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ARTICLE COMMENTARY

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Strategies for pneumococcal vaccination in older adults in the coming era

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ABSTRACT

Pneumonia, predominantly caused by *Streptococcus pneumoniae*, remains a leading cause of global mortality. The 23-valent Pneumococcal polysaccharide vaccine (PPSV23) and conjugate vaccines (PCVs) are vital measures to fight against it. This paper discussed the changes in pneumococcal vaccination strategies, particularly for older adults, as vaccine effectiveness and epidemiological patterns shift. While PPSV23 maintains effectiveness against invasive pneumococcal disease (IPD), its effectiveness against pneumococcal pneumonia is declining. Conversely, PCV13 consistently demonstrates effectiveness against both IPD and pneumonia. Consequently, the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends using PCVs, notably PCV20 and PCV15, over PPSV23. Japanese studies indicate a change in the efficacy/effectiveness of PPSV23 following PCV introduction in children, likely owing to serotype replacement and herd immunity. Additionally, recent data reveals a plateau in the reduction of PCV13 and PPSV23-covered serotypes, posing a challenge to current strategies. This paper indicates a paradigm shift in pneumonia management, acknowledging its chronic nature and potential to exacerbate other diseases. The future of pneumococcal vaccination lies in broader serotype coverage through PCVs, adapting to serotype changes driven by childhood vaccination programs. Furthermore, continuous research and vaccine development are crucial in this evolving field.

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Introduction

Pneumonia is one of the leading causes of global mortality, with *Streptococcus pneumoniae* as the most common causative agent.[1] Vaccination against this bacterium has become vital for prevention, initially provided by the pneumococcal polysaccharide vaccine, more recently known as the 23-valent pneumococcal polysaccharide vaccine (PPSV23).[2] Polysaccharide vaccines directly stimulate B-cell antigen receptors, inducing antibody production without requiring helper T-cells.[3] However, owing to this T cell-independent mechanism, memory B-cells are not generated, leading to serum antibody decline approximately 5 years later.[3] The pneumococcal conjugate vaccine (PCV) was developed to address this limitation by conjugating the capsular polysaccharide to a carrier protein.[4] This allows helper T-cell activation to enhance antibody affinity and induce memory B-cell activation.[4]

The current recommendations by the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) primarily focus on the use of PCVs, advocating for the exclusive administration of 20-valent pneumococcal conjugate vaccine (PCV20), or the sequential administration of 15-valent pneumococcal conjugate vaccine (PCV15) followed by PPSV23.[1] The rationale for this policy is that while the PCV, particularly PCV13, consistently demonstrates efficacy/effectiveness against IPD and pneumococcal pneumonia,[5] the PPSV23 maintains its effectiveness against IPD, but not consistently against pneumococcal pneumonia.[1,6,7] Equivalent immunogenicity and safety have been suggested for PCV20 alone or PCV15 followed by PPSV23 when compared to PCV13 alone or PCV13 followed by PPSV23.[5,8,9] Furthermore, cost-effectiveness analyses indicate that using PCV20 alone or PCV15 followed by PPSV23 resulted in significant cost reduction in adults aged 65 years and older.[5] All these findings formed the basis for the current recommendations.

To date, the recommendation status of pneumococcal vaccines for older adults varies among countries. Generally, developed nations, including the UK, Canada, France, and Germany, have started recommending PCV20.[1,10–13] PPSV23 is recommended in the US, the UK, and Canada, with the US and Canada suggesting sequential vaccination using PCV15 when administering PPSV23. In the national immunization program in Japan, routine PPSV23 vaccination is recommended for older adults, with sequential PCV13 or PCV15 vaccination deemed optional as of February 2024. In November 2023, 23 academic organizations in Japan submitted a petition to the government, advocating for the inclusion of routine PCV20 in the national immunization program; therefore, the national vaccination policy may change soon. These disparities can be attributed to differences in the following: epidemiological landscapes of pneumococcal serotypes, vaccine effectiveness data, healthcare system resources, policy, and regulatory factors, and divergent frameworks and assessment methodologies.[14] Given these circumstances, pneumonia vaccination strategies for older adults have become more complex.

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In this commentary, we discuss future strategies for pneumococcal vaccine administration in older adults, considering previous changes in vaccine efficacy/effectiveness, serotype replacement following childhood PCV vaccination, and the evolving understanding of pneumonia as a disease.

Recent data on the efficacy and effectiveness of PPSV23 against IPD and pneumococcal pneumonia in adult population

Recent data on PPSV23 shows consistent effects against IPD. However, a declining trend against pneumococcal pneumonia has been observed, given the increasing number of reports that fail to detect its effectiveness.[15] Turning out attention to IPD, a 2013 Cochrane meta-analysis reported a 74% efficacy against IPD.[16] Subsequently, a 2018 meta-analysis, assessing 21 studies with 826,109 adult participants, found no significant effect of PPSV23 on all-cause pneumonia, pneumococcal pneumonia, and pneumonia-related deaths, but did detect significant efficacy against IPD.[17] More recently, a 2023 meta-analysis reported a 45% effectiveness against vaccine-type serotype IPD (95% CI: 37%, 51%) across nine studies.[18]

Interestingly, while the efficacy of PPSV23 against IPD remains intact, numerous studies indicate a decline in its effectiveness against pneumococcal pneumonia.[15] This is particularly evident in data following the PCV13 introduction in children across various countries. A 2013 Cochrane Review reported a 54% effectiveness of PPSV23 against non-invasive pneumococcal pneumonia,[16] whereas a 2018 meta-analysis found no effectiveness against pneumococcal pneumonia.[17] Additionally, a 2023 meta-analysis across five observational studies examined the effectiveness of PPSV23 against PPSV23-type pneumococcal pneumonia, showing a pooled vaccine effectiveness of 18% (95% confidence interval [CI]: −4%, 35%; $I^2 = 0\%$), indicating no significant preventive effect.[18]

Research efforts in Japan encourage investigators to conduct randomized controlled trials (RCTs) and observational studies on PPSV23 efficacy/effectiveness in older adults and changes in pneumococcal serotype data, allowing a comprehensive understanding of the changes in PPSV23.[15,19–22] Table 1 presents a summary of PPSV23 efficacy and effectiveness with condition of pediatric PCV administration, and the prevalence of non-PCV13 and non-PPSV23 serotypes in pneumococcal pneumonia among older adults in Japan. Between 2005 and 2009, two RCTs were conducted before pediatric PCV7 introduction.[19,20] Kawakami et al.'s study on all-cause pneumonia reported that from October 2005 to November 2007, influenza-vaccinated individuals had an efficacy of 41.5% in those aged 75 and above and 62.7% in those with mobility issues (e.g., difficulty walking).[19] Similarly, Maruyama et al.'s study from March 2006 to March 2009 showed an efficacy of 44.8% against all-cause pneumonias and 63.8% against pneumococcal pneumonia.[20] Notably, non-PCV13 and non-PPSV23 serotype pneumococcal pneumonia accounted for 25% of cases in older adults during these periods.[23,24]

Following the PCV7 introduction but before PCV13, two studies further explored PPSV23 effectiveness.[21,22] Suzuki K et al. (our group) conducted a multicenter, case-control study from October 2010 to September 2014, detecting an effectiveness of 77% against pneumococcal pneumonia in individuals aged over 65 years, but found no effectiveness against all-cause pneumonia.[21] Suzuki M et al. performed a test-negative, case-control study using a multicenter registry of community-acquired pneumonia (CAP) from September 2011 to August 2014, reporting effectiveness of 27.4% against all-cause pneumococcal pneumonia and 33.5% against PPSV23-type pneumococcal pneumonia in individuals aged 65 years and over.[22]

Following the introduction of pediatric PCV13 in November 2013, the vaccination rate exceeded 95% in children under 5 years.[25] To assess the effectiveness of PPSV23 in the population aged 65 years and older post-introduction of the childhood PCV13, we conducted a nationwide, multicenter, case-control study from October 2016 to December 2019, involving 30 hospitals and 11 clinics in Hokkaido, Tohoku, Hokuriku, Kanto, Tokai, Kinki, Shikoku, and Kyushu.[15] In this study, no significant effectiveness was observed against all-cause pneumonia (−33%; 95% CI: −109%, 15%) and pneumococcal pneumonia (7%;

Table 1. Summary of PPSV23 efficacy and effectiveness, and non-PCV13 and non-PPSV23 serotypes of pneumococcal pneumonia in the older population in Japan, with condition of pediatric PCV vaccination.

Ref	Study period	Condition of pediatric PCV vaccination	Study design	VE (95%CI) for all-cause pneumonia	VE (95%CI) for pneumococcal pneumonia	Non-PCV13 and non-PPSV23 serotypes of pneumococcal pneumonia in older population
Kawakami et al.[19]	2005–2007	Pre-PCV7	Randomized Controlled trial	41.5% (2.7 to 65.5) (in subjects over 75 years old) 62.7% (25.7 to 82.1) (in subjects with difficulty walking)	Not assessed	Proportion of non-PCV13 and non-PPSV23 serotypes 25% (2006)[23,24]
Maruyama et al.[20]	2006–2009	Pre-PCV7	Randomized Controlled trial	44.8% (22.4 to 60.8)	63.8% (32.1 to 80.7)	Same as above
Suzuki K et al.[21]	2010–2014	Post-PCV7, Pre-PCV13	Case-control study	No effectiveness (24% [−32 to 66])	77% (34 to 92)	Proportion of non-PCV13 and non-PPSV23 serotypes 28% (2011– 2014)[26]
Suzuki M et al.[22]	2011–2014	Post-PCV7, Pre-PCV13	Case-control study (Test-negative design)	Not assessed	27.4% (3.2 to 45.6)	Same as above
Nakashima et al.[15]	2016–2019	Post-PCV13	Case-control study	No effectiveness (−33% [−109 to 15])	No effectiveness (7% [−150 to 65])	Proportion of non-PCV13 and non-PPSV23 serotypes 49% (2016–2017)[26]

Abbreviations: PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; VE, vaccine efficacy/effectiveness; PCV13, 13-valent pneumococcal conjugate vaccine.

95% CI: −150%, 65%). This lack of effectiveness is likely owing to serotype replacement and herd immunity effects following PCV13 introduction in children.[15] Notably, another study indicated the prevalence of non-PCV13 and non-PPSV23 serotypes in pneumococcal pneumonia increased from 28% (September 2011-August 2014) to 49% (May 2016-April 2017).[26] Given these dynamics, detecting PPSV23 effectiveness has become more complicated.

Recent data on the efficacy and effectiveness of PCV13 against IPD and pneumococcal pneumonia

The efficacy of PCV13 against IPD and pneumococcal pneumonia was initially demonstrated in the CAPiTA study, a randomized, double-blind, placebo-controlled trial conducted in the Netherlands from September 2008 to January 2010.[27] This study involved 84,496 adults aged 65 and older, reporting efficacies of 75% against vaccine-type IPD and 45.6% against vaccine-type pneumococcal pneumonia. Subsequent observational studies have reported similar findings regarding PCV13 effectiveness.[28,29] A test-negative, case-control study conducted in the US from April 2015 to April 2016 included 2,034 hospitalized patients with CAP who were aged 65 and older.[28] This study reported an effectiveness of 71.2% against vaccine-type pneumococcal pneumonia. Another test-negative study conducted in South Korea from 2015 to 2017 investigated the effectiveness of PPSV23 and PCV13 administration.[29] The study detected no effectiveness for PPSV23 in individuals aged 65–74 among hospitalized patients with CAP aged 65 and older. However, sequential PCV13/PPSV23 administration revealed a significant effectiveness of 80.3%, whereas PCV13 alone also showed a significant effectiveness of 66.4%. Regarding long-term efficacy, the post-hoc analysis of the CAPiTA study demonstrated the efficacy of PCV13 against vaccine-type IPD (66.7% after 1 year, 75.0% after 5 years) and vaccine-type, noninvasive, pneumococcal pneumonia (43.8% after 1 year, 45.0% after 5 years).[30] Subsequent analysis of the CAPiTA study in adults with chronic diseases (excluding immunodeficiency) demonstrated significant and sustained efficacy for PCV13 against vaccine-type pneumococcal CAP over an average of 4 years.[31] In contrast, the protective duration of PPSV23 has declined over time.[1,32] Although no trial has directly compared the effectiveness of PCV13 and PPSV23, a 2023 literature review of nine studies from high-income countries evaluated their effectiveness in the same adult population.[33] In this review, the point estimates of vaccine effectiveness for vaccine-type pneumococcal pneumonia were 2% to 6% for PPSV23 and 41% to 71% for PCV13. The point estimates for pneumococcal pneumonia or severe pneumococcal disease were −10% to 11% for PPSV23, 40% to 79% for PCV13, and 39% to 83% for sequential PCV13/PPSV23 administration. For all types of pneumonia or lower respiratory tract infections, the estimates were – 8% to 3% for PPSV23 and 9% to 12% for PCV13. Overall, the review revealed that PCV13 had better outcomes than PPSV23 for pneumococcal infections and all respiratory disease outcomes.[33]

The latest situation regarding serotype replacement and serotype coverage of pneumococcal vaccines

While serotype replacement has been observed in adult pneumococcal infections following the introduction of childhood PCV13, the decline in serotypes covered by both PCV13 and PPSV23 has plateaued.[1,5,34–36] A recent multi-country review found that serotypes covered by PCV13 still account for 34–54% of adult pneumococcal pneumonia cases after the introduction of PCV13 in children.[35] This indicates the continued presence of PCV13 serotypes as causative agents in adult pneumonia. Furthermore, a study across 33 high-income countries revealed that PCV13 serotypes comprised 30.6% of adult IPD cases in pediatric PCV13-using countries.[37] In the US, a surveillance study from 2018–2019 focusing on adults aged 65 years and older with IPD found that 27% of the serotypes were covered by PCV13, while an additional 35% were unique to PPSV23.[5] Another prospective study in the US involving adult patients aged 18 years and older hospitalized with pneumococcal pneumonia showed that 37.7% of the serotypes were of the PCV13 serotype.[38] Prior to the introduction of PCV13 in Japan (2011–2014), a study on individuals aged 65 years and older with pneumococcal pneumonia indicated a 52.7% prevalence of PCV13 serotypes.[34] This prevalence decreased to 30.4% between 2016 and 2017, but persisted at 38.5% from 2018 to 2020.[34]

Additionally, PCV15 and PCV20 offer expanded serotype coverage compared to PCV13.[5,35,37] A multi-country review estimated the serotype coverage rates for PCV15 and PCV20 to be between 43–60% and 63–72% in the adult population, respectively, after the introduction of childhood PCV13.[35] In the study evaluating high-income countries, it was found that in addition to the serotypes included in PCV13, PCV15 and PCV20 potentially cover an extra 10.6% and 34.6% of serotypes, respectively, in pediatric PCV13-using countries.[37] Similar trends were reported in studies on adult pneumococcal pneumonia in Japan, after the introduction of PCV13 in children, between 2018 and 2020.[34] The serotype coverage rates were reported as 38.5%, 43.3%, and 59.6% for PCV13, PCV15, and PCV20, respectively.[34] Particularly noteworthy is the high coverage rate for PCV20, which is somewhat comparable to that of PPSV23.[5,34,37]

Cost-effectiveness of pneumococcal vaccines

Recent studies on the cost-effectiveness of PCV15 and PCV20 have shown that both vaccines to significantly reduce costs in adults aged 65 years and older.[1,5,39] Analysis using three economic models – Tulane-CDC, Merck, and Pfizer – estimated that the cost benefit of using PCV20 could range from being cost-saving to costing 42,000 USD per quality-adjusted life year (QALY) gained.[1] Two economic models (Tulane-CDC and Merck) estimated that the cost benefit of using PCV15 in series with PPSV23 ranged from being cost-saving to 309,000 USD per QALY gained. The Tulane-CDC model found cost savings for the use of either PCV20 alone or PCV15 in series with PPSV23 in adults aged 65 years and older, in all scenarios considered. Additionally, a study from Japan suggests that replacing the current PPSV23 with a single-dose

PCV20 vaccination program in adults aged 65 years could be cost-saving from a healthcare payer's perspective, and could gain QALY, whereas a single-dose PCV15 vaccination program would incur a cost of ¥35,020 (approximately 318 USD) per QALY gained.[39] Based on these estimates, the PCV20 vaccination program has been identified as more cost-effective than the PCV15 vaccination program.

Paradigm shift in pneumonia management and future vaccination strategies for pneumococcal infections in the older adult population

Historically, research on pneumococcal vaccine efficacy/effectiveness has prioritized IPD over noninvasive pneumococcal pneumonia in developed countries.[16] This focus is understandable, as IPD is a primary contributor to morbidity and mortality in these countries.[40] Several studies underscore the public health impact of IPD. A systematic review of studies from 2000 to 2020 has reported a median in-hospital mortality of 23.0% and a median 30-day mortality of 18.9% for IPD.[41] Furthermore, a case-control study found that the case fatality rate for IPD was 26.1%, in contrast to a 11.4% case fatality rate for noninvasive pneumococcal infections.[42] The recommendation of PPSV23 as the mainstay vaccine for IPD may also be significant.[5] Specifically, the inconsistent findings regarding its effectiveness against pneumococcal pneumonia may have contributed to the focus of IPD in recent studies.[6] Although some argue that PPSV23 was primarily designed to prevent severe pneumonia rather than the disease itself, this raises a crucial question about whether the focus of pneumococcal vaccination should solely be on IPD prevention.

Our understanding of pneumonia as a disease is undergoing a paradigm shift. While traditionally viewed as an acute illness, emerging evidence highlights its potential as a chronic disease.[43] Some acute symptoms of pneumonia, including skeletal muscle weakness, acute kidney injury leading to chronic kidney disease, and delirium, may persist or exacerbate existing chronic conditions even after discharge.[44] Previous research indicated that 25.4% of admitted patients with pneumonia exhibited a reduction in activities of daily living at the time of discharge, and 28.1% were unable to return to their original residence.[45] Recognizing pneumonia as a risk factor for chronic diseases underscores its impact on long-term health outcomes.[43] Studies have revealed that pneumonia can increase the risk of cardiovascular diseases, including stroke and myocardial infarction, with a magnitude comparable to or even exceeding conventional risk factors, such as smoking, diabetes, and hypertension.[46] Therefore, in understanding pneumonia, it is crucial to consider its acute presentation and potential long-term effects, regardless of disease severity.[43]

Accordingly, future strategies should encompass a broader perspective on pneumonia prevention, addressing both mild and severe cases. PCVs, known for their high immunogenicity, consistent efficacy/effectiveness against IPD and pneumococcal pneumonia, and cost-effectiveness, warrant further attention.[5,8,9,28,39] The transition from PPSV to PCV is strategically advisable, especially with the growing adoption and continued development of PCVs in international frameworks.[1,10–13,47,48] Sequential administration of PPSV23 after PCV is also an option when the available PCV does not adequately cover epidemiological serotypes. Real-world data on the clinical effectiveness of new vaccines, such as PCV15 and PCV20, are also needed.[47] In the US, the ACIP has recommended pediatric PCV15 administration in 2022 and PCV20 administration in 2023.[47] Consequently, reduced PCV15 and PCV20 effectiveness may occur in adults owing to serotype replacement and herd immunity. Therefore, it is crucial to harmonize the vaccination strategies for older adults with current pediatric vaccination programs by serotype monitoring to develop an effective approach for both populations.[47] The ultimate goal is to develop a broad serotype-independent vaccine.[49] With the emergence of serotype replacements, the number of serotypes may continue to increase. Formulating a novel product that vaccines targeting highly conserved pneumococcal proteins such as pneumolysin, surface proteins A and C, which are common to virtually all serotypes, could offer a more durable strategy for eradicating all pneumococcal diseases.[49,50]

Conclusions

To reduce the disease burden in older adults, vaccination strategies should focus on preventing the broad spectrum of pneumonia, including IPD and noninvasive pneumococcal pneumonia. With these strategies, the focus on PCVs is anticipated for better outcomes, and adjustment for serotype changes remains crucial. Addressing challenges related to pneumococcal vaccines, epidemiologic research, vaccine development, ongoing efficacy/effectiveness evaluation, cost-effectiveness analysis should also be conducted to validate the current findings. The development of a broad serotype-independent vaccine is highly desirable.

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