding
Robert et al. [18]	PCV10 or PCV13	Retrospective cohort	Australia, HSCT, 2004–2019	IPD	PCV showed greater clinical effectiveness compared to PPSV. Following the introduction of PCV, the incidence of IPD significantly decreased in both auto-HSCT and allo-HSCT patients, dropping from 38.5 to 4.0 cases per 1000 individuals.

HSCT = hematopoietic stem cell transplantation; IPD = invasive pneumococcal disease.

Table 6. Summary of cost-effectiveness of PCV in immunocompromised individuals.

Author	Study vaccine	Study population	Finding
Smith et al. [52]	PCV13 vs. PPSV23	U.S.A., immunocompromised persons, 2007–2008	A single dose of PCV13 is more cost-effective for immunocompromised individuals than two doses of PPSV23.
Ngamprasertchai et al. [46]	PCV13 vs PPSV23	Thailand, immunocompromised	PCV13 is a cost-effective vaccine compared to PPSV23 and no vaccination, with an ICER of $627.24 per QALY gained.
Cho et al. [53]	PCV13 over PPSV23	U.S.A., immunocompromised	Adding one dose of PCV13 to the previously recommended PPSV23 regimen for adults with certain immunocompromised conditions reduces disease burden and costs, preventing 57 cases of IPD, 619 cases of hospitalized all-cause pneumonia, and 93 deaths, while saving 1360 QALYs.

QALYs= quality-adjusted life years; ICER= incremental cost-effectiveness ratio.

pneumococcal polysaccharide vaccine (PPSV23) [51]. The responses were consistent across multiple doses, supporting the use of PCV13 in this population. Similarly, Bhorat et al. found that a three-dose regimen of PCV13 was well tolerated and elicited significant immune responses in pneumococcal vaccine-naive, HIV-infected individuals [54].

In pediatric and adolescent oncology patients, Hung et al. demonstrated that a single dose of PCV13 was safe and immunogenic, with a significant proportion of patients achieving protective antibody titers post-vaccination [55]. In patients with sickle cell disease, Melica et al. showed that a PCV13/PPSV23 regimen improved the breadth and magnitude of antibody responses against a wide range of pneumococcal serotypes, with sustained immune responses over time [56].

In summary, PCV13 is effective in inducing an immune response and is generally well tolerated in immunocompromised patients, including those with HSCT, HIV, cancer, and sickle cell disease.

ACIP has recommended the use of either a single dose of PCV20 or PCV21 as previously recommended for adults with an immunocompromising condition, a CSF leak, or a cochlear implant who have started their pneumococcal vaccine series with PCV13 but have not received all recommended PPSV23 doses [57].

5.2. PCV15

The efficacy of the pneumococcal conjugate vaccine 15 (PCV15) in immunocompromised adults is supported by clinical studies and guidelines. The phase 3 clinical study of HSCTs showed that three doses of PCV15 were safe, well-tolerated, and could induce comparable immune responses to PCV13 for the 13 shared serotypes and a higher immune response for serotypes 22F and 33F [58].

The American Society of Clinical Oncology (ASCO) guidelines recommend pneumococcal vaccination for adults with cancer, including those undergoing hematopoietic stem cell transplantation (HSCT) and other immunocompromising treatments. These guidelines indicate that PCV15 can be used in a series with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) to enhance immunogenicity and protection against invasive pneumococcal disease (IPD). The American College of Rheumatology (ACR) also supports the use of PCV15 in immunocompromised patients, particularly those with rheumatic and musculoskeletal diseases who are on immunosuppressive medications. The ACR recommends a prime-boost strategy with PCV15 followed by PPSV23 to improve antibody responses.

5.3. PCV20

There is no study on PCV20 in immunocompromised individuals. However, based on the fact that PCV20 has demonstrated immunogenicity and safety in immunocompetent adults. Guidelines recommended PCV20 for immunocompromised hosts. Centers for Disease Control and Prevention (CDC) recommends one dose of PCV20 for adults aged 19–64 years with immunocompromising conditions, such as chronic renal failure, cochlear implants, or cerebrospinal fluid leaks. Clinical trials have shown that PCV20 is immunogenic and well tolerated in adults, including those with prior pneumococcal vaccination. A pivotal phase 3 randomized clinical trial demonstrated that PCV20 elicited robust immune responses to all 20 vaccine serotypes, with immunogenicity comparable to that of PCV13 and PPSV2323. The American Diabetes Association, in collaboration with the Advisory Committee on Immunization Practices (ACIP), also supports the use of PCV20 in adults with diabetes, who often have immunocompromising conditions. For immunocompromised conditions, cerebrospinal fluid leak, or cochlear implant, ACIP recommends one dose of PCV20 or PCV21 given at least 5 years after the most recent pneumococcal vaccination. Regardless of which vaccine is used (PCV20 or PCV21), their pneumococcal vaccinations are complete. No additional pneumococcal vaccines are recommended until at least age 50 years for other risk conditions [57].

6. The current evidence of the 21-valent and 24-valent conjugated pneumococcal vaccine

6.1. PCV21

The current evidence on the efficacy of the 21-valent conjugated pneumococcal vaccine (CAPVAXIVE) indicates that it is effective in inducing robust immunogenic responses against multiple pneumococcal serotypes. A phase 1/2 trial published in The Lancet Infectious Diseases assessed the safety, tolerability, and immunogenicity of PCV21 in healthy adults. The study found that CAPVAXIVE was well tolerated and induced functional OPA antibodies against all vaccine serotypes. The vaccine was noninferior to the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for the 12 shared serotypes and superior for the nine unique serotypes included in PCV21 [59]. In a phase 3 clinical study

involving pneumococcal vaccine-naïve individuals aged 50 years and older, PCV21 demonstrated noninferiority to PCV20 for the 10 shared serotypes and induced statistically significantly greater opsonophagocytic activity (OPA) geometric mean titers (GMTs) for 10 of the 11 serotypes unique to CAPVAXIVE [60]. Specifically, the vaccine showed a significant increase in the proportion of individuals achieving a ≥4-fold rise in OPA responses for these unique serotypes, except for serotype 15C. These findings support the use of CAPVAXIVE for the prevention of pneumococcal disease in adults, demonstrating its efficacy in generating strong immunogenic responses against a broad range of pneumococcal serotypes.

In addition, the study that assessed the cost-effectiveness of PCV21 in U.S. adults aged 50 years or older found that PCV21 is potentially cost-effective compared to currently approved pneumococcal vaccines in adults aged 50 years or older from both the societal and healthcare perspectives [61]. Furthermore, the results from a cost-effectiveness analysis of PCV among adults in Canada reported that PCV21 appears to be a cost-effective option compared to the current standard of care in Canada, especially for adults aged 65 and older [62]. The decision between using PCV21 or PCV20 depends on factors such as the dominant serotypes in circulation, the indirect benefits of childhood vaccination programs, differences in individual and population risk levels, and the relative costs of the vaccines.

6.2. PCV24

The 24-valent conjugated pneumococcal vaccine based on the multiple antigen-presenting system (MAPS) technology (Pn-MAPS24v) has been evaluated in clinical trials. The phase 1 randomized controlled trial (RCT) in toddlers revealed that a single dose of Pn-MAPS24v showed an acceptable safety profile and elicited IgG and OPA responses to PCV13 common serotypes and most unique serotypes [63]. A phase 1/2 study compared a novel 24-valent pneumococcal vaccine with PCV13 in healthy adults aged 18 to 64 years and in older adults aged 65 to 85 years and reported good tolerability, and the 24-valent PCV showed similar or higher immunogenicity (both IgG and OPA) in shared serotypes compared with PCV13 [64]. Another phase 1/2 study evaluating the safety, tolerability, and immunogenicity of a 24-valent pneumococcal conjugate vaccine in naïve healthy adults aged 18 to 64 years compared with PCV20 reported a similar safety profile to PCV20 at all doses, with the 2.2 µg dose showing increased serotype coverage and decreased carrier suppression [65].

However, a cost-effectiveness analysis using a Markov model, comparing the 24-valent pneumococcal conjugate vaccine with PCV21, one of the currently recommended U.S. pneumococcal vaccination strategies in older adults (aged ≥65 years), reported that the 21-valent pneumococcal conjugate vaccine was economically favorable compared with the 24-valent pneumococcal conjugate vaccine and all other vaccination strategies [66]. Further studies are required to determine the future direction and recommendations of new conjugated pneumococcal vaccines, especially in special groups such as older adults and patients with immunocompromised conditions.

7. Conclusion

PCV plays a critical role in protecting elderly and immunocompromised individuals from pneumococcal infections and their complications, which are associated with high morbidity and mortality in these populations. PCV13 effectively reduces the incidence of vaccine-type pneumococcal CAP, nonbacteremic CAP, and invasive pneumococcal disease, with a favorable safety profile. Studies show that PCV15 induces comparable immune responses to PCV13 and PPSV23 for shared serotypes, with superior responses for 22F and 33F. It is recommended for elderly and immunocompromised adults, including those with cancer or rheumatic diseases, often in combination with PPSV23 for enhanced protection. The immune responses to PCV are strong, and immune correlates have been defined. However, the responses vary by serotype. Therefore, PCV20 or PCV21 is recommended. Although clinical evidence on cost-effectiveness is limited, current data support its use.

The higher coverage of 21-valent and 24-valent conjugated pneumococcal vaccines is promising. Future studies focusing on immunogenicity, efficacy, and effectiveness, as well as cost-effectiveness, especially in high-risk populations, such as older adults and immunocompromised individuals, are required in order to drive public health policy.

8. Expert opinion

A single dose of the higher-valent PCV20 or a 15-valent PCV followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been recommended for adults aged 50–64 years with risk conditions for pneumococcal disease and for all adults aged ≥65 years [67–70]. However, data on real-world implementation of higher-valent PCV20 are not yet available.

Current PCV vaccines have been successful in reducing invasive pneumococcal disease burden and appear to be cost-effective, especially after PCV13 or PCV15 introduction. The serotype replacement effect has not been observed in many countries, which may be limited by the country surveillance system and exposure patterns to pneumococcal serotypes. The serotypes prevalent in countries/regions might be different among the pediatric age group and the older age group. The circulating serotypes across different geographical regions are different; therefore, active surveillance is an important tool to assess circulating serotypes and herd effects on pneumococcal disease in both pediatric and older populations.

In terms of immune correlates of protection, which vary depending on serotypes, genetics, and race, this has raised concerns. A level of 0.35 µg/ml of IgG anti-capsular antibody (measured by enzyme-linked immunosorbent assay) was shown to be correlated with efficacy/protection (CoP). However, the protective level is highly dependent on serotype. In vitro opsonophagocytosis assays (OPAs) have been shown to be the best functional correlate of protection in various studies. OPA titers, particularly with a threshold of 1:8, have been shown to be better predictors of vaccine effectiveness against invasive pneumococcal disease than ELISA antibody concentrations. Standardized immunological assays for assessing immune correlates are critical and remain to be evaluated.

The immune response stimulated by high-valent PCV has been demonstrated to be noninferior to PCV13. However, the immune responses were slightly lower than those of PCV13 for shared serotypes. The magnitude of the responses against shared serotypes was slightly lower but did not go beyond the noninferiority margin. The immune responses are reduced in immunocompromised conditions; however, PCV has demonstrated the effectiveness and cost-effectiveness of these populations.

Despite limited data, PCVs are a key preventive tool for immunocompromised individuals, offering improved and longer-lasting protection. Higher-valent PCVs (PCV20 or PCV21), which offer expanded serotype coverage, are recommended. If PCV15 is administered, follow it with PPSV23 after the recommended interval of at least 8 weeks. The durability of protection and the optimal booster regimens in immunocompromised populations remain unclear. Further studies are needed to refine vaccination timing, optimize dosing strategies, and evaluate long-term immunity across specific immunocompromised conditions.

Vaccine effectiveness has been assessed using various methodologies, often resulting in differing estimates depending on study design, population, and outcome measures. These variations can significantly influence the interpretation of vaccine impact. Without accurate and consistent clinical effectiveness data, it is impossible to reliably estimate cost-effectiveness, as economic models depend heavily on real-world effectiveness to project health and economic outcomes.

The effectiveness data in older age groups and immunocompromised populations are limited. More data on real-world effectiveness for PCV20 or 21 in these two groups are needed. There is a need for robust data, which remains to be demonstrated, especially when introduced in countries where the prevalent serotypes might be different from the serotypes in the current PCV vaccines. The scanty data on durability of the immune response and effectiveness in immunocompromised populations are also important for policy. Different PCVs for pediatric and older age groups might be needed.

Author contributions

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Declaration of interest

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