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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.

1. Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality throughout the world [1]. *Streptococcus pneumonia* 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 of concealment method. All analyses were conducted using "RevMan version 5.3" software.

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