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Review article

CARDIOVASCULAR EFFECTS OF DUAL VACCINATION WITH PNEUMOCOCCAL PV23 AND INFLUENZA: A SYSTEMATIC REVIEW

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Abstract: The pneumococcal vaccine may reduce cardiovascular events. This systematic review examines the impact of PV23 and seasonal influenza vaccination on major cardiovascular outcomes compared to unvaccinated populations. We systematically reviewed clinical trials, cohort studies, and case-control studies published between 2000 and 2019 evaluating cardiovascular outcomes in adults vaccinated with PV23 and seasonal flu vaccines versus unvaccinated adults. Nineteen articles encompassing 617,411 patients were included. PV23 vaccination alone was not significantly associated with reduced acute myocardial infarction risk (RR 1.21 [95% CI: 1.18–1.23]). Dual vaccination showed a protective effect against stroke (RR 0.52 [95% CI: 0.45–0.61]) and significantly improved heart failure outcomes (RR 0.26 [95% CI: 0.22–0.31]). PV23 and dual vaccination also decreased episodes of acute heart failure decompensation and stroke development.

Keywords: Influenza vaccination, pneumococcal vaccine, myocardial infarction, heart failure, stroke.

INTRODUCTION

Cardiovascular events represent one of the most serious complications of community-acquired pneumonia, increasing 30-day mortality more than fivefold (1, 2). Violi et al. conducted a prospective study of 1,182 patients hospitalized for pneumonia, finding that 32.2% experienced in-hospital cardiovascular morbidity, and 2.4% died from cardiovascular events within 30 days (3).

Patients with pneumonia have a higher cardiovascular risk both in the short and long term, with events most frequent in the first year of follow-up (2, 4, 5). Previous studies have evaluated the association between respiratory tract infections and the first occurrence of myocardial infarction and stroke (6, 7, 8). *Streptococcus pneumoniae* remains the most frequently identified pathogen in community-acquired pneumonia (9). The 23-valent pneumococcal polysaccharide vaccine (PV23) effectively prevents invasive pneumococcal disease and pneumonia in adults over 50 (10, 11), similar to the 13-valent pneumococcal conjugate vaccine (12). PV23 is currently recommended for individuals aged 65 and older, as well as those at risk (13).

Most pneumococci are encapsulated pathogens with surfaces covered by polysaccharides, a major determinant of pathogenicity (14). Acquired immunity to pneumococcal capsular polysaccharides is robust in early adulthood but declines with age, especially in individuals over 70 or 80 years old (15). In young adults, immunity is stimulated by occasional episodes of asymptomatic colonization (16, 17), while in older adults, lower colonization rates result in a higher risk of pneumococcal disease (15). Pneumonia prevalence is highest at the extremes of age, and older adults—who tend to have an elevated risk of cardiovascular disease along with more comorbidities—may benefit from pneumococcal vaccination. This study aims to assess whether pneumococcal vaccination impacts cardiovascular event reduction, as current evidence shows mixed results and a need for consensus.

Evidence-Based Medicine emphasizes a critical gap: there are insufficient randomized controlled trials (RCTs) evaluating the impact of pneumococcal vaccination on cardiovascular disease (18). Mixed results from existing studies underscore the need for large, targeted RCTs that include a wide range of cardiovascular disease presentations, such as different etiologies, arrhythmias, and ejection fraction variations, with a focus on younger populations (under 65) who are less studied (19). Additionally, understanding regional differences, especially in areas with distinct pneumonia seasons, may provide insights into vaccine effectiveness based on serotype distribution, vaccine uptake, and monitoring practices.

METHODS

We conducted an evaluation of existing evidence on cardiovascular effects that may be associated with the use of PV23, employing the following steps:

1. A search strategy was developed to investigate potential adverse cardiovascular effects related to the vaccine. The relevant databases for this strategy were identified.

2. Eligibility criteria for the articles were defined to allow comparison between patients vaccinated only with PV23 and those who additionally received the influenza vaccine.

3. Statistical analysis was performed using data published in the selected articles.

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy

The initial part of this systematic review was conducted by two researchers (AS and CR) through independent searches in electronic databases, including MEDLINE, Scopus, and LILACS, covering the first two decades of the 21st century. Articles from 2020 onward were excluded to avoid potential biases related to the COVID-19 pandemic, ensuring that observed vaccine effects were not influenced by the disease or related vaccination efforts. No language restrictions were applied.

The research question was framed using the PICO strategy (Population, Intervention, Comparison, Outcome). The search terms included: "Cardiovascular Diseases," "Pneumococcal Vaccines," "Myocardial Infarction," "Mortality," "Arteriosclerosis," "Cardiovascular Diseases/mortality," "Coronary Disease," "Myocardial Ischemia," "Angioplasty, Balloon, Coronary," "Coronary Artery Bypass," "Heart Failure," "Heart Failure/complications," "Heart Failure/mortality," "Heart Failure, Systolic," "Heart Failure, Diastolic," "Heart Failure, Diastolic/complications," "Heart Failure, Diastolic/mortality," "Cardiac Edema," "Patient Admission," "Hospital Mortality," "Stroke," "Stroke/mortality," "Brain Infarction," "Posterior Cerebral Artery Infarction," "Cerebral Artery," "Lacunar Stroke," "Angina," "Unstable Angina," "Intracranial Hemorrhages," "ST-Elevation Myocardial Infarction," and "Non-ST Elevation Myocardial Infarction." Terms that could restrict or reduce the results, as well as those potentially introducing biases toward unrelated cardiovascular effects in older populations, were excluded.

Eligibility Criteria

Case-control studies, cohort studies, and clinical trials conducted in adult humans that reported relative risk and 95% confidence intervals were included. These studies evaluated cardiovascular outcomes in the study population, comparing individuals vaccinated with the pneumococcal polysaccharide vaccine PV23 alone and those dually vaccinated with PV23 and influenza (Table 1).

Data Extraction

Two independent researchers collected information from the articles and recorded it in standardized formats to apply the methodologies described above. The collected data included authors, publication year, study design, country, study population, number of participants, duration of follow-up, person-years of follow-up, reported outcomes, effect measures (RR; adjusted HR or OR), and funding sources. Discrepancies were resolved through discussion between the researchers.

Table 1. *PICOS criteria for eligibility of studies*

Population	Persons 65 years and over, healthy or with age-typical underlying diseases living in any countries and not belonging to indigenous minority populations
Intervention	Vaccination with PPV23
Comparator	Dually vaccinated for PV23 and influenza.
Outcomes	Cardiovascular Diseases
Study Design	RCTs and Observational studies, if adjusted at least for age and comorbidities

Statistical Analysis

A systematic review and meta-analysis of studies evaluating pneumococcal vaccination alone and those evaluating dual influenza plus pneumococcal vaccination were performed. The Mantel-Haenszel method was used to obtain relative risks (RRs) and 95% confidence intervals (95% CI) for the evaluated outcomes. The RR was calculated for vaccinated, unvaccinated, and dual vaccination groups, the latter if the primary study reported it.

Heterogeneity between studies was assessed using Cochran's Q statistic. The degree of heterogeneity was tested with I^2 statistics using Review Manager software; values < 25% indicated low heterogeneity, while values between 25% - 60% and > 60% indicated moderate and high heterogeneity, respectively. Meta-analysis was conducted using Review Manager 5.0.24 (COCHRANE Library software).

Funding

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RESULTS

The initial database search yielded 1,902 articles. Figure 1 illustrates the search process and reasons for initial exclusion, with 1,881 articles discarded due to duplicate titles, title content, abstracts, and non-primary studies. Ultimately, 21 studies were selected, of which 2 were excluded: one was a case series, and the other evaluated mortality from pneumonia as the primary outcome, which did not align with the objective of this systematic review. This left 19 studies for complete review, encompassing a total of 617,411 patients. Table 1 displays the selected studies and their characteristics.

The quality of the cohort and case-control studies was assessed using the Newcastle-Ottawa scale, resulting in 14 studies classified as good quality, 4 studies of acceptable quality, and one randomized clinical trial with a Jadad score of 1 point (indicating low quality).

Regarding demographic aspects, all included studies provided information about the age and gender of patients, with an average age of 69 years. The population was predominantly male, with 337,567 men (54.6%) represented (Table 2).

PV23 and Acute Myocardial Infarction

Nine studies were included in this analysis. The unvaccinated group comprised 165,062 participants, while 65,880 were vaccinated against pneumococcus. No decrease in the incidence of acute myocardial infarction was found among immunized patients, with a relative risk (RR) of 1.21 (95% CI: 1.18-1.23), indicating an increased risk of heart attack. However, the heterogeneity rate was very high (I^2 = 98%), precluding definitive conclusions. Studies showing a protective effect of PV23 vaccination for myocardial infarction contributed little weight in terms of the number of cases and follow-up time; the study with the greatest weight was that of Siriwardena (25), which indicated a neutral effect on infarction outcomes (Figure 2).

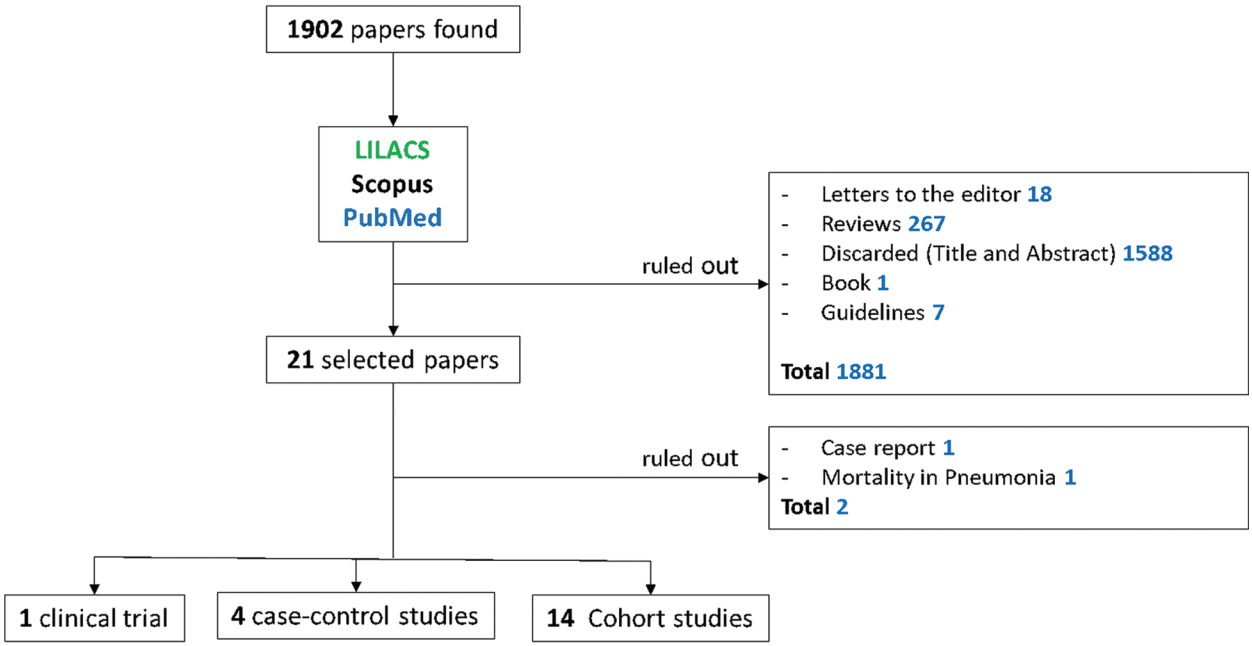

Figure 1. *Search results, selection and, inclusion of studies*

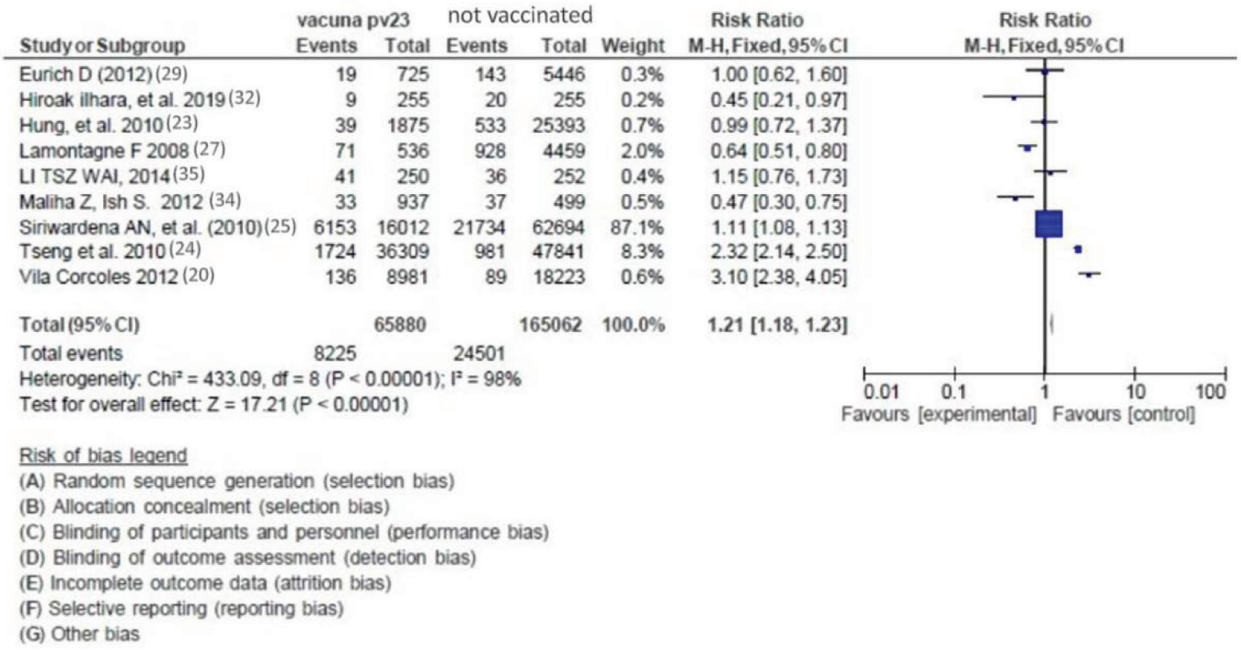

Figure 2. *PV23 and Acute Myocardial Infarction*

Table 2. *Studies characteristics*

	First author, year	Sample size	Mean age	Follow	Male	Primary	outcome influenza	Vaccine Pneumo-coccal vaccine	CVD	Adjusted for variables	**Mortality in vaccinated pV23**	**Reported results**	**Type of study**	**Newcastle-Ottawa Quality Scale**
1	Vila-Corcoles et to the. 2012, Spain (20)	27204	71.7 (SD: 8.6)	1 year.	8074 (44.3)	Hospitalized for AMI and/ or ischemic stroke	14368 (52%)	8981 (34%)	1733	Yes	Not reported	stroke: HR: 0.65 (CI: 0.42-0.99) P: 0.046 AMI HR: 0.83 (CI: 0.56-1.22) P: 0.347	Cohorts	**Selection:** 3/4 **Comparability:** 2/2 **Outcomes:** (cohort)/ exposure (case–control) 3/3
2	Ochoa-Gondar O et al. 2014, Spain (21)	27204	> 80 years old (20.2%) 70-79 years old (34.12%) 60-69 years old (45.5%)	3 years	12082 (44.4%)	Hospitalized for AMI, mortality due to AMI at 30 days and death from all causes	14,368 (52%)	8,981 (34%)	1,733	yes	Not associ-ated with a reduction in death from AMI or from all causes	AMI HR: 0.95 (CI: 0.76-1, 18) P: 0.63	cohorts	**Selection:** 3/4 **Comparability:** 2/2 **Outcomes:** (cohort)/ exposure (case–control) 3/3
3	Vila-Corcoles A, et al. 2014, Spain (22)	27204	> 80 years (20.2%) 70-79 years (34.12%) 60-69 years (45.5%)	3 years	12082 (44.4%)	Hospital-ization for ischemic stroke and death from any cause.	14368 (52%)	8981 (34%)	1733	if	PPV23 was not associated with reduced risk of death from stroke or death from any cause.	PV23 did not alter stroke risk: HR: 1.04 95% CI (0.83 - 1.3) P: 0.752.	Prospective cohort	**Selection:** 3/4 **Comparability:** 2/2 **Outcomes:** (cohort)/ exposure (case–control) 3/3

4	Hung IF, et al. 2010 (23)	36636	75	15 months.	16611 (45%)	Rates of death, hospitalization, pneumonia, ischemic stroke, AMI, admission to ICU or coronary care unit	2076	7292: PV23 and influenza, 1875 (5.1%) received PPV only	2118 (8)	Yes	PV23-Influenza risk of death [HR], 0.65; 95% CI, 0.55–0.77; P<0.001).	Pneumonia HR: 0.57 (95% CI: 0.51-0.64) p < 0.001. Coronary ICU admission: HR 0.59 (95% CI 0.44-0.79) p < 0.001. ICU admission: HR: 0.45 (95% CI 0.22-0.94) p < 0.03. CVA (HR, 0.67; 95% CI, 0.54-0.83; p < 0.001). AMI (HR, 0.52; 95% CI, 0.38-0.71; p < 0.001)	Prospective cohort	***Selection*** 3/4 ***Comparability*** 0/2 ***Results*** (cohort)/ exposure (case–control) 3/3
5	Tseng et al. 2010, United States(24).	84170	58.4 +/- 7.1	56.4 months	84170 (100%)	Incidence of acute myocardial infarction and stroke.	NR	47861 (56.8%)	AMI before the study 6020 (7.2%) Stroke before the study 2849 (3.4%)	Yes	NR	No association between pneumococcal vaccination and reduced risk of AMI (HR 1.09; CI95: 0.98- 1.21) or stroke (adjusted HR 1.14 CI95% 1.00-1.31)	Prospective cohort. California, USA	***Selection 3/4 Comparability 2/2 results (cohort)/ exposure (case–control) 2/3***
6	Siriwardena AN, et al. 2010, United Kingdom (25)	Cases: 16012. Controls: 62694	40 - 64 years: 33.4%. >equalto 65 years: 66.6%	67 months	cases: 6168 (38.5%) controls: 24171 (38.5%)	Association of influenza vaccination and PV23 with AMI	vaccine in the previous year cases (52.9%) and Controls: (51.2%)	Only pneumococcus: (3.6%). Dual vaccination: (31.7%)	chronic heart disease: 12%. ACV or TIA 6.25%. PAD: 4.194%	Yes	NR	Pneumococcal vaccination not associated with AMI reduction (OR 0.96, 95% CI 0.91–1.02)	Case–control	***Selection 2/4 Comparability 2/2 results (cohort)/ exposure (case–control) 3/ 3***
7	Siriwardena AN, et al. 2014, United Kingdom (26)	Cases: 47011 Controls: 47011	< 65 years 23.2%. ≥ 65: 76.8%	7.9 years	Cases 22,584 (48.0%) Controls 22,584 (48.0%)	Stroke or TIA associated with pneumococcal vaccination	Influenza vaccine the previous year: 7021 (7.4%)	For pneumococcus 12,153 (12.9%) Dual vaccination: 48,673 (51.7%)	FCC: 17519 (8.8%) PAD: 2467 (1.35%)	Yes	Notreported	Pneumococcal vaccination was not associated with a reduction in the risk of stroke or TIA	Case-control Study	***Selection 3/4 Comparability 2/ 2 Outcome (cohort)/ exposure (cases–controls) 3/3***

8	Lamontagne F, et al. 2008 (27)	4995 (Cases n = 999), (Controls n = 3996)	Cases 59.2 Controls 58.8	6 years	Cases 684 (68.5%); Control 2736 (68.5%)	Association of pneumococcal vaccination and AMI rate.	NR	Cases 71 (7.1%); Controls 465 (11.6%)	NR	Yes	NR	Vaccination 1 year before AMI OR: 0.85; (95% CI: 0.54 to 1.33). Vaccination > 2 years before AMI: OR: 0.33 (95% CI: 0.20-0.46) to 0.46).	Case-control study	***Selection 2/4 Comparability 1/2 Results (cohort)/ exposure (case-control) 3/3***
9	Meyers D, et al. 2003, United States(28)	Cases = 335 Controls = 199	66 +/- 11	5 months	Cases 63% control 34%	Association between pneumococcal vaccine and myocardial infarction	Cases: 177 Controls: 126	Cases 107 Controls: 78	172 (32.2%)	Yes	NR	Neither influenza nor pneumococcus vaccination reduced AMI	Study cases and controls	***Selection 3/4 Comparability 1/2 Results (cohorts)/exposure (cases–controls) 2/3***
10	Eurich DT, et al. 2012, Canada (29)	6171	59	2000 - 2002	3261 (53%)	Association between acute coronary syndrome and pneumococcal vaccination status	NR	725 (12%)	1105	Yes	Composite of death or hospitalization for ACS: HR 0.42 (0.27 - 0.66, p < 0.001) Onlydeath: HR: 0.92 (0.33-2.6)	Hospitalization for ACS: HR: 0.35 (0.21-0.57)	Cohort study	***Selection 2/4 Comparability 2/2 Results (cohort)/exposure (cases–controls) 3/3***
11	Ahmed MB, et al. 2016, United States (30)	5290	83	13 years	2539 (48%)	-Primary: incidence of heart failure and mortality from any -Secondary: cardiovascular and non-cardiovascular cause of death, hospitalization for all causes	NR	1,424 (26.92%)	Coronary heart disease: 17.22%; AMI: 7.88%; stroke 3.8%; Heart failure 19.9%. Total: CVD: 2587 (48.9%)	If	Octogenarians: I- all causes: HR: 1.23 (1.09–1.49); II-Cardiovascular HR: 1.45 (1.06–1.98) III-Non-cardiovascular HR: 1.10 (0.87–1.40)	Heart failure (Octogenarians) HR: 1.37 (1.01–1.85); P = 0.044 Heart failure in 65-79 years) HR: 0.88 (0.74-1.04); P = 0.126	Prospective epidemiologicalstudy (cohort)	***Selection: 3/4 Comparability: 1/2 Outcome; 3/3***
12	Wen-Chih Wu, et al. 2014, United States (31)	107045	72	7 years	105,118 (98.2%)	Mortality at 30 days and at 1 year.	2087	7108	AMI: 3636 (33.8%)	Yes	Mortality at 30 days: OR: 0.66 (0.42-1.05), Mortality at 1 year: OR: 0.76 (0.61-0.95)	NR othersofinterest	Retrospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3

13	HiroakiIhara, et al. 2019, Japan (32, 5, 10)	PPSV 23	64	5 years	67.85%	on the risk of hospitalization and death from pneumonia and acute cardiac events	391 (76.6%)	255 (50%)	Total:495 (97.05%) . Coronary heart disease: 27.64%, FCC: 25.29%. stroke: 21.96%. PSE: 2.15%.	yes	Mortality from all causes: HR: 0.62, [CI] 95%; 0.46–0.83, P = 0.002). Cardiac death: HR: 0.36; CI 95%; 0.18 to 0.71; p = 0.003)	Hospitalization for cardiac events: HR 0.44, 95% CI; 0.20-0.96, P = 0.040).	Retrospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
14	Mahamat Aba, et al. 2013, France (33)	68,897	75.2	1 year	39.8%	Demonstrate whether vaccination against pneumococcus and influenza reduces all causes of mortality and consumption of antibiotics	18,651 (27.1%)	pneumococcus alone: 3,769 (5.5%) dual vaccination: 21,303 (30.9%).	NR	Yes	Decrease in mortality in dual vaccination of 27 (95% CI 20-34) HR: 0.73 (0.66 0.80). In vaccination only for PV23 the mortality reduction-. 9 (95% CI: -8-23) HR: 0.91 (0.77-1.08)	Pneumococcal vaccine did not reduce antibiotic consumption	Prospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
15	Maliha Z, et al. 2012, United States (34)	1436	69 years (InterquartileRange 58 - 77)	6 months	1403	Associations between pneumococcal vaccine and mortality or AMI at 6 months of follow-up in hospitalized patients with suspected ACS	503 (35.0%) vaccinated 12 months prior	937 received pneumococcal vaccine; 667: dual vaccine	**-Coronary Disease:** 53.2% ***-History of AMI*** 22.9% **-FCC:** 18.45% -CVA: 11.9%	Yes	Mortality PV23 vs no vaccination: HR: 0.12 (95% CI 0.06 – 0.21) in dual vaccination: HR : 0.60 (0.42-0.85)	AMI in PV23 vs no vaccination: HR: 0.60 (95% CI: 0.32 - 1.10). In dual vaccination: HR: 0.22 (0.22-0.89) Prospective Cohort	Study	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
16	LI TSZ WAI. 2014, China (35)	1006	48	2 years	85.90%	Dual vaccination, only pneumococcus, only influenza and no vaccination on effects on general hospitalization, hospitalization for CVD, respiratory, neurological and mortality	254 (25.24%)	Only pneumococcus: 250 (24.8%). dual vaccination: 250 (24.8%).	534 (53.08%).	No	No differences in mortality between groups	Dual vaccination was the only independent factor associated with a reduction in the relative risk of hospitalization p<0.001. RR 0.288 CI95% 0.101 - 0.154.	Open-label randomized clinical study.	Jadad 1 point: lowquality

17	Shu Ren, et al. 2018, Australia (36)	863	72 years	7 – 11 years	45%	Hospitalization or mortality in vaccinated vs unvaccinated patient	Influenza: 190. Dual vaccinated: 451	26	0	Yes	No association found between PPV or influenza vaccine and time to event of CVD or all-cause mortality	Pv23 showed a 35% reduction in days hospitalized for CVD	Cohort-Study	Selection: 2/4 Comparison: 1/2 Outcome: 3/3
18	Joon Young Song, et al. 2018, South Korea. (37)	2119	76	During three influenza seasons from October 1 – April 30, 2014–2015, 2015–2016 and 2016–2017	1091 (51.5%)	Effectiveness of influenza and pneumococcal vaccination against pneumonia and acute exacerbation of cardio-pulmonary diseases	1302 (61.4%)	Vaccination PPV23:871 (41.1%) PCV13 vaccination: 74 (3.5%)	I) Stroke: 296 (14.0%) II) Chronic heart disease: 444 (21.0%)	If	PPV23 did not reduce mortality at 30 days.	PV23 did not significantly reduce pneumonia, exacerbation of cardio-pulmonary disease, or hospitalizations	Prospective Multi-centerCohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
19	Chang, et al. 2012, China (38)	43399	80 years	4 months	11147 (45.6%)	1: all-cause mortality 2: Incidence and hospitalization costs for CAP and influenza, enf. respiratory, COPD, FCC in seasonal influenza.	8142	8142 (33.32%)	10910.28 (44.66%)	Yes	All causes of mortality: Dual vaccination vs. unvaccinated group RR: 0.50 CI95 (0.39-0.63),	Hospitalization expenses for all diseases: Dual vaccination vs. unvaccinated group RR: 0.89 CI95 (0.83-0.96)	Retrospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3

PV23 and Heart Failure

A total of 34,677 patients from three studies were analyzed. Heart failure occurred in 209 vaccinated patients compared to 2,155 cases in unvaccinated patients, yielding an RR of 0.86 (95% CI: 0.75-1), suggesting a potential reduction in heart failure decompensation. However, the wide confidence interval, which includes 1, and the moderate heterogeneity (I^2 = 60%) indicate that further studies are needed to clarify the protective effect of PV23 vaccination (Figure 3).

PV23 and Stroke

The likelihood of experiencing a stroke was found to be 1.98 times higher (95% CI: 1.80-2.18) in individuals who received pneumococcal vaccination compared to those who were unvaccinated. These results are inconclusive due to the high rate of heterogeneity among the studies (I^2 = 97%) (Figure 4).

Mortality and PV23

To evaluate mortality outcomes, 128,479 patients were included, representing 20% of those identified in the meta-analysis. Across the 9 studies, 933 deaths were reported, revealing a statistically significant reduction in mortality risk associated with vaccination, with an RR of 0.83 (95% CI: 0.76-0.91) (Figure 5).

Acute Myocardial Infarction and Dual Vaccination

Dual vaccination did not demonstrate significant differences in the reduction of acute myocardial infarction (Figure 6).

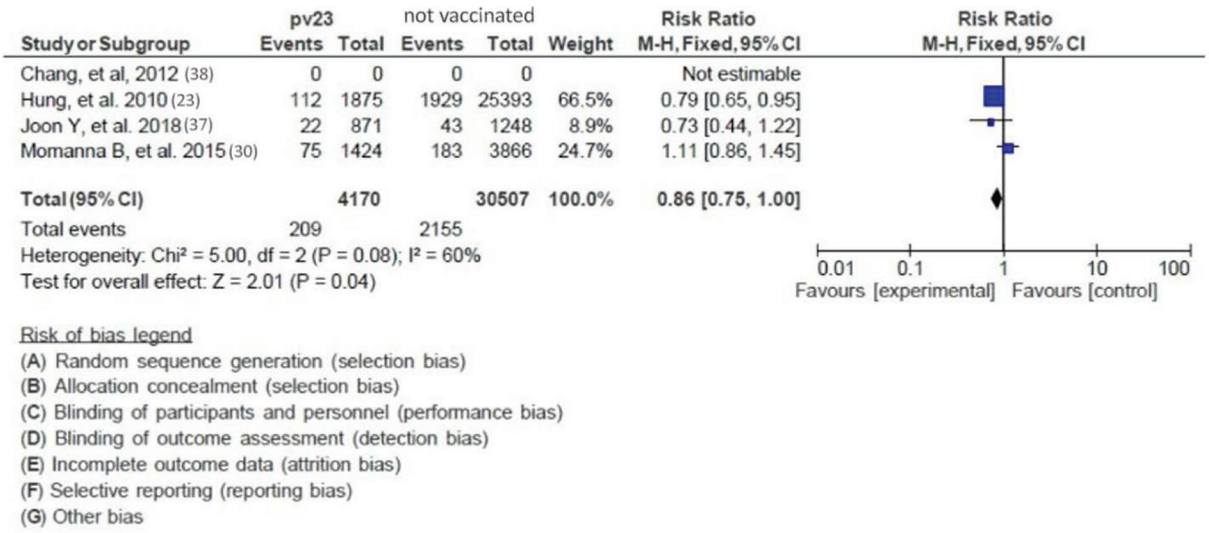

Figure 3. *PV23 and heart failure*

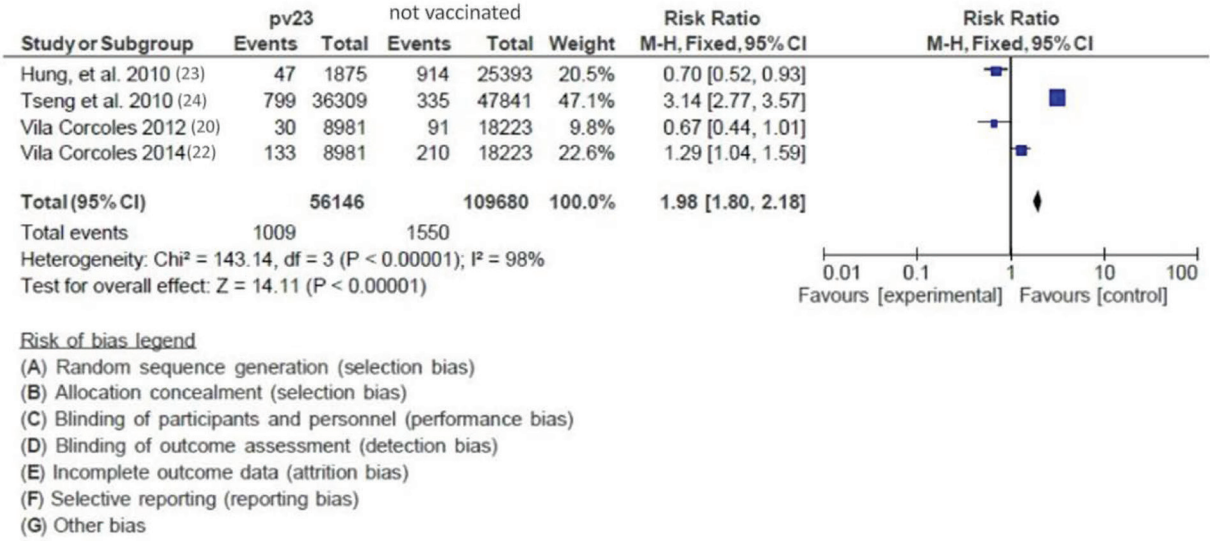

Figure 4. *PV23 and Stroke*

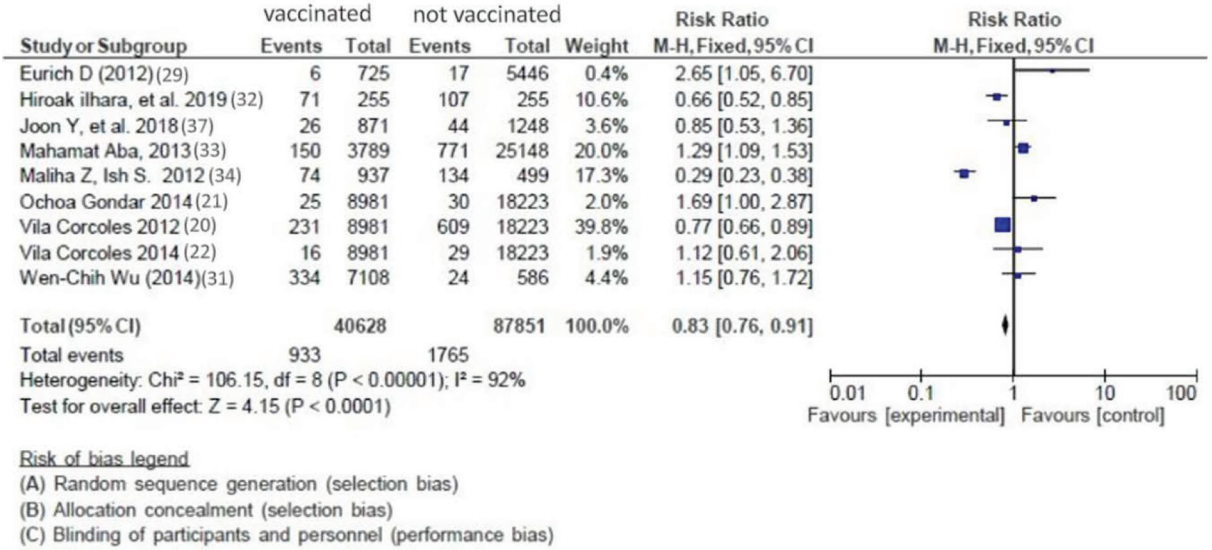

Figure 5. *Mortality and PV23*

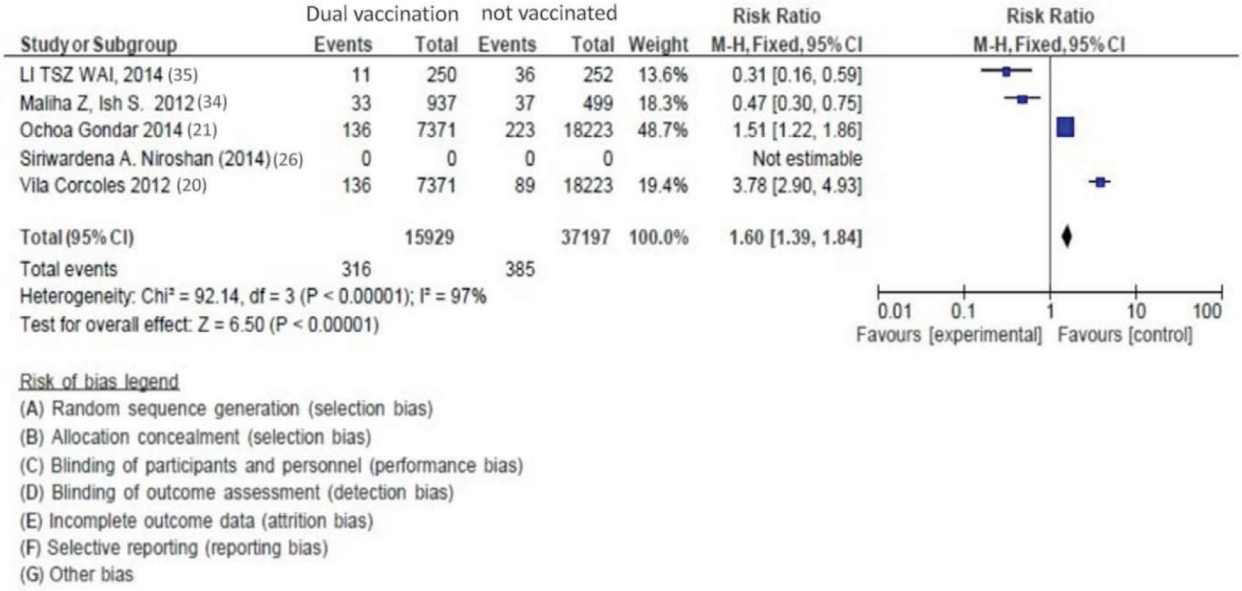

Figure 6. *Acute Myocardial Infarction and Dual Vaccination*

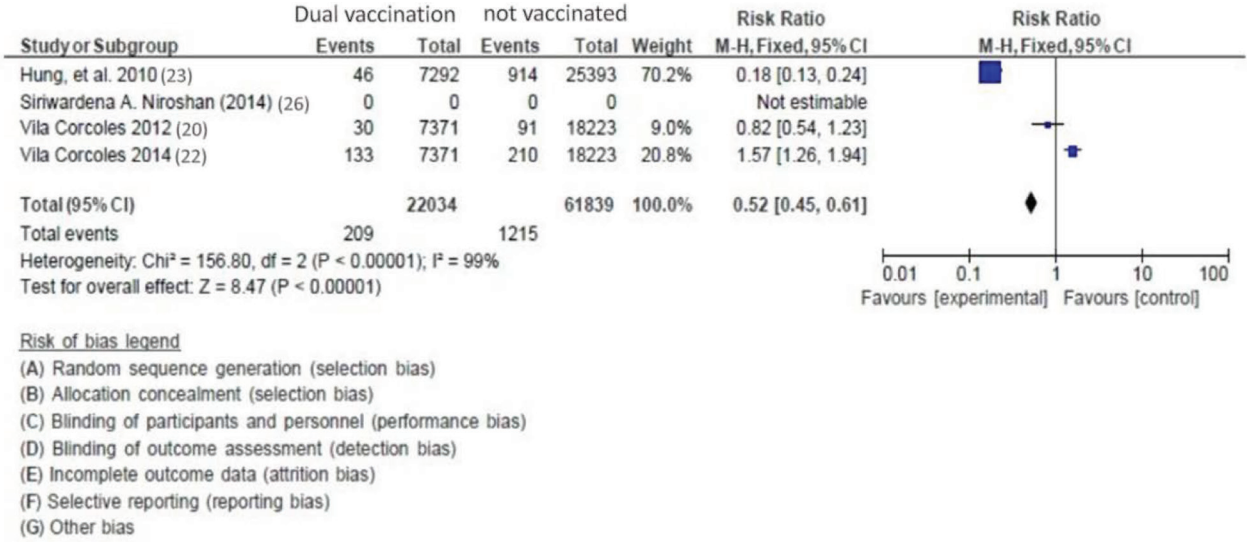

Figure 7. *ACV and dual vaccination*

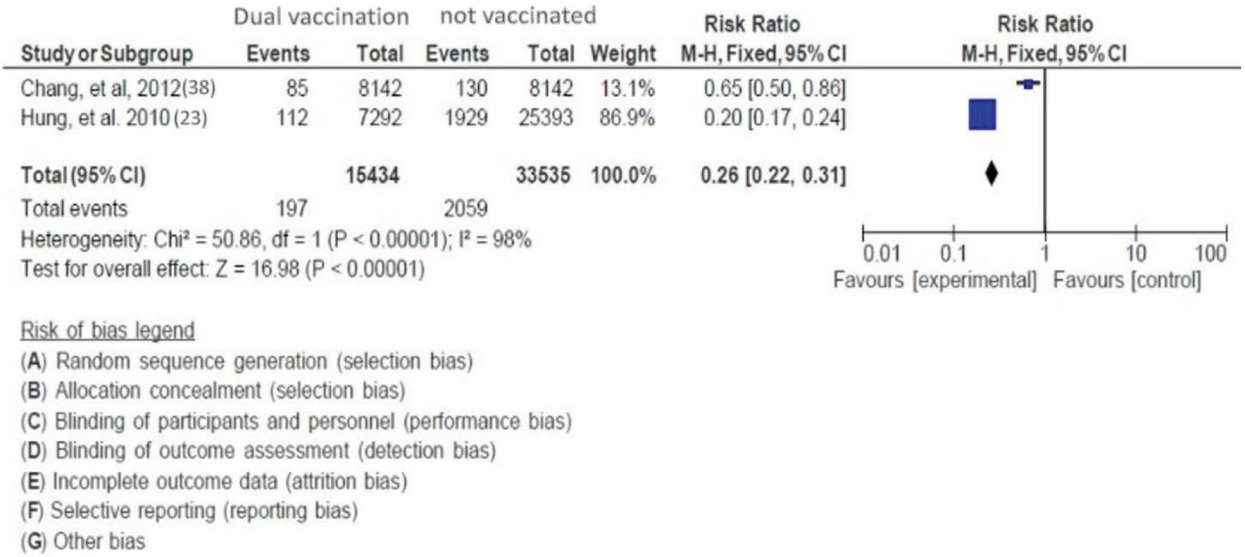

Figure 8. *Heart failure and dual vaccination*

Stroke and Dual Vaccination

Among a total of 83,873 individuals, 26% received dual vaccination. The Forest Plot analysis indicated a reduction in cerebrovascular events in more than half of the patients evaluated, suggesting a protective factor, with a narrow confidence interval and high statistical significance (RR 0.52 [95% CI: 0.45-0.61], P < 0.00001) (Figure 7).

Heart Failure and Dual Vaccination

Dual vaccination significantly reduced heart failure decompensation compared to single pneumococcal vaccination; however, the interpretation of these results is limited by the small number of studies evaluating this finding.

DISCUSSION

This systematic meta-analysis reviews the evidence regarding the effects of PV23 vaccination and dual vaccination (PV23 + seasonal influenza) on cardiovascular outcomes, given the current contradictions in the literature. Nineteen studies were evaluated, encompassing a significantly larger population than previous analyses.

As a conclusive result of this meta-analysis, evidence suggests a decrease in cerebrovascular events and episodes of decompensated heart failure among individuals who received dual vaccination. Post-viral bacterial pneumonia (39) is proposed as a serious complication of any lower respiratory tract influenza infection (26); thus, there is biological plausibility that dual vaccination (seasonal influenza and PV23) may offer better protection than single vaccination. However, no net protective effect for stroke or heart failure was found with PV23 alone.

The reduced mortality risk associated with the influenza vaccine, PPV, and the combined pneumococcal and influenza vaccinations has been documented. Evidence suggests that administering pneumonia and influenza vaccines during hospitalization is safe and reinforces the cardiovascular benefits of combined vaccination in hospital settings (40). However, the protective effect of dual vaccination on heart failure decompensation requires further investigation, given the small number of studies reporting this outcome. This consideration is particularly relevant for patients with a history of chronic heart failure.

All results were evaluated comparing individuals vaccinated with PV23 to those receiving dual vaccination. Acute myocardial infarction as a primary outcome showed no reduction in risk for either the PV23 group or the dual vaccination group (PV23 + seasonal influenza). This finding, indicating no benefit of vaccination in reducing acute myocardial infarction, cannot be conclusively accepted due to high heterogeneity among the studies, which limits the reliability of the results. The case-control study by Lamontagne et al. indicated a reduction in the risk of myocardial infarction when vaccination was administered between the second and fifth year post-vaccination, suggesting the need for stratifying results based on the time since vaccination (27). Conversely, the epidemiology of pneumonia has evolved significantly, especially after the introduction of pneumococcal vaccination, leading to an increase in other causes such as various viruses and pathogens like *S. aureus* and *Pseudomonas aeruginosa* (41).

In the studies included in this analysis, individuals were considered vaccinated against influenza if they had received the vaccine within the 12 months prior to inclusion. Notably, early seasonal influenza vaccination (September to mid-November) has been associated with a greater reduction in stroke risk compared to later vaccination (from mid-November onward) (26).

The vaccinated population ranged from 45 years to octogenarians, but the results were not stratified by age range. Momanna et al. 2016. evaluated mortality and heart failure decompensation in octogenarians and non-octogenarians (ages 65-79), finding better outcomes in non-octogenarians (30). These results are significant and may relate to the senescence of the immune system and its response to vaccination. Given the greater burden of comorbidities in octogenarians, further studies focusing on this population would be valuable.

Mortality for all causes was reported since not all registries specified mortality due to cardiovascular causes, as evidenced by the high rate of heterogeneity. The outcome of death favored vaccination with PV23 in decreasing mortality. Among the advantages of this meta-analysis, a mean follow-up of 48.1 months stands out, corresponding to double the follow-up duration of previous meta-analyses (42, 43). Furthermore, a greater number of studies were included. Rates of encephalitis/encephalomyelitis, Guillain-Barré Syndrome (GBS), or transverse myelitis were not elevated following the 2022-2023 seasonal influenza vaccinations among U.S. adults aged 65 and older (44). However, there was an increased rate of anaphylaxis post-influenza vaccination, which may have been influenced by concomitant vaccination. In a self-controlled risk interval study, no significant increase in risk was observed for most cardiovascular, neurological, or immunological adverse events following PPSV23. The updated safety profile of PPSV23 provides supportive evidence for establishing immunization strategies for older adults (45).

CONCLUSION

Future studies should conduct comprehensive risk-benefit assessments to ascertain the overall impact on cardiovascular health, weighing the benefits of vaccination against respiratory infections against potential risks. Public health policies may need to evolve based on emerging evidence, ensuring that dual vaccination is recommended as our understanding of cardiovascular effects improves. As with any vaccination program, addressing vaccine hesitancy and ensuring public confidence in the safety and efficacy of dual vaccination will be crucial.

Abbreviations

PV23 - pneumococcal 23-valent polysaccharide vaccine

RR - relative risks

HR or OR - Hazard ratios or Odds Ratios

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

KARDIOVASKULARNI EFEKTI KOD DVOSTRUKE VAKCINACIJE PNEUMOKOKNOM PV23 I VAKCINOM PROTIV GRIPA: SISTEMATSKI PREGLED

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Pneumokokalna vakcina može smanjiti kardiovaskularne komplikacije. Ova sistematska analiza ispituje uticaj vakcinacije PV23 i sezonske vakcine protiv gripa na glavne kardiovaskularne ishodne parametre u poređenju sa nevakcinisanim populacijama. Sistematski smo pregledali klinička ispitivanja, kohortne studije i case-control studije objavljene između 2000. i 2019. godine koje su procenjivale kardiovaskularne ishode kod odraslih vakcinisanih sa PV23 i sezonskim vakcinama protiv gripa u odnosu na nevakcinisane odrasle. Uključeno je devetnaest članaka koji obuhvataju 617.411 pacijenata. Vakcinacija PV23 sama po sebi nije bila značajno povezana sa smanjenim rizikom od akutnog infarkta miokarda (RR 1.21 [95% CI: 1.18–1.23]). Dvostruka vakcinacija pokazala je zaštitni efekat protiv moždanog udara (RR 0.52 [95% CI: 0.45–0.61]) i značajno poboljšala ishode kod srčane insuficijencije (RR 0.26 [95% CI: 0.22–0.31]). Vakcinacija PV23 i dvostruka vakcinacija takođe su smanjile epizode akutne dekompenzacije srčane insuficijencije i razvoj moždanog udara.

Ključne reči: Vakcinacija protiv gripa, pneumokokna vakcina, infarkt miokarda, srčana insuficijencija, moždani udar.

REFERENCES

1. Singanayagam A, Singanayagam A, Elder DH, Chalmers JD. Is community-acquired pneumonia an independent risk factor for cardiovascular disease? Eur Respir J. 2012; 39(1): 187-96. doi: 10.1183/09031936.00049111.

2. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA. 2015; 313(3): 264-74. doi: 10.1001/jama.2014.18229.

3. Violi F, Cangemi R, Falcone M, Taliani G, Pieralli F, Vannucchi V et al. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. Clin Infect Dis. 2017; 64(11): 1486-93. doi: 10.1093/cid/cix164. Erratum in: Clin Infect Dis. 2017; 65(8): 1431-3. doi: 10.1093/cid/cix563.

4. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. Lancet. 2013; 381(9865): 496-505. doi: 10.1016/S0140-6736(12)61266-5.

5. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. Lancet Infect Dis. 2010; 10(2): 83-92. doi: 10.1016/S1473-3099(09)70331-7.

6. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004; 351(25): 2611-8. doi: 10.1056/NEJMoa041747.

7. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. Eur Heart J. 2008; 29(1): 96-103. doi: 10.1093/eurheartj/ehm516.

8. Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. Lancet. 1998; 351(9114): 1467-71. doi: 10.1016/s0140-6736(97)11084-4.

9. Bjarnason A, Westin J, Lindh M, Andersson LM, Kristinsson KG, Löve A, et al. Incidence, etiology, and outcomes of Community-Acquired Pneumonia: a population-based study. Open Forum Infect Dis. 2018; 5(2): ofy010. doi: 10.1093/ofid/ofy010.

10. Andrews NJ, Waight PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012; 30(48): 6802-8. doi: 10.1016/j.vaccine.2012.09.019.

11. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. Vaccine. 2016 Mar; 34(13): 1540-50. doi: 10.1016/j.vaccine.2016.02.024.

12. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015; 372(12): 1114-25. doi: 10.1056/NEJMoa1408544.

13. ACIP updates its pneumococcal vaccine recommendations for adults 65 years of age and older. https://www.immunize.org/technically-speaking/20191219.asp. Accessed February 21, 2020.

14. Centers for Disease Control and Prevention; Hall E, Wodi AP, Hamborsky J, Morelli V, Schillie S. Epidemiology and prevention of vaccine-preventable diseases. eds. 14th ed. Washington, DC Public Health Foundation, 2021.

15. Adler H, Ferreira DM, Gordon SB, Rylance J. Pneumococcal capsular polysaccharide immunity in the elderly. Clin Vaccine Immunol. 2017; 24(6): e00004-17. doi: 10.1128/CVI.00004-17.

16. Gray BM, Converse GM 3rd, Dillon HC Jr. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. J Infect Dis. 1980; 142(6): 923-33. doi: 10.1093/infdis/142.6.923.

17. van Deursen AM, van den Bergh MR, Sanders EA; Carriage Pilot Study Group. Carriage of Streptococcus pneumoniae in asymptomatic, community-dwelling elderly in the Netherlands. Vaccine. 2016; 34(1): 4-6. doi: 10.1016/j.vaccine.2015.11.014.

18. Ren S, Newby D, Li SC, Walkom E, Miller P, Hure A, et al. Effect of the adult pneumococcal polysaccharide vaccine on cardiovascular disease: a systematic review and meta-analysis. Open Heart. 2015; 2(1): e000247. doi: 10.1136/openhrt-2015-000247.

19. Ciszewski A. Cardioprotective effect of influenza and pneumococcal vaccination in patients with cardiovascular diseases. Vaccine. 2018; 36(2): 202-6. doi: 10.1016/j.vaccine.2017.11.078.

20. Vila-Corcoles A, Ochoa-Gondar O , Rodriguez-Blanco T, Gutierrez-Perez A, Vila-Rovira A, Gomez F, et al. Clinical effectiveness of pneumococcal vaccination against acute myocardial infarction and stroke in people over 60 years: the CAPAMIS study, one-year follow-up. BMC Public Health. 2012; 12: 222. doi: 10.1186/1471-2458-12-222.

21. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, de Diego-Cabanes C, Hospital-Guardiola I, Jariod-Pamies M et al. Evaluating the clinical effectiveness of pneumococcal vaccination in preventing myocardial infarction: The CAPAMIS study, three -year follow-up. Vaccine. 2014; 32(2): 252-7. doi: 10.1016/j.vaccine.2013.11.017.

22. 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. doi: 10.1016/j.jstrokecerebrovasdis.2013.12.047.

23. Hung IF, Leung AY, Chu DW, Leung D, Cheung T, Chan CK, et al. Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: a prospective cohort study. Clin Infect Dis. 2010; 51(9): 1007-16. doi: 10.1086/656587.

24. Tseng HF, Slezak JM, Quinn VP, Sy LS, Eeden SK-VD, Jacobsen SJ. Pneumococcal vaccination and risk of acute myocardial infarction and stroke in men. JAMA. 2010; 303(17): 1699-706. doi:10.1001/jama.2010.529.

25. Siriwardena AN, Gwini SM, Coupland CAC. Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case–control study. CMAJ. 2010; 182(15): 1617-23. doi:10.1503/cmaj.091891.

26. Siriwardena AN, Asghar Z, Coupland CCA. Influenza and pneumococcal vaccination and risk of stroke or transient ischaemic attack-matched case control study. Vaccine. 2014; 32(12): 1354-1361. doi:10.1016/j.vaccine.2014.01.029.

27. Lamontagne F, Garant MP, Carvalho JC, Lanthier L, Smieja M, Pilon D. Pneumococcal vaccination and risk of myocardial infarction. CMAJ. 2008; 179(8): 773-7. doi: 10.1503/cmaj.070221.

28. Meyers DG, Beahm DD, Jurisich PD, Milford CJ, Edlavich S. Influenza and Pneumococcal vaccinations fail to prevent myocardial infarction. Heart Drug. 2004; 4(2): 96-100. doi: 10.1159/000077705.

29. Eurich DT, Johnstone JJ, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Pneumococcal vaccination and risk of acute coronary syndromes in patients with pneumonia: population-based cohort study. Heart. 2012; 98(14): 1072-7. doi:10.1136/heartjnl-2012-301743.

30. Ahmed MB, Patel K, Fonarow GC, Morgan CJ, Butler J, Bittner V, et al. Higher risk for incident heart failure and cardiovascular mortality among community-dwelling octogenarians without pneumococcal vaccination. ESC Heart Fail. 2016; 3(1): 11-7. doi: 10.1002/ehf2.12056.

31. Wu WC, Jiang L, Friedmann PD, Trivedi A. Association between process quality measures for heart failure and mortality among US veterans. Am Heart J. 2014; 168(5): 713-20. doi: 10.1016/j.ahj.2014.06.024.

32. 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. doi: 10.1016/j.vaccine.2019.08.088.

33. Mahamat A, Daurès JP, Wazières B de. Additive preventive effect of influenza and pneumococcal vaccines in the elderly. Hum Vaccines Immunother. 2013; 9(1): 128-35. doi: 10.4161/hv.22550.

34. Zahid M, Singla I, B. Good C, A. Stone R, Kim S, J. Fine M, et al. Associations between Pneumococcal vaccination and adverse outcomes in patients with suspected acute coronary syndrome. Advances in Infectious Diseases. 2012; 2(4): 122–34. doi: 10.4236/aid.2012.24021.

35. Li T. Efficacy of combined influenza and 23-valent pneumococcal polysaccharide vaccines in chronic smokers. (Thesis). University of Hong Kong, Pokfulam, Hong Kong SAR; 2014. Available from: http://dx.doi.org/10.5353/th_b5293004.

36. Ren S, Holliday E, Hure A, Peel R, Hancock S, Leigh L, et al. Pneumococcal polysaccharide vaccine associated with reduced lengths of stay for cardiovascular events hospital admissions: Experience from the Hunter Community Study. Vaccine. 2018; 36(49): 7520-4. doi: 10.1016/j.vaccine.2018.10.064.

37. Song JY, Noh JY, Lee JS, Wie SH, Kim YK, Lee J, et al. Effectiveness of influenza and pneumococcal polysaccharide vaccines against influenza-related outcomes including pneumonia and acute exacerbation of cardiopulmonary diseases: Analysis by dominant viral subtype and vaccine matching. PLoS One. 2018; 13(12): e0207918. doi: 10.1371/journal.pone.0207918.

38. Chang YC, Chou YJ, Liu JY, Yeh TF, Huang N. Additive benefits of pneumococcal and influenza vaccines among elderly persons aged 75 years or older in Taiwan – A representative population-based comparative study. J Infect. 2012; 65(3): 231-8. doi:10.1016/j.jinf.2012.04.014.

39. Metersky ML, Masterton RG, Lode H, File TM, Babinchak T. Epidemiology, microbiology, and treatment considerations for bacterial pneumonia complicating influenza. Int J Infect Dis. 2012; 16(5): e321-31. doi: 10.1016/j.ijid.2012.01.003.

40. Ma J, Mena M, Mandania RA, Ghosh A, Dodoo C, Dwivedi AK, et al. Associations between combined Influenza and Pneumococcal pneumonia vaccination and cardiovascular outcomes. Cardiology. 2021; 146(6): 772-80. doi: 10.1159/000519469.

41. Metlay JP, Waterer GW, Long AC,Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019; 200(7): e45-e67. doi:10.1164/rccm.201908-1581ST.

42. Ren S, Newby D, Li SC, Walkom E, Miller P, Hure A, et al. Effect of the adult pneumococcal polysaccharide vaccine on cardiovascular disease: a systematic review and meta-analysis. Open Heart. 2015; 2(1): e000247. doi: 10.1136/openhrt-2015-000247.

43. Vlachopoulos CV, Terentes-Printzios DG, Aznaouridis KA, Pietri PG, Stefanadis CI. Association between pneumococcal vaccination and cardiovascular outcomes: a systematic review and meta-analysis of cohort studies. Eur J Prev Cardiol. 2015; 22(9): 1185-99. doi: 10.1177/2047487314549512.

44. Shi XC, Gruber JF, Ondari M, Lloyd PC, Freyria Duenas P, Clarke TC, et al. Assessment of potential adverse events following the 2022-2023 seasonal influenza vaccines among U.S. adults aged 65 years and older. Vaccine. 2024; 42(15): 3486-92. doi: 10.1016/j.vaccine.2024.04.051. Epub 2024 May 3.

45. Yoon D, Jeon H, Kim JH, Lee H, Shin J. Cardiovascular, neurological, and immunological adverse events and the 23-valent Pneumococcal polysaccharide vaccine. JAMA Netw Open. 2024; 7(1): e2352597. doi: 10.1001/jamanetworkopen.2023.52597.

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