Mortality reduction with 23-valent pneumococcal polysaccharide vaccine: a systematic review and meta-analysis

Muhammed Shabil[1,2†], Shilpa Gaidhane[3†], Suhas Ballal[4], Sanjay Kumar[5], Mahakshit Bhat[6], Shilpa Sharma[7], M. Ravi Kumar[8], Sarvesh Rustagi[9], Mahalaqua Nazli Khatib[10*], Nishant Rai[11,12], Sanjit Sah[13,14], Edward Mawejje[15*], Ganesh Bushi[16], Kiran Bhopte[17], Rachna Kathuria[18] and Ambanna Yappalparvi[19]

Abstract

Background Pneumococcal disease, caused by *Streptococcus pneumoniae*, imposes a significant global health burden, particularly affecting vulnerable groups such as the elderly and immunocompromised. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is designed to protect against 23 serotypes of Streptococcus pneumoniae. However, there is ongoing debate about its effectiveness in reducing all-cause mortality. This systematic review and meta-analysis aimed to evaluate the efficacy of PPV23 in reducing all-cause and pneumonia-related mortality among adults.

Methods A systematic search was conducted across PubMed, Embase, and Web of Science, focusing on studies that evaluated the mortality outcomes of adults vaccinated with PPV23 compared to non-vaccinated adults. Both randomized controlled trials (RCTs) and observational studies were included, while case reports, case series, and non-human studies were excluded. Data extraction and quality assessment were facilitated by Nested Knowledge software, using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for RCTs.

Results The search yielded 826 records, with 19 studies meeting the inclusion criteria. The pooled analysis of four RCTs showed no significant reduction in all-cause mortality (RR = 1.030; 95% CI: 0.945, 1.122). However, analysis of pneumonia-related mortality across various studies indicated a significant reduction (HR = 0.504; 95% CI: 0.316, 0.693). Moderate to high heterogeneity was noted in mortality studies, and a potential publication bias was identified.

Conclusion The findings suggest that while PPV23 may not significantly reduce all-cause mortality, it is effective in reducing pneumonia-related mortality among adults, particularly in those at higher risk. These results support the continued use of PPV23 in targeted adult populations, emphasizing the need for more primary studies to explore its effectiveness across diverse groups.

†Muhammed Shabil and Shilpa Gaidhane contributed equally to this work.

*Correspondence:
Mahalaqua Nazli Khatib
nazlikhatib@dmiher.edu.in
Edward Mawejje
emawejje62@gmail.com

Full list of author information is available at the end of the article

Introduction

Pneumococcal disease, caused by *Streptococcus pneumoniae*, presents a significant global health burden. It manifests in forms ranging from mild respiratory infections to severe diseases such as pneumonia, meningitis, and sepsis [1, 2]. Particularly vulnerable populations include young children, the elderly, and individuals with compromised immune systems [3]. The 23-valent pneumococcal polysaccharide vaccine (PPV23), also known as Pneumovax 23, targets 23 serotypes of the bacterium [4]. It has been a cornerstone in the prevention strategy against pneumococcal diseases for adults over 50 years of age and younger adults at increased risk of pneumococcal disease [5].

Despite the widespread use of PPV23, debates persist regarding its effectiveness, especially concerning mortality reduction in adult populations. While numerous studies have explored the vaccine's efficacy in preventing invasive pneumococcal disease (IPD), fewer have specifically addressed its role in reducing mortality [6–12]. This research gap is significant given the critical role of mortality in evaluating the impact of vaccination programs on public health. Historically, the introduction of PPV23 was based on its potential to elicit a serotype-specific immune response capable of reducing the incidence of IPD, a major contributor to pneumococcal mortality [13, 14]. Initial studies demonstrated promising results, suggesting a significant reduction in IPD incidence among vaccinated individuals [15–17]. However, the translation of these findings into a demonstrable mortality benefit has been inconsistently reported, with studies yielding varying results, from substantial benefits to negligible effects [6, 7, 18–20]. This inconsistency may stem from several factors, including study design, population heterogeneity, differing definitions of outcomes, and the evolution of pneumococcal serotypes. Moreover, introducing pneumococcal conjugate vaccines (PCVs) for children has altered the epidemiological landscape of pneumococcal disease through herd immunity, indirectly affecting the serotype distribution and the disease burden in adults [21, 22]. These changes necessitate a reassessment of PPV23's impact on mortality among different adult populations. Given the substantial investment in vaccination programs and the critical implications for public health policy, a systematic review and meta-analysis are warranted to consolidate the existing data on the effectiveness of PPV23 in reducing mortality due to pneumococcal disease. Such a synthesis can provide a clearer picture of the vaccine's impact, inform stakeholders, and guide future vaccination strategies.

This systematic review and meta-analysis aimed to comprehensively evaluate the available evidence on the mortality risk reduction associated with PPV23. This investigation focused on adult populations globally, considering variations in vaccine performance across different demographic and clinical backgrounds. By integrating data from multiple studies, we aimed to address the following question: Did PPV23 reduce mortality in adults? This research systematically gathered and analyzed randomized controlled trials (RCTs) and observational studies that reported on mortality outcomes following vaccination with PPV23.

Method

This study was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (Table S1) [23]. The protocol was registered in PROSPERO under the registration number: CRD42024560236. We used a semi-automated software named Nested Knowledge for conducting this systematic review.

Eligibility criteria

For our systematic review and meta-analysis, we included studies that met specific eligibility criteria to capture a comprehensive and relevant dataset. The population of interest consisted of adults aged 18 years and older, reflecting the primary demographic targeted by the PPV23 immunization programs. Studies focused on the intervention of PPV23 administration, allowing us to assess the direct impact of this vaccine on adult populations. We considered studies that used either no vaccination as comparators to isolate the effects of PPV23 and differentiate its effectiveness from other interventions. The primary outcome of interest for this review was all-cause mortality, which provided a broad measure of the vaccine's impact on survival. Secondary outcomes included pneumonia-related mortality. Eligible study designs encompassed randomized controlled trials (RCTs) and observational studies, including cohort and case-control studies, to ensure a robust analysis of available evidence across different research settings. Case reports, case series, and non-human studies were excluded. Articles not available in the English language were excluded.

Literature search

We conducted comprehensive searches across multiple databases including PubMed, Embase, and Web of Science through June 15, 2024. Our strategy utilized a combination of keywords: "23-valent pneumococcal

polysaccharide vaccine," "PPV23," "Pneumovax 23" for vaccine-related terms and "mortality," "death," "deaths," "fatal," "fatality," "survive*," "survival*," and "died" for mortality-related outcomes. These terms were linked using Boolean operators to ensure a comprehensive retrieval of relevant literature. Although we imposed no initial restrictions on publication date or language to broaden the search scope, only English-language articles were reviewed in detail due to the language capabilities of our team. The complete search strategy, including the exact Boolean combinations used, is detailed in Table S2.

Screening
Initially, all records identified from the database searches were compiled into a centralized database and screened based on their titles and abstracts to eliminate clearly irrelevant studies, such as those not involving adults, not using PPV23, or not focusing on mortality outcomes. Subsequently, studies that passed this preliminary screening underwent a detailed full-text review by two independent reviewers to assess eligibility based on predefined criteria regarding the study population, intervention, comparators, outcomes, and design. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer if necessary. Studies that met all inclusion criteria after this thorough review were selected for final analysis.

Data extraction and quality assessment
Data from the included studies were systematically extracted and managed using the semi-automated software tool, Nested Knowledge, to ensure accuracy and consistency [24]. We extracted a range of critical data from each study, including study identification details such as authors, publication year, and country. Study design elements, including whether the study was an RCT, cohort study, or case-control study, were noted. Detailed demographic information on the study populations, such as age, sex, and comorbidities, was gathered to evaluate the generalizability and relevance of the findings. Outcomes of interest, particularly all-cause mortality, and pneumonia-related mortality, were recorded, including the number of events, participant totals in each group, and statistical measures like hazard ratios (HR), odds ratios (OR), Relative risk (RR), and their confidence intervals (CI). The extraction process involved two independent reviewers to minimize errors, with any discrepancies resolved through discussion or by consulting a third reviewer, ensuring a thorough and precise data collection phase. The quality assessment of observational studies was carried out using the Newcastle-Ottawa Scale (NOS) [25], and the Cochrane Risk of Bias 2 (RoB 2) tool was used for RCTs.

Statistical analysis
In this meta-analysis, we aggregated HR and 95% CI for mortality data from the studies. A random-effects model was selected to synthesize these data due to the anticipated differences across the included studies. Heterogeneity was quantitatively assessed using I^2 and Tau^2 statistics, with Tau^2 computed using the maximum likelihood method [26, 27]. A threshold of $p < 0.05$ was set for statistical significance. Doi plots with the LFK index were used to detect any publication bias [28, 29]. 95% prediction interval is also calculated [30, 31]. The number of deaths in the vaccinated and unvaccinated groups were pooled along with the sample sizes from both groups from RCTs to calculate the RR. The statistical analyses, including meta-analysis and publication bias assessments, were conducted using R software, version 4.3 [32].

Results
Literature search
In the literature search across PubMed, Embase, and Web of Science databases yielded a total of 826 records. After the removal of 385 duplicate records, 441 studies remained for screening. Upon initial screening of titles and abstracts, 332 records were excluded, leaving 109 studies for full-text retrieval and detailed assessment. All 109 reports were successfully retrieved and assessed for eligibility based on our predefined criteria. During this phase, 90 studies were excluded for reasons such as not reporting the outcome of interest (64 studies) and not involving exposures of interest (26 studies). Ultimately, 19 studies [6–12, 18–20, 33–41] met al.l the inclusion criteria and were included in the final analysis (Fig. 1).

Characteristics of included studies
The important characteristics of the included studies are summarized in Table 1. The studies encompassed RCTs, prospective and retrospective cohort studies, and case-control studies, offering a comprehensive view of data derived from both experimental and observational research designs. Geographically, the research was conducted across multiple continents in countries such as Spain, China, Uganda, Taiwan, South Korea, Japan, Canada, Germany, Sweden, and France. Participant demographics were varied, targeting adults with specific health conditions such as chronic obstructive pulmonary disease (COPD), HIV-1 infection, chronic renal failure, and generally older adults in nursing homes and community settings. Sample sizes ranged dramatically, from small-scale studies with just over 500 participants to large-scale research involving over one million individuals, enhancing the robustness and applicability of the findings. The age groups in these studies mostly focused on older adults, with many specifically including participants aged 60 years and older, aligning with the
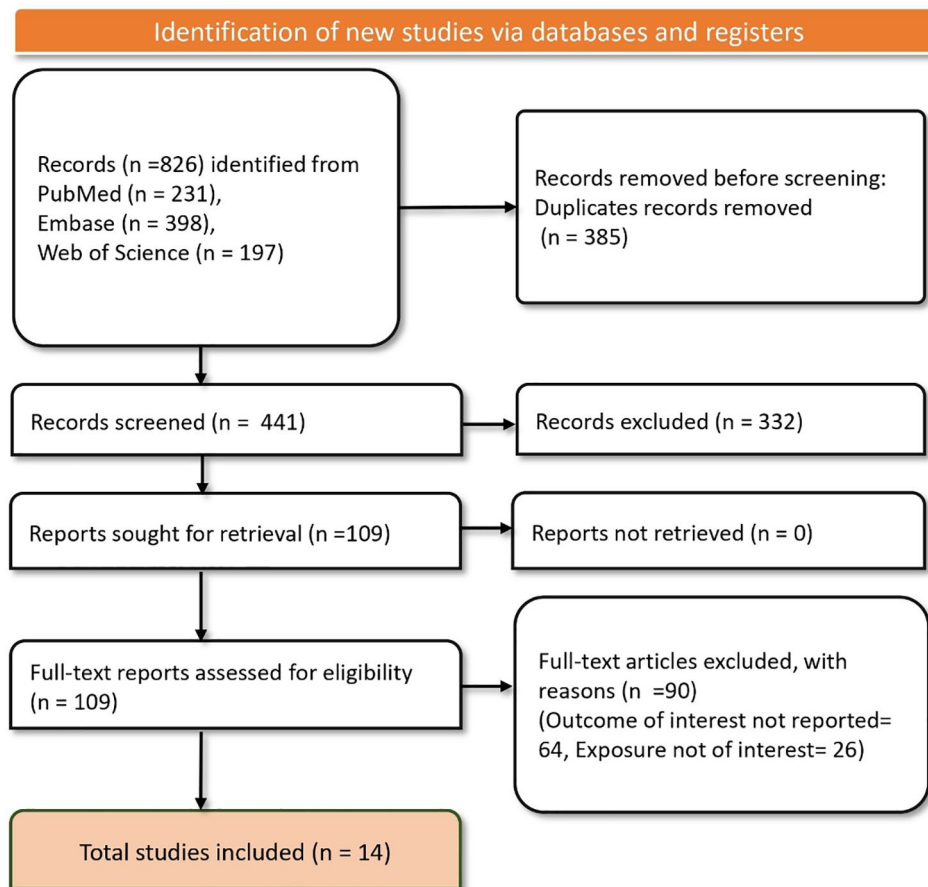
Fig. 1 PRISMA flow diagram depicting the article selection and screening process

primary demographic for whom PPV23 is recommended. The gender distribution varied, with some studies, like Alfageme 2006, predominantly involving male participants (96.6%), while others featured a more balanced gender mix. Effectiveness was quantified using HR and OR across various studies. The quality assessment of the studies is provided in Table S3.

All-cause mortality
The meta-analysis of four RCTs reported the impact of vaccination on all-cause mortality. The analysis included data from studies conducted by Alfageme et al. [18], French et al. [33], Maruyama et al. [11], and Ortqvist et al. [37]. The pooled results from these four studies included a total of 360 events from 1,721 vaccinated participants and 348 events from 1,730 non-vaccinated participants, resulting in a pooled RR of 1.030 (95% CI: 0.945, 1.122). The heterogeneity among these studies was low, with an I^2 of 0%. Overall, the meta-analysis shows a pooled risk ratio slightly above 1, indicating no significant reduction in all-cause mortality among the vaccinated compared to the non-vaccinated groups across the studies analyzed (Fig. 2).

The meta-analysis of several studies assessed the effect of interventions on mortality which reported HR based on Cox regression. The pooled HR across all included studies was 0.904 (95% CI: 0.800 to 1.009) suggesting a non-significant reduction in mortality risk associated with the intervention. The prediction interval was [0.569, 1.239], indicating variability in the effect size across different settings and populations. The analysis showed high heterogeneity with an I^2 of 64% which suggests that the observed variability in HRs is not solely due to chance but may be influenced by differences in study design, populations, or interventions across the studies (Fig. 3).

Pneumonia related mortality
The meta-analysis summarized the impact of interventions on pneumonia-related mortality, evaluating hazard ratios (HR) from several studies. The pooled HR for these studies was 0.504 (95% CI: 0.316 to 0.693), indicating a significant reduction in pneumonia-related mortality across the included studies. The prediction interval ranged from 0.090 to 0.918, suggesting that in a new study, the actual HR might fall within this range. The heterogeneity among these studies was reported as I^2 = 0%,

Table 1 Basic characteristics of the included studies

Study	Study Design	Country	Study population	Sample size	Age	Male (%)	All-cause mortality with vaccination	Pneumonia related mortality
Alfageme 2006 [18]	RCT	Spain	Patients with COPD	596	65.8	96.6	NA	NA
Chan 2012 [6]	Prospective cohort study	China	Nursing home older adults	532	85.7	39.8	HR = 0.54 (95% CI: 0.35 to 0.84)	HR = 0.60 (95% CI: 0.35 to 0.99)
Córcoles AV 2006 [40]	Prospective cohort study	Spain	Community-dwelling individuals aged ≥ 65 years	11,241	≥ 65	43	HR = 0.97 (95% CI: 0.86–1.09)	HR = 0.41 (95%: 0.23 to 0.72)
Corcoles AV 2014 [41]	Population-based cohort study	Spain	Individuals aged ≥ 65 years	27,204	71.7	44.6	HR = 0.97 (95% CI: 0.89 to 1.05)	NA
French 2000 [33]	RCT	Uganda	HIV-1-infected adults	1392	31	29	HR = 1.08 (95% CI: 0.87 to 1.33)	NA
Gondar 2014 [20]	Population-based cohort study	Spain	Individuals aged ≥ 65 years	27,204	71.7	44.6	HR = 0.97 (95% CI: 0.89 to 1.05)	NA
Hsieh 2013 [7]	Case control study	Taiwan	Elderly aged 75 years and older	1,063,116	≥ 75	NA	NA	OR = 0.06
Hsieh 2016 [19]	Case-control study	Taiwan	Patients with chronic renal failure	545	> 50	NA	OR = 0.691 (95% CI: 0.460 to 1.039)	NA
Hung CC 2004 [8]	Prospective cohort study	Taiwan	HIV-1-infected patients	508	37	8.8	HR = 0.733 (95% CI: 0.236 to 2.274)	NA
Hyun 2023 [34]	Prospective cohort study	South Korea	Patients aged ≥ 19 years with CAP	5009	70.3	63.1	OR = 0.507 (95% CI: 0.267 to 0.961)	NA
Ihara 2019 [35]	Case-control study	Japan	Dialysis patients	510	64	59.2	HR = 0.62 (95% CI: 0.46 to 0.83)	HR = 0.91 (95% CI: 0.29 to 2.83)
Inoue S 2011 [9]	Prospective cohort study	Japan	Patients of chronic pulmonary diseases ≥ 60 years of age	1378	73	58.4	HR = 0.795 (95% CI: 0.499 to 1.264)	NA
Johnstone J 2010 [36]	Case-control study	Canada	Adults with CAP	2950	68	52	HR = 0.92 (95% CI: 0.79 to 1.06)	NA
Kolditz 2018 [10]	Retrospective cohort study	Germany	Individuals aged ≥ 65 years	738,927	76	38	Age 60 to 79 years: RR = 0.82 (95% CI: 0.73 to 0.91), Age ≥ 80 years: RR = 1.00 (95% CI: 0.94 to 1.07)	NA
Maruyama T 2010 [11]	RCT	Japan	Nursing home residents	1006	84.7	22.1	NA	NA
Ochoa-Gondar 2008 [12]	Prospective cohort study	Spain	Older adults with chronic respiratory diseases	1298	≥ 75	73	HR = 1.20 (95% CI: 0.91 to 1.59)	HR = 0.87 (95% CI: 0.33 to 2.28)
Ortqvist 1998 [37]	RCT	Sweden	Non-immunocompromised middle-aged and elderly people	691	69·4	50	RR = 0.95 (95% CI: 0.53 to 1.59)	NA
Pierre E 2023 [38]	Case-control study	France	Dialysis patients	1849	68.5	64.7	HR = 0.96 (95% CI: 0.78 to 1.19)	NA
Tsai YH 2015 [39]	Case-control study	Taiwan	Individuals aged ≥ 75 years	1,078,955	81.67	52.16	OR = 0.07 (95% CI: 0.069 to 0.072)	OR = 0.07 (95% CI: 0.059 to 0.082)

Abbreviations CAP - Community-Acquired Pneumonia, CI - Confidence Interval, COPD - Chronic Obstructive Pulmonary Disease, HR - Hazard Ratio, NA - Not Available, NIDDM - Non-Insulin-Dependent Diabetes Mellitus, OR - Odds Ratio, RCT - Randomized Controlled Trial, RR - Relative Risk
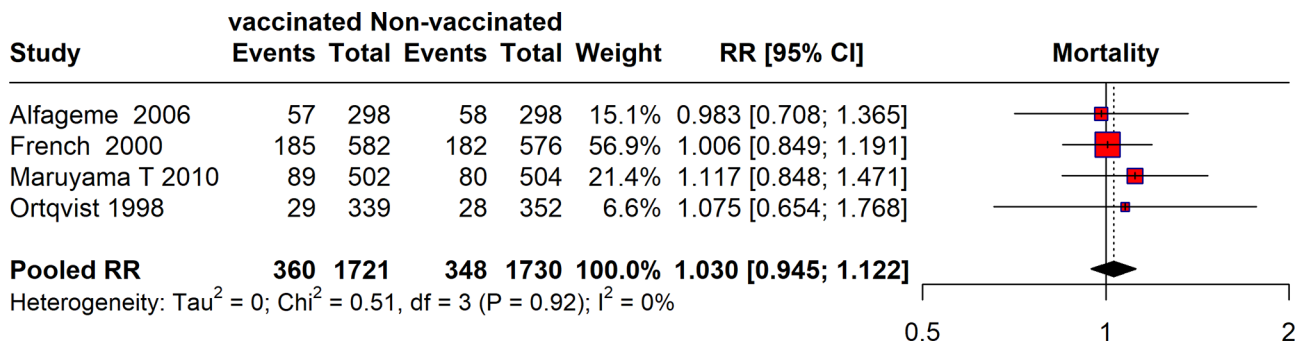
Study	vaccinated Events	Total	Non-vaccinated Events	Total	Weight	RR [95% CI]	Mortality
Alfageme 2006	57	298	58	298	15.1%	0.983 [0.708; 1.365]	
French 2000	185	582	182	576	56.9%	1.006 [0.849; 1.191]	
Maruyama T 2010	89	502	80	504	21.4%	1.117 [0.848; 1.471]	
Ortqvist 1998	29	339	28	352	6.6%	1.075 [0.654; 1.768]	
Pooled RR	**360**	**1721**	**348**	**1730**	**100.0%**	**1.030 [0.945; 1.122]**	

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.51$, df = 3 (P = 0.92); $I^2 = 0\%$

0.5   1   2

Fig. 2 Forest plot depicting risk of all-cause mortality between vaccinated and unvaccinated Individuals from RCTs

Study	HR	SE	Mortality	95%-CI	Weight
Chan 2012	0.5400	0.1250		0.540 [0.295; 0.785]	8.2%
Córcoles AV 2006	0.9700	0.0587		0.970 [0.855; 1.085]	12.6%
Corcoles AV 2014	0.9700	0.0408		0.970 [0.890; 1.050]	13.7%
French 2000	1.0800	0.1173		1.080 [0.850; 1.310]	8.6%
Gondar 2014	0.9700	0.0408		0.970 [0.890; 1.050]	13.7%
Hung CC 2004	0.7330	0.5199		0.733 [-0.286; 1.752]	1.0%
Ihara 2019	0.6200	0.0944		0.620 [0.435; 0.805]	10.1%
Inoue S 2011	0.7950	0.1952		0.795 [0.413; 1.177]	5.0%
Johnstone J 2010	0.9200	0.0689		0.920 [0.785; 1.055]	11.9%
Ochoa-Gondar 2008	1.2000	0.1735		1.200 [0.860; 1.540]	5.8%
Pierre E 2023	0.9600	0.1046		0.960 [0.755; 1.165]	9.5%
Pooled HR				**0.904 [0.800; 1.009]**	**100.0%**
Prediction interval				**[0.569; 1.239]**	

0.5   1   1.5   2

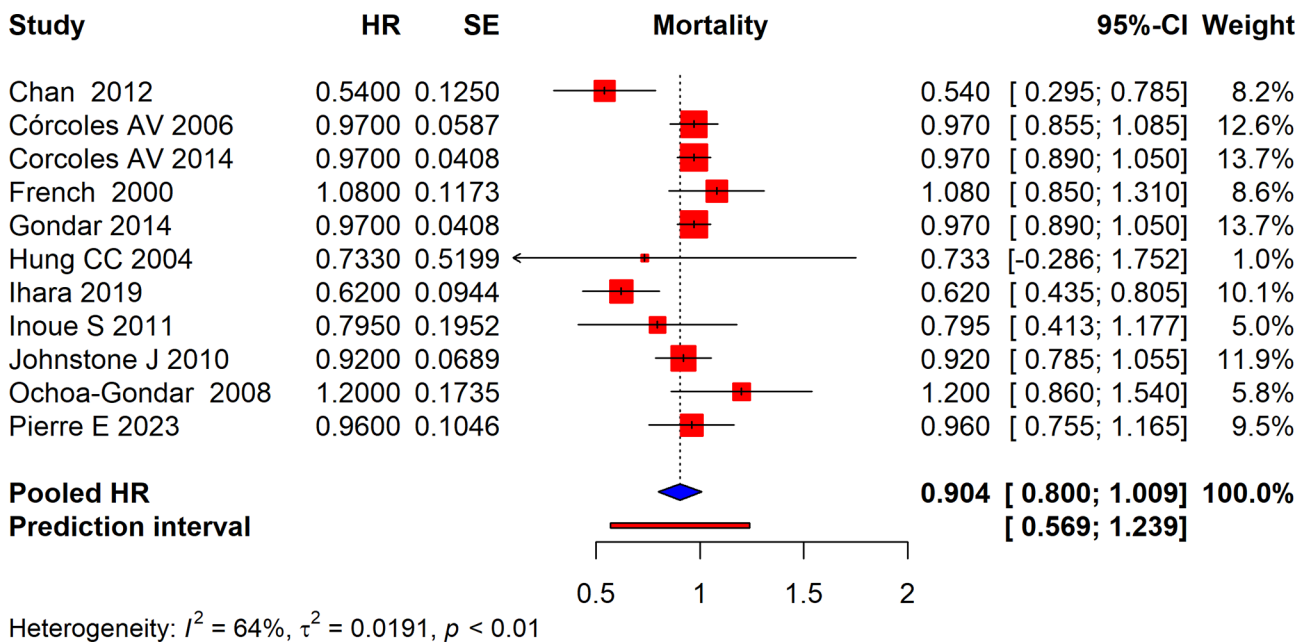Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.0191$, $p < 0.01$

Fig. 3 Forest plot depicting pooled Hazard ratios for all-cause mortality with vaccination

indicating negligible variability among the studies, and suggesting that the observed effects are consistent across different research settings and populations (Fig. 4).
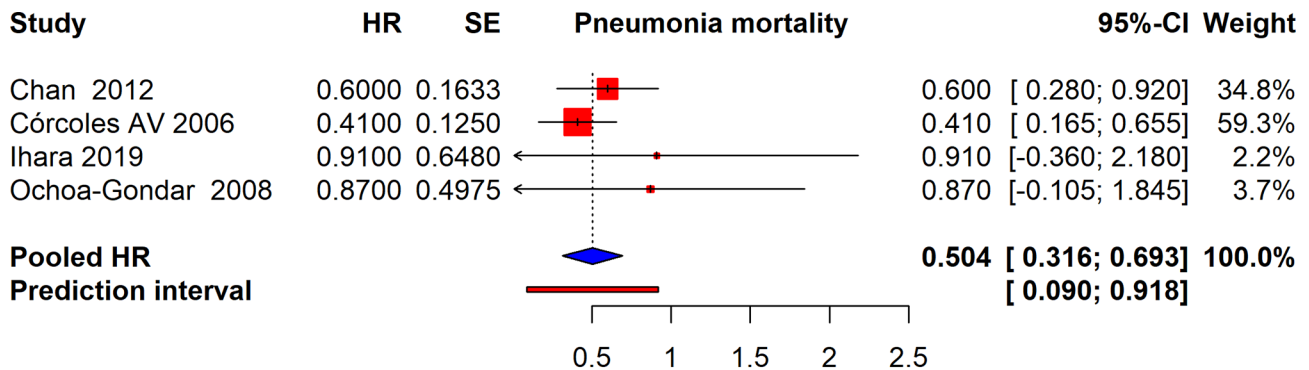
Publication bias

The assessment of publication bias in our meta-analysis was conducted using the Doi Plot and the LFK index. This approach is critical for identifying systematic discrepancies in the published literature concerning all-cause mortality outcomes associated with the interventions studied. The Doi Plot visualizes the relationship between the effect sizes of the included studies and their corresponding standard errors, providing a graphical representation of potential asymmetry in study reporting. Ideally, if no publication bias exists, the plot should display symmetry around the pooled effect estimate. However, our analysis revealed a significant deviation from this pattern. This asymmetry was quantitatively measured using the LFK index, which was calculated to be -2.25 for our dataset.

An LFK index value outside the range of -1 to +1, such as our finding of -2.25, indicates substantial asymmetry. This result suggests a significant presence of publication bias, potentially due to the underrepresentation of smaller studies or studies with non-significant, neutral, or negative results (See Fig. 5).

Discussion

This systematic review and meta-analysis have evaluated the effectiveness of PPV23 in reducing all-cause and pneumonia-related mortality among adult populations globally. Our analysis included a diverse set of studies encompassing RCTs and observational studies from various geographical locations. The pooled results for all-cause mortality did not demonstrate a significant reduction among those vaccinated with PPV23. This finding is crucial as it suggests that while PPV23 may be effective in preventing invasive pneumococcal disease, its impact on reducing all-cause mortality is not pronounced as

Study	HR	SE	Pneumonia mortality	95%-CI	Weight
Chan 2012	0.6000	0.1633		0.600 [0.280; 0.920]	34.8%
Córcoles AV 2006	0.4100	0.1250		0.410 [0.165; 0.655]	59.3%
Ihara 2019	0.9100	0.6480		0.910 [-0.360; 2.180]	2.2%
Ochoa-Gondar 2008	0.8700	0.4975		0.870 [-0.105; 1.845]	3.7%
Pooled HR				**0.504 [0.316; 0.693]**	**100.0%**
Prediction interval				**[0.090; 0.918]**	

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$

Fig. 4 Forest plot depicting pooled Hazard ratios for pneumonia-related mortality with vaccination

DOI Plot of Meta-Analysis

LFK index -2.25
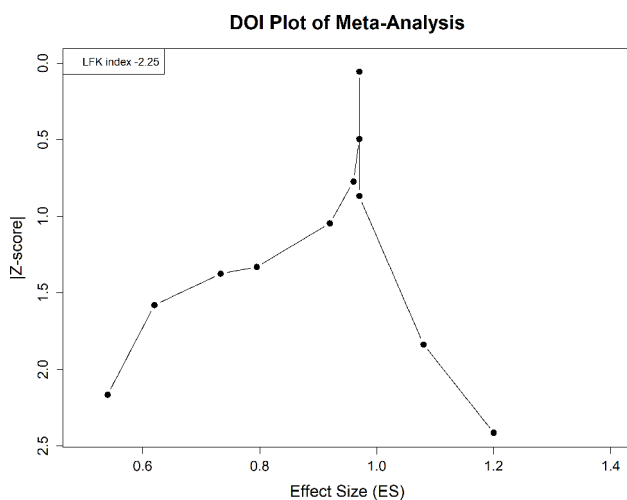
Fig. 5 Forest plot depicting pooled Hazard ratios for pneumonia-related mortality with vaccination

previously perceived. In contrast, the pooled analysis for pneumonia-related mortality showed a significant reduction in death rates among those receiving PPV23. This result indicates a more direct benefit of the vaccine in preventing deaths from pneumonia, particularly in older adults and those with pre-existing health conditions such as COPD or chronic renal failure. The substantial reduction in pneumonia-related mortality shows the importance of targeted vaccination programs within these high-risk groups.

Our analysis revealed moderate to high heterogeneity in the pooled estimates for all-cause mortality but found minimal heterogeneity in pneumonia-related mortality outcomes. This discrepancy may stem from differences in study populations, variations in vaccine administration protocols, or differences in healthcare settings across the included studies. For instance, higher heterogeneity in all-cause mortality could reflect the broader effects of various co-morbid conditions and lifestyle factors that are not directly influenced by pneumococcal vaccination. A prior systematic review indicated that both PCV13 and

PPSV23 are effective in preventing vaccine-type invasive pneumococcal disease (VT-IPD) and vaccine-type pneumococcal pneumonia in adults [42]. Another meta-analysis demonstrated that the PPSV23 vaccination provides a significant protective benefit against invasive pneumococcal diseases (IPDs). However, this analysis did not show a significant impact of PPV23 on all-cause pneumonia or pneumococcal pneumonia [43].

Recent evidence shows the significant herd protection effects conferred by the widespread implementation of pneumococcal conjugate vaccines (PCVs) in national immunization programs (NIPs) for children since the 2000s [44]. Studies indicate that these effects extend beyond the pediatric population, impacting adult and elderly groups by reducing the circulation of vaccine-related serotypes (VRTs) and associated pneumococcal diseases [45, 46]. The reduction in pneumonia-related mortality among adults, as highlighted in our findings, may not solely be attributable to the direct effects of the PPV23. It is plausible that this reduction is also indirectly influenced by long-term PCV usage in children, which contributes to decreased transmission of virulent pneumococcal strains capable of causing severe disease in adults, particularly the elderly and immunocompromised. This phenomenon illustrates the broader, community-wide benefits of pediatric vaccination programs and supports the integration of both PPV23 and PCVs in comprehensive pneumococcal disease prevention strategies. By incorporating PCVs into childhood vaccination schedules, countries have effectively reduced the reservoir of pathogenic pneumococci, which might otherwise contribute to higher rates of morbidity and mortality in non-vaccinated adult populations. This discussion warrants further investigation into how pediatric vaccination impacts adult health outcomes and emphasizes the need for ongoing surveillance and research to optimize pneumococcal vaccination strategies across all age groups.

The findings from this review have significant implications for public health, especially concerning vaccination

strategies in adults. While PPV23 shows limited efficacy in reducing all-cause mortality, its role in preventing pneumonia-related deaths is evident and supports continued use, particularly in populations at increased risk of severe pneumococcal infections. Health policymakers should consider these findings in the broader context of community health and resource allocation, emphasizing the need for targeted vaccination programs alongside other preventive health measures. Moreover, the introduction of PCVs and their effect on herd immunity might also influence the future role of PPV23, particularly in how both vaccines are integrated within national immunization schedules to maximize public health outcomes. Further research is needed to explore the long-term effectiveness of PPV23 in diverse populations, particularly in low and middle-income countries where the burden of pneumococcal disease is highest. Studies should also focus on evaluating the combined impact of PPV23 and PCVs in reducing mortality across different age groups and clinical conditions. Studies needed to assess how PPV23 can be delivered alongside other vaccines [47, 48]. Additionally, exploring patient-centered outcomes and quality of life post-vaccination could provide deeper insights into the benefits of pneumococcal vaccination beyond mortality reduction.

One of the key strengths of this study is its comprehensive and systematic approach to synthesizing existing data from a diverse range of RCTs and observational studies. Furthermore, the inclusion of a wide geographic and demographic variety of studies enhances the generalizability of the findings, making the conclusions relevant for public health strategies worldwide. Additionally, the critical assessment of publication bias and heterogeneity among the studies adds to the credibility and depth of the analysis, ensuring that the results reflect a balanced view of the available evidence.

This review has some limitations that may impact the interpretation and generalizability of its findings. The variability in study designs and participant demographics across the included studies introduces potential inconsistencies. These variations can affect the applicability of the results to broader populations, as different study designs and population characteristics may influence the outcomes of interest. Observational studies, which form a significant portion of the data included in this analysis, are inherently susceptible to biases. These biases can arise from several sources, including selection bias, recall bias, and confounding factors, which may compromise the validity of the findings. While our methodological approach was rigorous entailing a comprehensive literature search and a critical appraisal of studies to minimize errors the analysis is potentially limited by publication bias. This bias was suggested by the Doi Plot and LFK index, which indicated an underreporting of non-significant or negative outcomes. Such a bias could lead to an overestimation of the benefits of the interventions being assessed. The scope of this review was restricted to articles published in English, which may have excluded relevant studies published in other languages. This language limitation could potentially introduce bias, limiting the comprehensiveness of the analyzed data and affecting the overall conclusions drawn from the review. These limitations necessitate a cautious interpretation of the results, suggesting that further studies, particularly those addressing the identified biases and including a broader range of languages and study designs, are needed to provide a more definitive conclusion on the impact of the PPV23 vaccine.

Conclusion

While the PPV23 may not significantly impact all-cause mortality, our findings confirm its efficacy in reducing pneumonia-related mortality, particularly in high-risk adult populations. This indicates the importance of targeted vaccination programs, which should be strategically tailored to maximize health outcomes for vulnerable groups. Policy frameworks should be revised to reflect these findings, prioritizing vaccine distribution to populations that stand to benefit most, such as the elderly and immunocompromised, and incorporating these insights to optimize resource allocation. Additionally, future research should focus on conducting large-scale studies across varied demographic settings to refine vaccination strategies further, investigate the long-term effects of PPV23, and provide valuable information to guide ongoing public health decisions and vaccination strategies.

Declarations

Ethical approval
Not required.

Competing interests
The authors declare no competing interests.

Author details
[1]University Center for Research and Development, Chandigarh University, Mohali, Punjab, India

[2]Medical Laboratories Techniques Department, AL-Mustaqbal University, Hillah, Babil 51001, Iraq

[3]One Health Centre, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education, Wardha, India

[4]Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to be University), Bangalore, Karnataka, India

[5]Department of Allied Healthcare and Sciences, Vivekananda Global University, Jaipur, Rajasthan 303012, India

[6]Department of Medicine, National Institute of Medical Sciences, NIMS University Rajasthan, Jaipur, India

[7]Chandigarh Pharmacy College, Chandigarh Group of Colleges-Jhanjeri, Mohali, Punjab 140307, India

[8]Department of Chemistry, Raghu Engineering College, Visakhapatnam, Andhra Pradesh 531162, India

[9]School of Applied and Life Sciences, Uttaranchal University, Dehradun, Uttarakhand, India

[10]Division of Evidence Synthesis, Global Consortium of Public Health and Research, Datta Meghe Institute of Higher Education, Wardha, India

[11]Department of Biotechnology, Graphic Era, Deemed to be University, Clement Town Dehradun, Dehradun 248002, India

[12]Department of Allied Sciences, Graphic Era Hill University Clement Town Dehradun, Dehradun 248002, India

[13]Department of Paediatrics, Hospital and Research Centre, Dr. D. Y. Patil Medical College, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra 411018, India

[14]Department of Public Health Dentistry, Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra 411018, India

[15]School of Public Health, Makerere University College of Health Sciences, Mulago Hill, Kampala, Uganda

[16]Center for Global Health Research, Saveetha Institute of Medical and Technical Sciences, Saveetha Medical College and Hospital, Saveetha University, Chennai, India

[17]IES Institute of Pharmacy, IES University, Bhopal, Madhya Pradesh 462044, India

[18]New Delhi Institute of Management, Tughlakabad Institutional Area, New Delhi, India

[19]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India

References
1. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Lancet Global Health. 2018;6(7):e744–57.
2. Dhoubhadel BG, Morimoto K. Prevention of pneumococcal diseases: the challenge remains. Lancet Global Health. 2022;10(10):e1375–6.
3. Kumar P, Neyazi A, Rillera Marzo R, Augusto Guimaraes C, Barboza J, Abu Serhan J. H, Mycoplasma pneumoniae returns: understanding its spread and growing impact. Evid. 2024;2(1).
4. Savoy M, Pneumococcal Vaccine MSD, Manual Professional, Edition. MSD Manual; 2024 [updated 2024/04. https://www.msdmanuals.com/en-in/professional/infectious-diseases/immunization/pneumococcal-vaccine
5. Lawrence H, Pick H, Baskaran V, Daniel P, Rodrigo C, Ashton D, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: a case-control test-negative design study. PLoS Med. 2020;17(10):e1003326.
6. Chan T-C, Hung IF-N, Luk JK-H, Shea Y-F, Chan FH-W, Woo PC-Y, Chu L-W. Prevention of mortality and pneumonia among nursing home older adults by dual pneumococcal and seasonal influenza vaccination during a pandemic caused by novel pandemic influenza A (H1N1). J Am Med Dir Assoc. 2012;13(8):698–703.
7. Hsieh M-J, Tsai Y-H, Chang C-J, Wen Y-W, Hu H-C, Chao Y-N, et al. The efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing pneumonia and invasive pneumococcal disease in the elderly aged 75 years and older in Taiwan. Chest. 2013;144(4):254A.
8. Hung C-C, Chen M-Y, Hsieh S-M, Hsiao C-F, Sheng W-H, Chang S-C. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study. Vaccine. 2004;22(15–16):2006–12.
9. Inoue S, Watanuki Y, Kaneko T, Sato T, Miyazawa N, Kaneko T, et al. Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in older patients: prospective cohort study. BMJ open. 2011;1(1):e000105.
10. Kolditz M, Schmitt J, Pletz MW, Tesch F. Impact of pneumococcal polysaccharide vaccine on incidence and mortality after pneumonia in adults aged ≥ 60 years—a population-based retrospective cohort study. Clin Microbiol Infect. 2018;24(5):500–4.
11. Maruyama T, Taguchi O, Niederman MS, Morser J, Kobayashi H, Kobayashi T et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. BMJ. 2010;340.
12. Ochoa-Gondar O, Vila-Corcoles A, Ansa X, Rodriguez-Blanco T, Salsench E, de Diego C, et al. Effectiveness of pneumococcal vaccination in older adults with chronic respiratory diseases: results of the EVAN-65 study. Vaccine. 2008;26(16):1955–62.
13. Belmonti S, Rossetti B, Modica S, Paglicci L, Borghetti A, Ciccullo A, et al. Long-term serological response to 13-valent pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in HIV-infected adults. Infect Dis Therapy. 2019;8:453–62.
14. Ravichandran S, Erra-Diaz F, Karakaslar OE, Marches R, Kenyon-Pesce L, Rossi R, et al. Distinct baseline immune characteristics associated with responses to conjugated and unconjugated pneumococcal polysaccharide vaccines in older adults. Nat Immunol. 2024;25(2):316–29.
15. Bukhanova D, Sergeeva M, Belov B, Tarasova G, Cherkasova M, Muraviev YA, et al. Immunogenicity and efficiency of a 23-valent pneumococcal vaccine in patients with rheumatoid arthritis: results of a 5-year follow up study. Mod Rheumatol J. 2018;12(4):85–8.
16. Shimbashi R, Suzuki M, Chang B, Watanabe H, Tanabe Y, Kuronuma K, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in adults, Japan, 2013–2017. Emerg Infect Dis. 2020;26(10):2378.
17. Azuma M, Oishi K, Akeda Y, Morino S, Motoki Y, Hanibuchi M, Nishioka Y. Safety and immunogenicity of sequential administration of PCV13 followed by PPSV23 in pneumococcal vaccine-naïve adults aged ≥ 65 years: comparison of booster effects based on intervals of 0.5 and 1.0 year. Vaccine. 2023;41(5):1042–9.
18. Alfageme I, Vazquez R, Reyes N, Muñoz J, Fernández A, Hernández M, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax. 2006;61(3):189–95.
19. Hsieh M-J, Yu C-C, Hu H-C, Thai Y-H. No preventive effects of 23-valent pneumococcal polysaccharide vaccine in patients with chronic renal failure. Eur Respiratory Soc; 2016.
20. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, de Diego-Cabanes C, Hospital-Guardiola I, Jariod-Pamies M, Group ER. Evaluating the clinical effectiveness of pneumococcal vaccination in preventing myocardial infarction: the CAPAMIS study, three-year follow-up. Vaccine. 2014;32(2):252–7.
21. Verma R, Khanna P. Pneumococcal conjugate vaccine: a newer vaccine available in India. Hum Vaccines Immunotherapeutics. 2012;8(9):1317–20.
22. Wasserman M, Chapman R, Lapidot R, Sutton K, Dillon-Murphy D, Patel S, et al. Twenty-year public health impact of 7-and 13-valent pneumococcal conjugate vaccines in US children. Emerg Infect Dis. 2021;27(6):1627.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372.
24. Shabil M, Khatib MN, Banda GT, Zahiruddin QS, Ballal S, Bansal P, et al. Effectiveness of early Anakinra on cardiac function in children with multisystem inflammatory syndrome of COVID-19: a systematic review. BMC Infect Dis. 2024;24(1):847.

25. Shabil M, Khatib MN, Zahiruddin QS, Rekha M, Kaur M, Rani B, et al. Dengue infection during pregnancy and adverse birth outcomes: a systematic review and Meta-analysis. Rev Med Virol. 2024;34(5):e2582.
26. Langan D, Higgins JP, Jackson D, Bowden J, Veroniki AA, Kontopantelis E, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Res Synthesis Methods. 2019;10(1):83–98.
27. Gandhi AP, Shamim MA, Padhi BK. Steps in undertaking meta-analysis and addressing heterogeneity in meta-analysis. Evid. 2023;1(1):44–59.
28. Shabil M, Yadav A, Shamim MA, Ahmed M, Satapathy P, Zaidan AA, et al. Prevalence of hepatitis B and C infections among HIV-positive men who have sex with men: a systematic review and meta-analysis. Health Sci Rep. 2024;7(6):e2206.
29. Shabil M, Bushi G, Khatib MN. A commentary on psychological health among healthcare professionals during COVID-19 pandemic: an updated meta-analysis. Indian J Psychiatry. 2024;66(8):763–4.
30. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ open. 2016;6(7):e010247.
31. Pandey P, Shabil M, Bushi G. Comment on Sodium fluorescein and 5-aminolevulinic acid fluorescence-guided biopsy in brain lesions: a systematic review and meta-analysis. J Neurooncol. 2024:1–2.
32. Wen X, Thomas MA, Liu L, Moe AA, Duong PH, Griffiths ME, Munlyn AL. Association between maternal e-cigarette use during pregnancy and low gestational weight gain. Int J Gynaecol Obstet. 2023;162(1):300–8.
33. French N, Nakiyingi J, Carpenter L, Lugada E, Watera C, Moi K, et al. 23–valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. Lancet. 2000;355(9221):2106–11.
34. Hyun H, Jang A-Y, Suh JW, Bae I-G, Choi WS, Seo YB et al. Community-acquired pneumococcal pneumonia in highly vaccinated Population: analysis by Serotypes, Vaccination Status, and Underlying Medical conditions. J Korean Med Sci. 2023;38(42).
35. Ihara H, Kikuchi K, Taniguchi H, Fujita S, Tsuruta Y, Kato M, et al. 23-valent pneumococcal polysaccharide vaccine improves survival in dialysis patients by preventing cardiac events. Vaccine. 2019;37(43):6447–53.
36. Johnstone J, Eurich DT, Minhas JK, Marrie TJ, Majumdar SR. Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. Clin Infect Dis. 2010;51(1):15–22.
37. Örtqvist Å, Hedlund J, Burman L-Å, Elbel E, Höfer M, Leinonen M, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Lancet. 1998;351(9100):399–403.
38. Pierre É, Pladys A, Bayat-Makoei S, Tattevin P, Vigneau C. Pneumococcal vaccination coverage at the initiation of chronic dialysis, and its association with mortality during the first year. Vaccine. 2023;41(24):3655–62.
39. Tsai Y-H, Hsieh M-J, Chang C-J, Wen Y-W, Hu H-C, Chao Y-N, et al. The 23-valent pneumococcal polysaccharide vaccine is effective in elderly adults over 75 years old—Taiwan's PPV vaccination program. Vaccine. 2015;33(25):2897–902.
40. Vila-Córcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodríguez T, et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis. 2006;43(7):860–8.
41. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, de Diego-Cabanes C, Satue-Gracia E, Vila-Rovira A, et al. Evaluating clinical effectiveness of pneumococcal vaccination in preventing stroke: the CAPAMIS Study, 3-year follow-up. J Stroke Cerebrovasc Dis. 2014;23(6):1577–84.
42. Farrar JL, Childs L, Ouattara M, Akhter F, Britton A, Pilishvili T, Kobayashi M. Systematic review and Meta-analysis of the efficacy and effectiveness of Pneumococcal vaccines in adults. Pathogens. 2023;12(5):732.
43. Latifi-Navid H, Latifi-Navid S, Mostafaiy B, Jamalkandi SA, Ahmadi A. Pneumococcal disease and the effectiveness of the PPV23 vaccine in adults: a two-stage bayesian meta-analysis of observational and RCT reports. Sci Rep. 2018;8(1):11051.
44. van Werkhoven CH. Herd effects of child vaccination with pneumococcal conjugate vaccine against pneumococcal non-invasive community-acquired pneumonia: what is the evidence? Hum Vaccin Immunother. 2017;13(5):1177–81.
45. Weinberger B. Vaccination of older adults: Influenza, pneumococcal disease, herpes zoster, COVID-19 and beyond. Immun Ageing. 2021;18(1):38.
46. Palmborg A, Skovdal M, Molden T, Åhman H, Chen L, Banefelt J. Invasive pneumococcal disease among the elderly in the later era of paediatric pneumococcal conjugate vaccination-A longitudinal study over 10 years based on public surveillance data in the nordics. PLoS ONE. 2023;18(6):e0287378.
47. Gupta S, Basu S, Banerjee R. Efficacy of single-dose HPV vaccine over no vaccination and standard multiple dose regimen: a systematic review and meta-analysis of available evidence. Evid. 2024;2(2).
48. Bonanni P, Steffen R, Schelling J, Balaisyte-Jazone L, Posiuniene I, Zatoński M, Van Damme P. Vaccine co-administration in adults: an effective way to improve vaccination coverage. Hum Vaccines Immunotherapeutics. 2023;19(1):2195786.

Publisher's note