

Review

Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials



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ABSTRACT

Background: Data on the efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPV-23) in preventing adult community-acquired pneumonia (CAP) among the target population of individuals aged over 65 years and high-risk individuals aged 19–64 years are conflicting. As the Advisory Committee on Immunization Practices (ACIP) has recently demonstrated PPV-23 is likely beneficial to immunocompromised adults by the Grading, Assessment, Development, and Evaluation (GRADE) framework, we conducted meta-analysis to examine its efficacy in an immunocompetent population.

Methods: We searched the PUBMED, EMBASE, and Cochrane Library databases for randomized trials. Overall relative risks (RRs) with 95% confidential intervals (CIs) were calculated, and the Cochrane Q test (p , I^2) was performed. Outcomes were assessed by the GRADE framework.

Results: Seven randomized trials involving 156,010 participants were included in this meta-analysis. High-quality evidence revealed that PPV-23 was weakly associated with the prevention of all-cause pneumonia ([RR] 0.87, [95%CI] 0.76–0.98, $p = 0.11$, $I^2 = 43\%$), especially among the target population ([RR] 0.72, [95%CI] 0.69–0.94, $p = 0.58$, $I^2 = 0\%$), the elderly group aged over 40 years ([RR] 0.80, [95%CI] 0.69–0.94) and the Japanese population ([RR] 0.72, [95%CI] 0.59–0.88, $p = 0.24$, $I^2 = 30\%$). The target population included adults aged over 65 years and patients at high risk of pneumonia due to chronic lung disease, chronic obstructive pulmonary disease or living in a nursing home. Protective trends of PPV-23 in the outcomes of pneumococcal pneumonia ([RR] 0.54, [95%CI] 0.18–1.65, $p = 0.01$, $I^2 = 77\%$) and mortality due to pneumonia ([RR] 0.67, [95%CI] 0.43–1.04, $p = 0.67$, $I^2 = 0\%$) were observed, although the results were statistically insignificant, possibly due to the small number of trials included. PPV-23 did not prevent all-cause mortality ([RR] 1.04, [95%CI] 0.87–1.24, $p = 0.95$, $I^2 = 0\%$).

Conclusions: PPV-23 provided weak protection against all-cause pneumonia in an immunocompetent population, especially among the target population. The additional benefit of PPV-23 in preventing CAP further supports its application in the target population.

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1. Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality throughout the world [1]. *Streptococcus pneumoniae* is the cause of 2.2–50.9% [2] of CAP cases, and the

23-valent pneumococcal polysaccharide vaccine (PPV-23) includes serotypes covering more than 90% of the isolates that cause invasive pneumococcal diseases (IPD) [3,4]. Therefore, PPV-23 is considered to have potential for the prevention of CAP. The vaccine has been used for more than 30 years, and its efficacy in preventing IPDs is relatively clear [5]; however, data regarding its efficacy in preventing adult CAP, including pneumococcal pneumonia, are conflicting [5,6]. Furthermore, the efficacy of the vaccine among the target population of persons aged more than 65 years and high-risk individuals aged 19–64 years [7] is unclear [5,6].

Many meta-analyses [5,6] have focused on the overall efficacies of pneumococcal polysaccharide vaccines (PPV), from 2-valent to

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23-valent vaccines, as well as on the efficacy of PPV against pneumococcal diseases, such as IPD. However, clinicians have primarily focused on the efficacy of PPV-23 because it is currently the only PPV valence used in clinical practice to prevent CAP. The additional benefit of PPV-23 in the prevention of CAP supports this application. Hence, a systematic review is required to independently assess the efficacy of PPV-23 specifically, rather than all PPVs, in preventing CAP. As the Advisory Committee on Immunization Practices (ACIP) has recently demonstrated that PPV-23 is likely beneficial to immunocompromised adults [8] based on the Grading, Assessment, Development, and Evaluation (GRADE) framework, we conducted a systematic review and meta-analysis of randomized trials to examine the effectiveness of PPV-23 among immunocompetent adults using the GRADE approach.

2. Methods

2.1. Search strategy

We searched the PUBMED, EMBASE, and Cochrane Library databases from their inception dates to April 7, 2015 using the Medical Subject Heading (Mesh) terms “pneumococcal vaccines”, “randomized controlled trial”, and “controlled clinical trial” and the corresponding free words, “pneumococcal vaccination”, “randomly”, “randomized”, and “randomised”. Further details are presented in Appendix 1. In addition, the reference lists of the systematic reviews, meta-analyses, review articles and other relevant reports were reviewed without language limits to ensure that all eligible studies were included.

2.2. Study selection

To reduce the probability of bias as much as possible, studies were included in the meta-analysis if they met the following criteria: (1) a randomized trial comparing one PPV-23 group with a control group (placebo, influenza vaccine (IV) or no intervention) and (2) examination of at least one of the following clinical outcomes: all-cause pneumonia, pneumococcal pneumonia, all-cause mortality and mortality due to pneumonia. Studies were excluded for the following reasons: (1) observational studies, case reports, quasi-random trials and animal studies; (2) the intervention was limited to conjugate vaccines or non-23-valent PPV; (3) the aim was to investigate the immunogenicity, safety or cost-effectiveness of vaccines; (4) the age of the subjects was less than 15 years; and (5) the subjects were patients with an immunocompromising condition, such as HIV infection, functional asplenia, or malignant diseases.

2.3. Data extraction

The retrieved articles were evaluated according to the inclusion criteria by two investigators. The following information was extracted from these studies: the author, publication year, country, intervention description, longest follow-up period, study setting, episodes or number of participants who experienced the event being studied, number of subjects included, and age range of the study population. Study quality was determined based on the use of random sequence generation, allocation concealment, blinding and the number of patients lost to follow-up. Disagreements between reviewers were resolved by consensus.

2.4. Outcomes of meta-analysis

The following 4 outcomes were assessed: (1) all-cause pneumonia, as confirmed by clinical symptoms and chest radiographs; (2)

pneumococcal pneumonia, as confirmed clinically and radiographically with isolation of *Streptococcus pneumoniae* from a culture of a non-sterile sample, such as sputum; (3) all-cause mortality; and (4) mortality due to pneumonia.

2.5. Quality assessment

Two reviewers rated the quality of each randomized trial with respect to the use of methods of random sequence generation, concealment of allocation, and blinding and the number of patients lost to follow-up. Studies were classified as adequate, unclear or inadequate depending on the use of random sequence generation and allocation concealment. Studies using the blinding method were categorized into the following 3 groups: double-blind (staff and participants blinded); control (staff and participants likely knew the patients allocated to receive the pneumococcal vaccine, but another vaccine was used in the control group); and open (no vaccine was used in the control group). Lost to follow-up was calculated as the number of missing patients.

Each outcome was evaluated using the GRADE framework. Outcome assessment quality was classified into 4 grades: high, moderate, low and very low [9]. Randomized trials and observational studies were initially assumed to have high- and low-quality evidence, respectively, and their quality levels were upgraded or downgraded according to the criteria [9] presented in Appendix 2 (Table S1). Two investigators reached consensus on the outcome assessment qualities of the included studies.

2.6. Data synthesis and statistical analysis

We assessed the heterogeneity of the randomized trials using the Cochrane Q test. A p value of below 0.1 indicated potential heterogeneity, and the I^2 statistic was used to quantify the extent of heterogeneity [10]. For studies with a p value less than 0.1 [11], the random effects model and corresponding forest plots were used to calculate the overall relative risks (RRs); otherwise the Mantel–Haenszel fixed effects model was applied. Heterogeneity was assessed as the number of episodes or the number of participants who experienced the event.

If heterogeneity were identified in outcomes involving more than 4 trials, then analyses of these outcomes were stratified with respect to the study population, intervention type, study setting and study population age. According to the recommendations of the ACIP [7], the study populations were divided into 2 groups: the target population (adults aged over 65 years and individuals aged 19–64 years at high-risk of pneumonia due to chronic lung illness or living in a nursing home) and others (healthy military trainees aged 17–20 years and adults with a history of CAP). The interventions were divided into 3 types: PPV-23 and IVs, PPV-23 and a steroid, and PPV-23 alone. The study setting was classified into 3 groups: Western Europe, the United States, and Japan. The population ages were divided into 2 groups: elderly (>40 years) and young (<20 years) individuals. To better understand the efficacy of PPV-23 in each high-risk group, we conducted subgroup analyses of the target population. The following 3 subgroups were examined: chronic obstructive pulmonary disease (COPD) patients, chronic lung disease (CLD) patients, and individuals aged over 60 years.

To determine whether the meta-analysis outcome was stable, we performed sensitivity analyses by excluding studies with sample sizes of less than 100 or more than 100,000, those with an unclear blinding method, and those with an unclear allocation or concealment method. All analyses were conducted using “RevMan version 5.3” software.

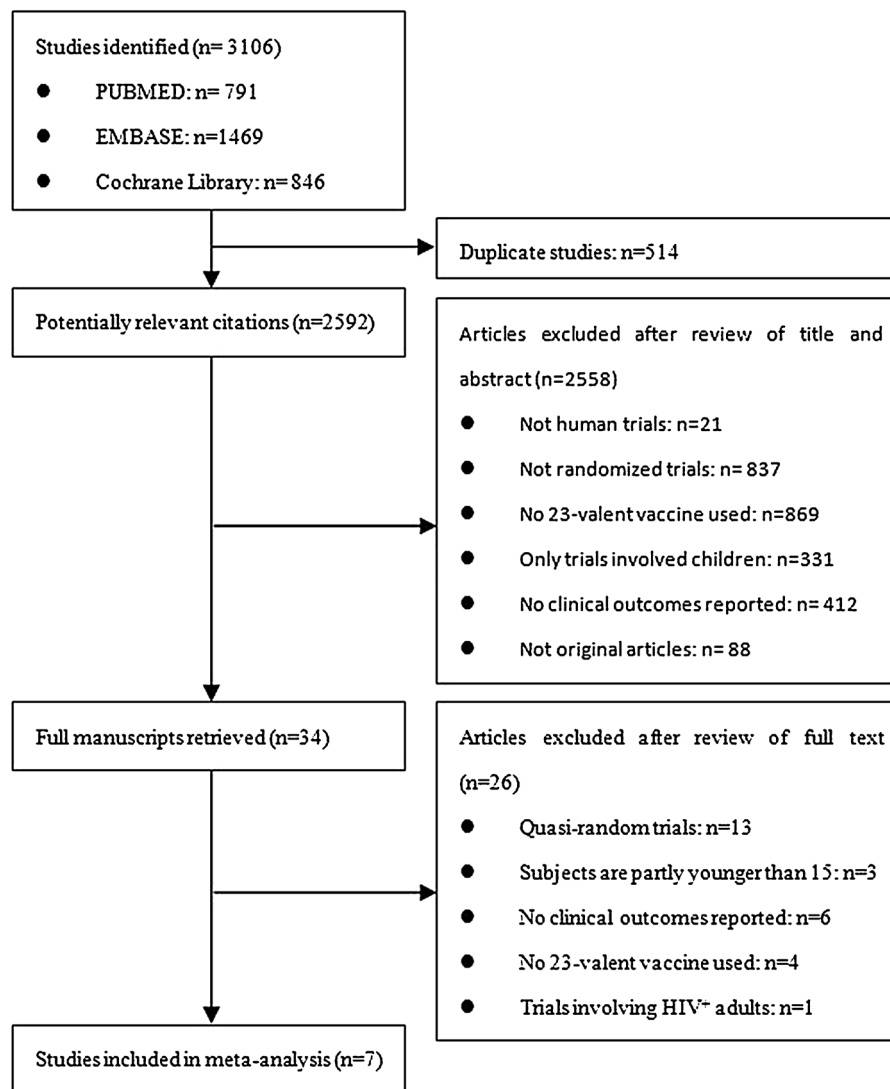


Fig. 1. Flow diagram of study selection.

Table 1
Characteristics of included randomized trials.

Author	Year	Country	Vaccine	Control	Study population	Outcome ^a	Follow-up (year)
Alfageme [15]	2006	Spain	PPV-23	No vaccine	596 COPD patients aged 61–73	1, 2, 3, 4	3
Furumoto [16]	2008	Japan	PPV-23 + IV	IV	167 patients with CLD aged 40–80	1, 3	2
Kawakami [13]	2010	Japan	PPV-23 + IV	IV	778 patients aged 65 or older	1, 3, 4	2
Maruyama [14]	2010	Japan	PPV-23	Placebo	1006 nursing home residents aged 55–105	1, 2, 3, 4	3
Ortqvist [18]	1998	Sweden	PPV-23	Placebo	691 patients who had a CAP history aged 50–85	1, 2, 3, 4	4.3
Russell [12]	2015	America	PPV-23	Placebo	152,723 healthy military trainees aged 17–20	1, 3	6.7
Steentoft [17]	2006	Denmark	PPV-23 + steroid	Steroid	49 COPD patients aged 47–86	1, 3	NR

Abbreviations: PPV-23: 23-valent pneumococcal polysaccharide; IV: influenza vaccine; CAP: community acquired pneumonia; COPD: chronic obstructive pulmonary disease; CLD: chronic lung disease; NR, not reported.

^a Outcomes: (1) all-cause pneumonia, confirmed by clinical symptoms and chest radiographs; (2) pneumococcal pneumonia, confirmed clinically and radiographically with *Streptococcus pneumoniae* isolated from a culture of non-sterile samples, such as sputum; (3) all-cause mortality; (4) mortality due to pneumonia.

3. Results

3.1. Identification of trials

The literature search identified a total of 3106 potentially pertinent articles, and the full texts of 34 of those articles were reviewed. Finally, 7 randomized trials including 156,010 participants were found to meet the inclusion criteria for this meta-analysis: (Russell, 2015) [12], (Kawakami, 2010) [13], (Maruyama, 2010) [14],

(Alfageme, 2006) [15], (Furumoto, 2008) [16], (Steentoft, 2006) [17] and (Ortqvist, 1998) [18]. Fig. 1 presents the study selection process. Furthermore, some important studies that were excluded are presented in Appendix 3.

Three (43%) of the studies were conducted in Western Europe, 1 (14%) was conducted in the United States, and 3 (43%) were conducted in Japan. In the control group, a placebo was used in 3 (43%) trials, IV was used in 2 (29%) trials, and no vaccine was used in 2 (29%) trials. The participants of 5 (71%) trials were members of

Table 2
Quality assessment of outcomes by GRADE approach.

Outcome	No. of trials	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Quality	Importance
All-cause pneumonia	7	Randomized trials	Not serious ^a	Not serious	Not serious ^b	Not serious	None	High	Critical
Pneumococcal pneumonia	3	Randomized trials	Not serious	Serious ^c	Serious ^d	Serious ^e	None	Very low	Critical
All-cause mortality	5	Randomized trials	Not serious	Not serious	Not serious ^b	Not serious	None	High	Critical
Mortality due to pneumonia	4	Randomized trials	Not serious	Not serious	Not serious ^b	Serious ^f	None	Moderate	Critical

Abbreviation: GRADE: the Grading, Assessment, Development, and Evaluation.

Note:

^a Risk of bias: We did not downgrade for risk of bias, because in the meta-analysis of 7 randomized trials, blinding of 2 trials was open, allocation concealment of 2 trials was unclear, lost to follow-up of 1 trial was not reported and the most serious lost to follow-up of the rest was less than 15%.

^b Indirectness: We did not downgrade for indirectness, because our study population were all immunocompetent adults, not only the target population aged over 65 or at high risk. And vaccine efficacy among target population would be discussed in stratified analyses.

^c Inconsistency: We downgraded for inconsistency, because Cochrane Q test indicated heterogeneity was statistically significant ($p = 0.01$, $I^2 = 77\%$).

^d Indirectness: We downgraded for indirectness because the diagnosis of pneumococcal pneumonia was presumptive with *Streptococcus pneumoniae* isolated from a culture of non-sterile samples, such as sputum.

^e Imprecision: We downgraded for imprecision, because pooled relative risk (RR) was 0.54 and 95% confident interval (CI) was 0.18–1.65, whose upper limit was higher than 1.

^f Imprecision: We downgraded for imprecision, because overall RR was 0.67 and CI was 0.43–1.04, whose upper limit was larger than 1.

Table 3
Summary of findings.

Outcome	No. of patients			Relative effect (95% CI)	Absolute effect	Heterogeneity test
	Total no. (trials)	PPV-23	Control			
All-cause pneumonia	156,010 (7)	410/77,899	480/78,111	RR 0.87 (0.76–0.98)	1 fewer per 1000 (from 0 fewer to 1 fewer)	$p = 0.11$, $I^2 = 43\%$
Pneumococcal pneumonia	2293 (3)	33/1139	58/1154	RR 0.54 (0.18–1.65)	23 fewer per 1000 (from 41 fewer to 33 more)	$p = 0.01$, $I^2 = 77\%$
All-cause mortality	3238 (5)	205/1617	198/1621	RR 1.04 (0.87–1.24)	5 more per 1000 (from 16 fewer to 29 more)	$p = 0.95$, $I^2 = 0\%$
Mortality due to pneumonia	3071 (4)	32/1530	48/1541	RR 0.67 (0.43–1.04)	10 fewer per 1000 (from 18 fewer to 1 more)	$p = 0.67$, $I^2 = 0\%$

Abbreviations: RR: relative risk; CI: confidential interval.

the target population of persons aged over 65 years and adults at high risk of pneumonia due to chronic lung illness or living in a nursing home. The subjects of 2 (29%) trials were healthy military trainees aged 17–20 years and subjects with a history of CAP. The longest follow-up period was reported in 6 (86%) articles and was not reported in 1 (14%) article. Data that are not presented and further details of the included studies are listed in Table 1.

The quality assessment of each study is presented in Appendix 2 (Table S2). The random sequence generation method was adequate in 4 (57%) trials and unclear in 3 (43%) trials. The allocation concealment method was adequate in 6 (86%) trials and unclear in 1 (14%) trial. The blinding method was described as “double-blind” in 3 (43%) trials, “control” in 2 (29%) trials, and “open” in 2 (29%) trials. The percentage of subjects lost to follow-up was below 1% in 5 (71%) trials, 14.3% in 1 (14%) trial, and unclear in 1 (14%) trial.

The quality assessments of all outcomes using the GRADE method are presented in Table 2. The qualities of evidence for all-cause pneumonia and all-cause mortality were high, that for mortality due to pneumonia was moderate, and that for pneumococcal pneumonia was very low.

3.2. Meta-analysis

Based on the results of the Cochrane Q test, all-cause pneumonia ($p = 0.11$, $I^2 = 43\%$), all-cause mortality ($p = 0.95$, $I^2 = 0\%$) and mortality due to pneumonia ($p = 0.67$, $I^2 = 0\%$) were examined using the fixed effects model, and pneumococcal pneumonia was examined using the random effects model ($p = 0.01$, $I^2 = 77\%$).

The pooled RRs indicated that PPV-23 reduced the incidence of all-cause pneumonia ([RR] 0.87, [95%CI] 0.76–0.98). It also exhibited a trend of reducing the incidences of pneumococcal pneumonia ([RR] 0.54, [95%CI] 0.18–1.65) and mortality from pneumonia ([RR] 0.67, [95%CI] 0.43–1.04), but these results were statistically insignificant, possibly because of the small number of trials included. PPV-23 did not decrease all-cause mortality ([RR] 1.04, [95%CI] 0.87–1.24). A summary of the findings is presented in Table 3, and the corresponding forest plots are presented in Fig. 2.

Sensitivity analyses were performed by excluding studies with a risk of bias (Russell, 2015) [9], (Alfageme, 2006) [15], (Furumoto, 2008) [16], (Kawakami, 2010) [13] and (Steenoft, 2006) [17]. And it demonstrated that the results were stable.

Due to the potential heterogeneity ($p = 0.11$, $I^2 = 43\%$) of the data on all-cause pneumonia, we stratified the analysis with respect to the study setting, type of intervention, study population and study population age. Analysis stratified for study setting revealed that PPV-23 had a preventive effect in Japan ([RR] 0.72, [95%CI] 0.59–0.88, $p = 0.24$, $I^2 = 30\%$) but not in Western Europe ([RR] 0.98, [95%CI] 0.76–1.27, $p = 0.29$, $I^2 = 20\%$) or the United States ([RR] 0.96, [95%CI] 0.78–1.18). Analysis stratified for study population demonstrated that PPV-23 protected target adults, which included those aged over 65 years and those aged 19–64 years at high risk of pneumonia ([RR] 0.72, [95%CI] 0.69–0.94, $p = 0.58$, $I^2 = 0\%$); however, it did not protect young healthy military trainees aged 17–20 years or individuals with a history of CAP history ([RR] 1.00, [95%CI] 0.84–1.19, $p = 0.36$, $I^2 = 0\%$). An analysis stratified for population age revealed that PPV-23 was effective in elderly individuals aged more than 40 years ([RR] 0.80, [95%CI] 0.69–0.94, $p = 0.12$, $I^2 = 42\%$) but not in young individuals aged less than 20 years ([RR] 0.96, [95%CI] 0.78–1.18). Administration of PPV-23 in combination with IV had no additional protective effect over administration of PPV-23 alone ([RR] 0.84, [95%CI] 0.64–1.10, $p = 0.62$, $I^2 = 0\%$). To better understand the efficacy of PPV-23 for each high-risk population, we also conducted subgroup analyses of all-cause pneumonia. These analyses revealed that the protective effects of PPV-23 in all high-risk populations were consistent with those in the target adults; however, these results were statistically insignificant, probably due to the small number of trials included. Further details are shown in Table 4.

4. Discussion

This systematic review of randomized trials aimed to determine the effectiveness of PPV-23 among immunocompetent adults. High-quality evidence according to the GRADE framework revealed

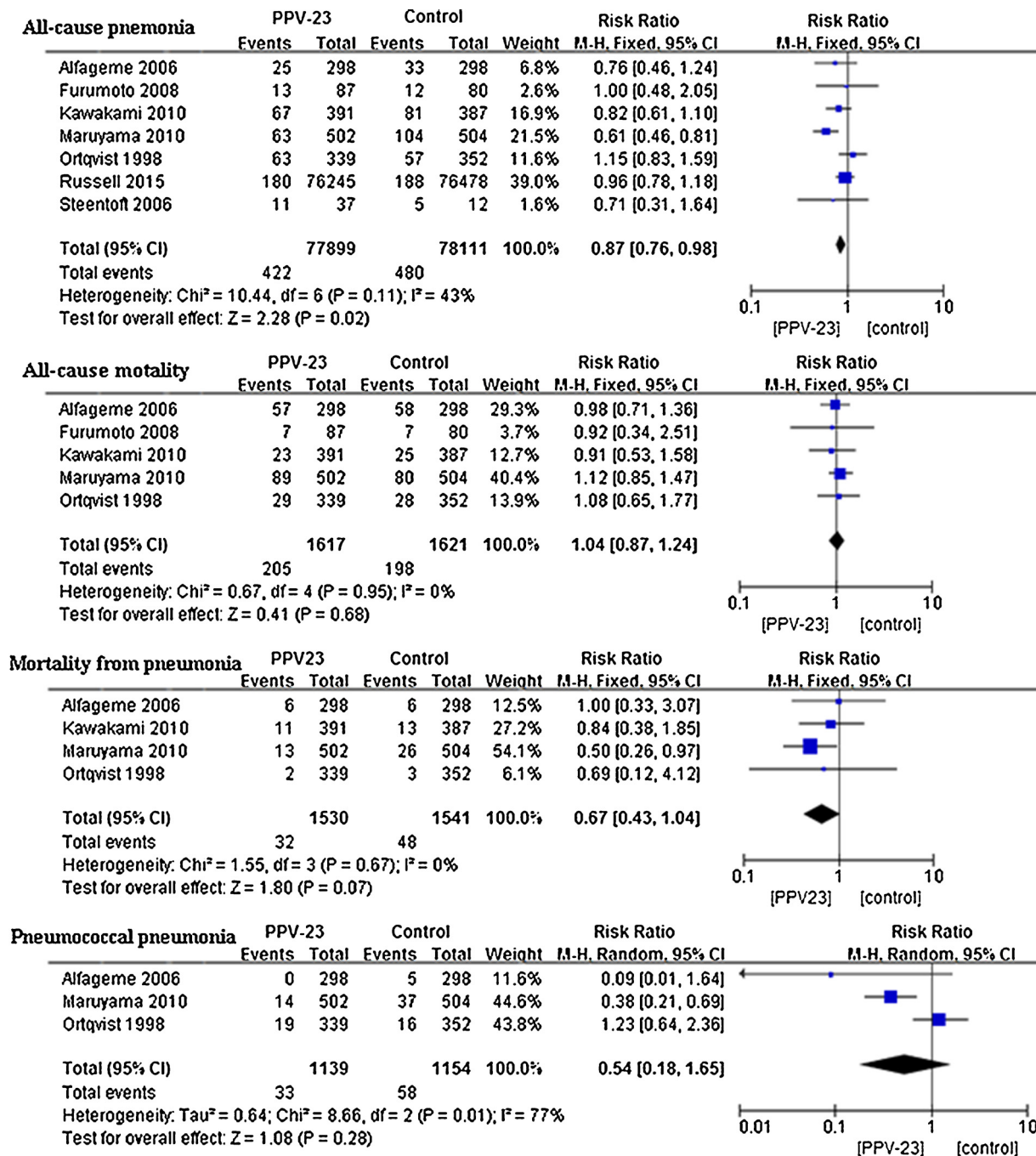


Fig. 2. Forest plots of meta-analyses for 4 outcomes. Note: The results for pneumococcal pneumonia were examined using the random effect models, and those for the other outcomes were examined using the fixed effects model. A summarized value of less than 1 indicated a protective effect of the vaccine, and a value of greater than 1 indicated an adverse effect of the vaccine.

that PPV-23 administration was weakly associated with the prevention of all-cause pneumonia, especially among target adults, including those aged over 65 years and those aged 19–64 years at high risk of pneumonia, the elder group (>40 years) and Japanese individuals. PPV-23 also exhibited protective trends in preventing pneumococcal pneumonia and mortality due to pneumonia, but these results were statistically insignificant, possibly because of the small number of trials included. PPV-23 did not reduce all-cause mortality.

We observed that PPV-23 had a weak protective effect on all-cause pneumonia. The additional benefit of PPV-23 in the prevention of CAP supports its application. However, our findings differ

from those reported by numerous meta-analyses [5,6]. For example, an updated Cochrane review [5] reported that PPV was not able to prevent all-cause pneumonia. The PPV valence may be an important confounder. The following 5 randomized trials in the Cochrane review were focused on PPV-23: (Alfageme, 2006) [15]; (Furumoto, 2008) [16]; (Kawakami, 2010) [13]; (Maruyama, 2010) [14]; (Ortqvist, 1998) [18]. All of these 5 studies were included in our meta-analysis, and the findings of these five trials are consistent with those of our overall meta-analysis. The findings of Huss [6] differed from those of our meta-analysis even though they considered the valences of the vaccines. This discrepancy is likely due to the different trials included in these two meta-analyses; we

Table 4
Stratified analyses of all-cause pneumonia.

Variable or subgroup	Included trials ^b	No. of participants	RR (95%CI)	Heterogeneity test
Study setting				
Western Europe	1, 5, 7	152,723	0.98 (0.76–1.27)	$p = 0.29$, $I^2 = 20\%$
The United States	6	1336	0.96 (0.78–1.18)	None
Japan	2, 3, 4	1951	0.72 (0.59–0.88)	$p = 0.24$, $I^2 = 30\%$
Type of interventions				
PPV-23 + IV	2, 3	945	0.84 (0.64–1.10)	$p = 0.62$, $I^2 = 0\%$
PPV-23 + steroid	7	49	0.71 (0.31–1.64)	None
Only PPV-23	1, 4, 5, 6	155,016	0.85 (0.64–1.13)	$p = 0.02$, $I^2 = 70\%$
Study population				
Target population ^a	1, 2, 3, 4, 7	3287	0.72 (0.69–0.94)	$p = 0.58$, $I^2 = 0\%$
Other ^c	5, 6	153,414	1.00 (0.84–1.19)	$p = 0.36$, $I^2 = 0\%$
Population age				
Elderly (>40 years)	1, 2, 3, 4, 5, 7	3287	0.80 (0.69–0.94)	$p = 0.12$, $I^2 = 42\%$
Young (<20 years)	6	1336	0.96 (0.78–1.18)	None
Subgroup of targeted population^a				
Adults with COPD	1, 7	645	0.75 (0.49–1.14)	$p = 0.90$, $I^2 = 0\%$
Adults with CLD	1, 2, 7	812	0.80 (0.56–1.16)	$p = 0.79$, $I^2 = 0\%$
Adults aged over 60	1, 3	1374	0.80 (0.62–1.03)	$p = 0.79$, $I^2 = 0\%$

Abbreviations: RR: relative risk; CI: confidential interval. PPV-23: 23-valent pneumococcal polysaccharide; IV: influenza vaccine; COPD: chronic obstructive pulmonary disease; CLD: chronic lung disease.

^a Target population: adults aged over 65 or high-risk adults with CLD, COPD or living in nursing home.

^b Included trials: (1) (Alfageme, 2006) [15]; (2) (Furumoto, 2008) [16]; (3) (Kawakami, 2010) [13]; (4) (Maruyama, 2010) [14]; (5) (Ortqvist, 1998) [18]; (6) (Russell, 2015) [12]; (7) (Steentoft, 2006) [17].

^c Other: adults who were young healthy military trainees or had a history of community-acquired pneumonia.

excluded some quasi-randomized trials [19,20] that were included in their meta-analysis, and we included some more recent randomized controlled trials (RCTs) [12–14] that were not included in their meta-analysis.

Given the possible heterogeneity and weak efficacy of PPV-23 in the prevention of all-cause pneumonia, we performed stratified analysis based on study setting and determined that PPV-23 had no protective effect on adults in Europe or the United States but did had a protective effect in adults in Japan. The reduced heterogeneity observed in stratified analysis indicated that it was rational. Several studies [21,22] have reported discrepancies in the incidence of bacteremic pneumonia between black and white individuals, with control for other confounders. Hence, we speculate that racial discrepancies may influence the efficacy of PPV-23. However, as the number of trials included was limited and other confounders may have influenced the results, an RCT investigating racial discrepancies in this context may be required. PPV-23 also had a significant effect on the target group, which included individuals aged over 65 years and those aged 19–64 years at high risk of pneumonia, supporting the use of this vaccine among adults, as recommended by the ACIP [5]. The lack of heterogeneity in the analysis stratified by study population indicated that the results were reliable. For every high-risk group, PPV-23 had a protective trend; however, those results were statistically insignificant, possibly because a small number of trials were included. A systematic review [23] and a large cohort study [24] that were recently published have reported an additive protective of PPV-23 administered in combination with IV on CAP. Our study did not find a similar effect, and it is unclear whether the previous conclusion was reliable, as it was determined based on the results of observational trials. Hence, the efficacy of the concomitant use of PPV-23 and IV requires investigation through a large, double-blinded RCT.

The study (Russell, 2015) [12] that included 152,723 subjects accounted for 97.9% of the subjects of all 7 included trials (156,010 subjects). The age range of the subjects in that study was 17–20 years, which is significantly lower than those of the other included studies. Thus, that study may have influenced our final results. Consequently, we conducted sensitivity analysis with exclusion of

the study (Russell, 2015) and found that our findings were not significantly influenced. However, a reduction in the pooled RRs was observed in sensitivity analysis, indicating that the population age may nonetheless have acted as a confounder. Therefore, we performed analysis stratified by population age, and the results indicated that PPV-23 was effective in the elderly group (>40 years) but not in the young group (<20 years). Thus, PPV-23 exhibits greater efficacy against CAP in elderly adults than in younger adults.

Moderate-quality evidence according to the GRADE framework indicated that PPV-23 exhibits a protective trend in the reduction of mortality due to pneumonia, but this result was not statistically significant. By examining the forest plot, we found that the study (Ortqvist, 1998) [18] severely altered the results of this analysis due to inclusion of a low number of events. Our conclusion is consistent with that of a recent systematic review [25].

Although the observed protective effect of PPV-23 against pneumococcal pneumonia was statistically insignificant, the overall RR was 0.54, indicating a protective trend. The results of analysis that included only 3 trials were supported by very low-quality evidence due to severe heterogeneity, indirectness and imprecision. Thus, the effects of PPV-23 on pneumococcal pneumonia require further investigation.

The finding that PPV-23 had no preventive effect on all-cause mortality is consistent with what has been reported by most meta-analyses [5,6].

Our study has the following strengths. First, we focused on the efficacy of PPV-23 against CAP rather than against IPDs. The additional benefit of PPV-23 in preventing CAP supports this application. Second, we only included randomized trials because previous studies [6,26] have shown study quality is a key confounder. Third, we chose the transparent and objective GRADE approach to evaluate the overall quality of this series of trials. Fourth, we focused on PPV-23 because it covers more serotypes of *S. pneumonia* than PPVs of other valences and because PPV-23 is currently the only PPV valence used in clinical practice. Finally, the findings regarding critical outcomes (mortality from pneumonia, all-cause mortality and all-cause pneumonia) were supported by moderate- to high-quality evidence according to the GRADE framework.

There are several limitations of our meta-analysis. First, this review only included 7 randomized trials, which restricted analyses that could be performed. Second, the diagnosis of pneumococcal pneumonia was confirmed clinically and radiographically with isolation of *S. pneumoniae* from a culture of a non-sterile sample, such as sputum. With this method, it is easy to obtain an incorrect diagnosis because the pathogen may originate from colonization. Furthermore, we only selected outcomes related to CAP and ignored other outcomes that may be indirect indicators of CAP, such as IPD. Finally, our study population consisted of immunocompetent adults and did not include immunocompromised subjects [8] who had recently been evaluated by the ACIP using the GRADE strategy.

In addition to PPV-23, the 13-valent pneumococcal conjugate vaccine (PCV-13) is considered another important vaccine for preventing adult CAP, and it has been approved by the Food and Drug Administration (FDA) for use in adults aged over 50 years [27]. The most recently reported high-quality RCT of PCV-13 [28] has demonstrated that it is effective at preventing vaccine-type non-bacteremic and non-invasive pneumococcal CAP among adults aged 65 years or over; thus, this vaccine may be able to replace PPV-23. However, PPV-23 contains 11 unique serotypes that cause 38% of IPDs among individuals aged over 65 years [29]. Therefore, the use of both PCV-13 and PPV-23 in series may be the best vaccination method, as recommended by the ACIP [7]. Determining the optimal interval between the administration of PCV-13 and PPV-23 will be an area of increasing research interest in the future.

In conclusion, our study indicated that PPV-23 exhibits a weak protective effect on all-cause pneumonia among immunocompetent adults, especially the target population, which includes individuals aged over 65 years and those aged 19–64 years who were at high risk of pneumonia, elderly adults (>40 years) and Japanese adults. Thus, we propose that PPV-23 should be administered to the target population. Protective trends of PPV-23 were observed in the outcomes of pneumococcal pneumonia and mortality due to pneumonia were observed, although the results were statistically insignificant, possibly due to the small number of trials included. Hence, high-quality RCTs are warranted to determine the protective effect of PPV-23 against pneumococcal pneumonia and mortality due to pneumonia.

Contributors and authorship

All authors declare their individual contribution to the article. Bei He designed the study and performed critical revisions of the article; Wen-qi Diao performed the acquisition, analysis and interpretation of the data, and drafted the article; and Ning Shen, Pan-xi Yu and Bei-bei Liu participated in the acquisition, analysis and interpretation of the data. All authors approved the final version of the manuscript and its submission for publication.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2016.02.023>.

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