The effectiveness of 13-valent pneumococcal vaccine against community acquired pneumonia in young children: a systematic review and meta-analysis

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ABSTRACT

Objective. The present meta-analysis study aimed to evaluate the effectiveness of 13-valent pneumococcal conjugate vaccine (PCV) in reducing the morbidity from pneumonia among children under 5 years old.

Material and methods. Cochrane and Medline electronic databases were systematically searched for studies reporting effectiveness of 13-valent pneumococcal conjugate vaccine against pneumonia among children of the foreseen age group. To assess the effect measure, we used the odds ratio (OR) with 95% confidence intervals (95% CI) for dichotomous outcomes. The heterogeneity of the studies was assessed using I2 and Chi2 statistics.

Outcomes. The meta-analysis found a non-significant association between vaccinated children and the development of community-acquired pneumonia (OR=0.50; CI 95%: 0.44-0.57; Chi2=6.07; I2=18%). Vaccine effectiveness (VE) of 13-valent PCV was calculated as (1 – Mantel-Haenszel OR in vaccinated children compared to unvaccinated children) x100%. Thus, the VE of PCV 13 valent was estimated to be about 50%, according to the meta-analysis of the included studies.

Conclusions. Our study showed that the group of vaccinated children experienced 50% fewer cases of pneumonia than they would have had if they had not been vaccinated. These data bring additional evidence that vaccination is an effective strategy to prevent community acquired pneumonia in young children.

Keywords: vaccines, effectiveness, pneumonia, children

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is the most frequent bacterial agent of the community-acquired pneumonia (CAP) and one of the most common vaccine-preventable cause of death worldwide [1]. In the era before antibiotics, *S. pneumoniae* was estimated to be the cause of 95% of all cases of pneumonia [2]. Vaccination against pneumococcal infections, by inducing protection against the pathogen by mimicking its natural interaction with our immune system, is an effective preventive measure that may decrease the burden of pneumonia, especially in the pediatric population. The assessment of a vaccine performance, especially by the evaluation of the impact of vaccination, is possible by estimating vaccine effectiveness. The measurement of a vaccine's epidemiological effect from observational studies is referred to as effectiveness [3]. Vaccine effectiveness is often confused with vaccine efficacy but should be considered as a distinctly different, although related, concept [4]. Efficacy measured in clinical trials under ideal conditions may differ to effectiveness in the field under non-ideal conditions and in different populations [5]. Essentially, once a

vaccine is licensed and added to a recommended schedule, post-licensure studies are required to measure its effectiveness and impact on the population at large [6]. Vaccine effectiveness is a "real world" in a view of how a vaccine (which may have already proven to have high vaccine efficacy) reduces disease in a population. This measure assesses not just the vaccine itself, but also the immunization strategy, because it is also affected by other factors such as transportation and storage at appropriate temperatures, proper administration and timing of doses [7]. Generally, observational studies like cohort studies, case-control studies and screening programs are used to assess vaccine effectiveness. The most commonly used study design to assess a vaccine's effectiveness is the retrospective case-control analysis and the obtained odds ratio (OR) is used in the formula to deduct vaccine effectiveness, as follows: vaccine effectiveness = (1 - OR)×100 [7].

MATERIAL AND METHODS

This meta-analysis was conducted in the period from June to October 2022. Cochrane and Medline electronic databases were systematically searched for studies reporting effectiveness of 13-valent pneumococcal conjugate vaccine against pneumonia among children less than 5 years of age. We included case – control studies published between 2018 and 2022.

The search included MeSH (Medical Subject Headings) terms and keywords, combinations thereof. Search strategies using different Boolean operators were used. Search terms were used independently and/or in combination using "OR" or "AND" or "NOT". Basic search terms and phrases were "under five", "children", "child", "infant", and "pneumonia", "lower respiratory infection", "vaccination", "effectiveness", "impact".

The inclusion criteria were: articles written in English published in full in the period 2018-2022, age of the participants up to 5 years, observational case-control studies that asses vaccine effectiveness of 13-valent PCV, the comparison groups: cases (patients with CAP) and the control groups – children without the diagnosis of CAP. The outcomes of interest were hospitalizations due to pneumonia. Secondary outcomes such as serotype-specific disease, adverse events, immunogenicity (antibody levels) and *S. pneumoniae* nasopharyngeal carriage were considered complementary information.

Exclusion criteria included cohort studies, before-and-after studies, time series studies, inadequate age of participants, studies estimating effectiveness against other outcome than pneumonia, and incompletely presented studies (abstracts). According to the PRISMA guide, we followed recommended steps for a systematic review: identification, screening, eligibility and inclusion (Figure 1).

A 2-step selection process was performed. Titles and abstracts were first reviewed for duplication and inclusion criteria. Duplicates were excluded using EndNote. Reviewed articles were classified as potentially eligible, unclear or excluded. Citations on which eligibility reviewers disagreed were discussed or assessed by a third reviewer.

The Cochrane RevMan 5.4.1 software was used for statistical data processing. To assess the effect measure, we used the odds ratio (OR) with 95% confidence intervals (95% CI) for dichotomous outcomes. The heterogeneity of the studies was assessed using I^2 and Chi^2 statistics.

RESULTS

Our search identified 549 records of which 31 were screened by full text. Six observational case-control studies were included, reporting data on 11,661 children under 5 years of age (Table 1). The sixth study reveals unpublished data (Revenco, 2022): this is a case-control study in two main pediatric hospitals in Chisinau, Republic of Moldova – the Institute for Maternal and Child Healthcare and the Municipal Children's Clinical Hospital no.1. Data collection launched in December 2020 and is currently underway.

The meta-analysis found a reduction in risk of having community-acquired pneumonia in non-significant association between vaccinated children and the development of community-acquired pneumonia (OR=0.50; CI 95%: 0.44-0.57; Chi^2= 6.07; $I2$=18%). Vaccine effectiveness (VE) of 13-valent PCV was calculated as (1 - Mantel-Haenszel OR in vaccinated children compared to unvaccinated children) x100%. Thus, the VE of PCV 13 valent was estimated to be about 50%, according to the meta-analysis of the included studies. This value represents the ability of the vaccine to prevent community-acquired pneumonia in children under real conditions (Figure 2).

The confidence intervals overlap one another, but the upper and lower limits of the CI do not consistently line up on a vertical axis, indicating differences in the estimation of the effectiveness of 13-valent PCV in preventing pneumonia in children, across studies – this observation suggests the presence of small heterogeneity. Simultaneously, the quantitative analysis of heterogeneity finds a moderate homogeneity of the studies expressed by Chi^2 = 6.07 and I^2 = 18%.

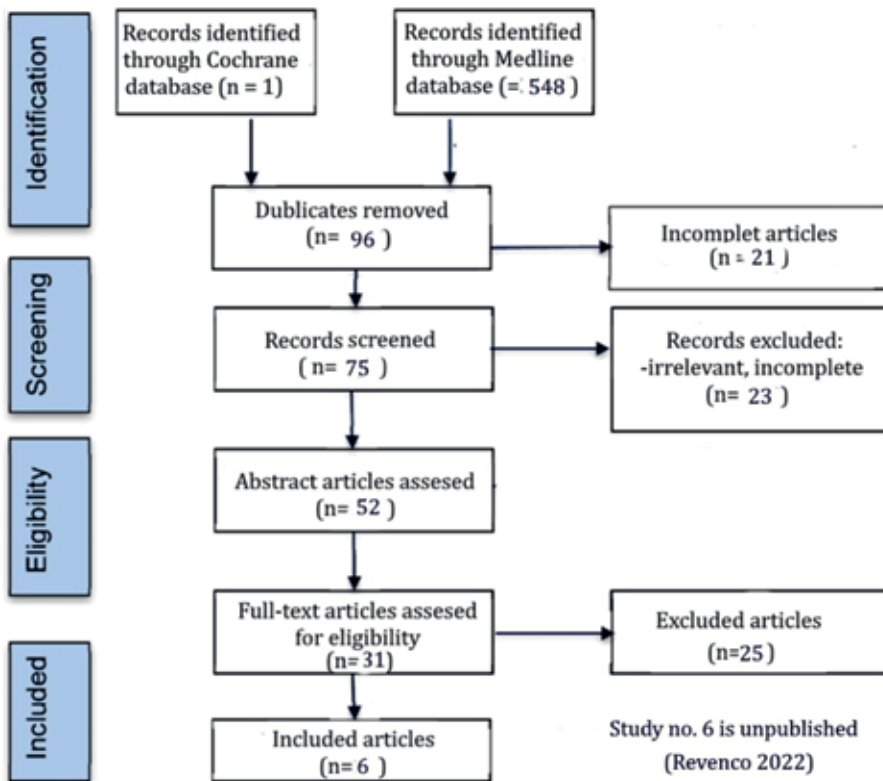Visual inspection of funnel plots did not reveal obvious asymmetry to suggest publication bias (Figure 3).

FIGURE 1. PRISMA flowchart for inclusion and exclusion of studies in the meta-analysis

TABLE 1. Characteristics of the included studies

| Author	Year of publication	Country	Type of study	Age (in months)	The number of the studied population
Bar-zeev [8]	2021	Malawi	Time-series and case-control	2.5-59	170
Lewnard [9]	2021	Israel	Case-control	<59	8775
Cohen [10]	2017	South Africa	Case-control	<59	1358
Tomczyk [11]	2018	Dominican Republic	Case-control	2-59	188
Dominguez [12]	2017	Spain	Case-control	7-59	814
Revenco	2022	Republic of Moldova	Case-control	2-59	356
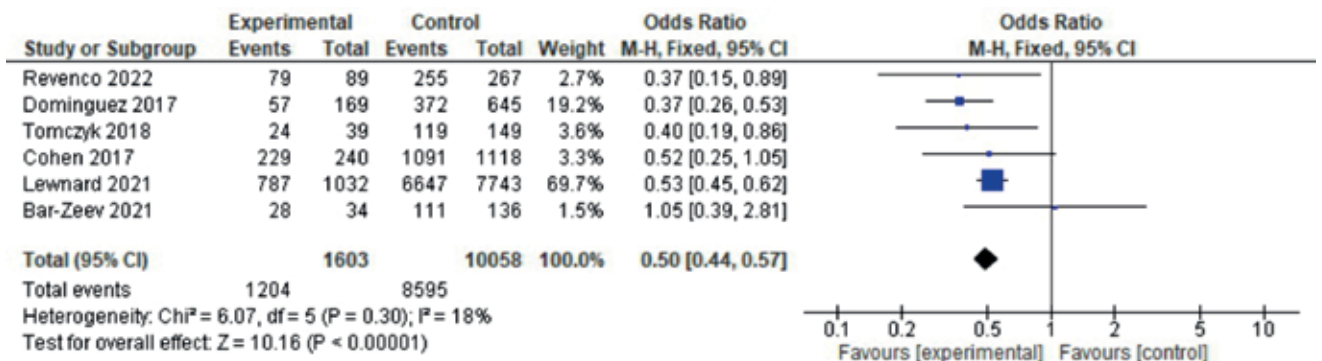
FIGURE 2. Vaccination with 13-valent PCV as a protective factor against community-acquired pneumonia in young children
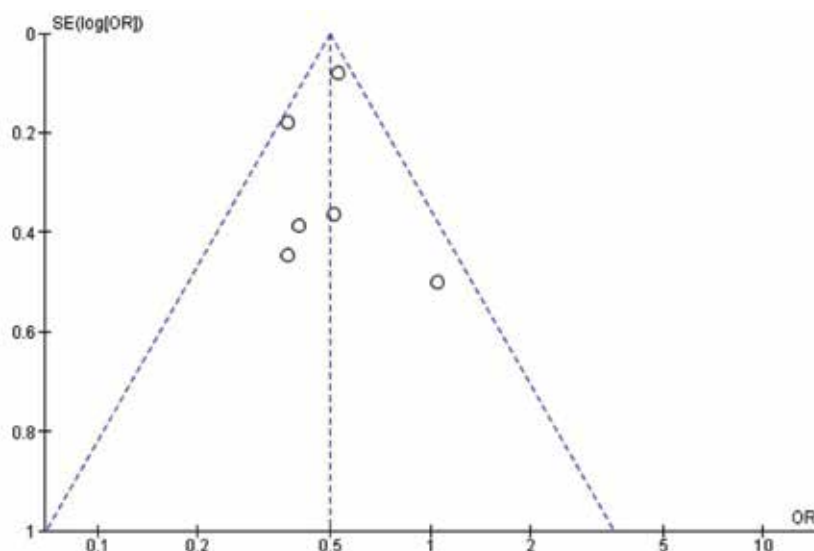
FIGURE 3. Funnel plot: symmetrical plot in the absence of bias

DISCUSSIONS

According to the latest reports, morbidity rates from childhood pneumonia experienced a steady decline, despite of the fact that a meaningful burden remains [13,14,15]. The management of childhood pneumonia involves substantial treatment and health care costs [16,17]. Nowadays there are a number of effective and relatively low-cost interventions to control severe diseases such as pneumonia [18,19]. Recent researches showed that vaccination with PCV 13 valent is a cost-effective strategy [20,21,22]. For instance, Chen et al. used ecological and economic models for a global analysis of 180 countries. The results of his study projected more than 1,18 million deaths and 457 million disease episodes annually before vaccination in children younger than 5 years (95% CI 0,780 – 1,76 million and 449 – 465 million, accordingly). Also, vaccination could prevent 34% of global deaths (0,399 million [95% CI 0,208 – 0,711 million]) and 12% of disease episodes (54,6 million [95% CI 51,8 – 58,6 million]) [22].

In consonance with the results of this meta-analysis, we sustain the assumption that vaccination with PCV 13 has a positive impact by reducing the frequency of hospitalizations due to community-acquired pneumonia in children younger than 5 years of age, as compared with those who are not vaccinated. To the best of our knowledge, this study is the first meta-analysis that captures only observational studies such as case-control studies. Previous systematic researches included also comparative data before and after vaccine laboratory surveillances, time series analysis and data from cohort studies [23, 24]. Furthermore, it is essential to mention that we selected as a study outcome pneumonia diagnosed clinically, which is relevant in terms of disease burden and for which there are available data sources for the impact assessment. This is the most commonly measured disease outcome in countries that studied the impact of the vaccination against pneumococcal diseases [25].

CONCLUSION

The group of vaccinated children experienced 50% fewer cases of pneumonia than they would have had if they had not been vaccinated. On the basis of our results, we can advocate that vaccination is an effective strategy to prevent community acquired pneumonia in young children. These findings call for renewed efforts on optimization of the vaccination rates in view of the fact that vaccine hesitancy is an alarming and widely spread phenomenon nowadays.

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