SHORT ARTICLE

23-valent pneumococcal polysaccharide vaccine (PPV23) for the prevention of invasive pneumococcal diseases (IPDs) in the elderly: is it really effective?

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Key words

Pneumococcal polysaccharide vaccine • Efficacy • Elderly

Summary

Introduction. *Incidence of invasive pneumococcal diseases (IPDs) in Italy is constantly increasing and that is particularly true among the elderly. 23-valent polysaccharide pneumococcal vaccine (PPV23) is recommended to this age group and offered in all Italian regions. However, efficacy of PPV23 on preventing IPDs is debated. We therefore performed a review of the most recent available meta-analyses in order to assess the efficacy of PPVs.*
Methods. *The literature search was conducted using PubMed and Scopus search engines. We used the following keywords: "pneumococcal", "polysaccharide", "vaccine", "efficacy", "elderly", "meta analysis". Only meta-analyses published in the last 7 years were selected. We examined the results of the selected meta-analyses and assessed their quality according to the PRISMA recommendations.*
Results. *The search returned 16 results in PubMed and 12 in Scopus: among them we selected 3 meta-analyses. According to our quality assessment, all meta-analyses showed generally positive results and almost all items of the PRISMA checklist were respected. However, the research protocol and the registration number were absent in all the 3 revisions and the flow-chart was not shown in Moberley's and Melegaro's works.*
In the study by Huss et al. the relative risk of developing IPDs among vaccinated subjects was 0.90 (95%CI: 0.46-1.77, I^2 4.9%), indicating a very slight benefit after vaccination. This contrasts with the results of the Cochrane Review by Moberley et al., in which the PPVs showed a protective efficacy in reducing the risk of IPDs of 74% (OR 0.26, 95%CI: 0.15-0.46) with no statistical heterogeneity (I^2 0%). Melegaro et al. found a reduction not statistically significant of the incidence of IPD of 65% (OR 0.35; 95%CI 0.08-1.49) among healthy elderly, while the global estimate of vaccine efficacy among high risk elderly was minimal (OR 0.80; 95%CI 0.22-2.88).
Conclusions. *Most of the studies suggest that the PPVs confer low protection against IPDs. Anyhow, their methodological heterogeneity does not allow definitive conclusions.*
While waiting to see the results of new trials about the efficacy of PPVs, in particular of PPV23, and the extension of the use of conjugate vaccine among the population over 65, stakeholders should be aware of the results of the meta-analyses discussed in this paper during the implementation of the vaccination programs for the elderly in Public Health.

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Introduction

Diseases caused by *Streptococcus pneumoniae* are responsible of high morbidity and mortality all over Europe [1]. In addition, the problem of multidrug resistance (MDR) has recently emerged, due to the great and often unnecessary usage of antibiotics for the treatment of acute otitis media (AOM) in children [2, 3]. For these reasons, the prevention of infections related to *S. pneumoniae* has become a priority in the Public Health field.
As for the rising and growing problem of MDR, the new vaccines which prevent diseases caused by the higher resistant and newly emerging serotypes seem to be an important tool for lowering the burden of disease due to *S. pneumoniae* [4-7].
Nowadays, there are two big classes of vaccines which protect from pneumococcal diseases [8]:

- the conjugate vaccines (PCVs), obtained by the conjugation of a carrier protein to the capsular polysaccharide;
- the polysaccharide vaccines (PPVs), containing the purified capsular polysaccharide.

The PCVs bring to the production of high antibody levels in children, elderly and immunocompromised individuals, and to a significant immune memory in response to the boosters [9]. Three different types of PCV are currently available: the 7-valent (PCV7), the 10-valent (PCV10) and the 13-valent (PCV13). All the PCVs are demonstrated to be effective against both invasive (i.e. Invasive Pneumococcal Diseases, IPDs, such as meningitis, sepsis and bacteriemic pneumonia) and non-invasive (e.g. AOM) pneumococcal diseases, but Italian Vaccination Plan suggests their usage only in children under the age of 5 [10]. As the Advisory Committee on Immunization Practices del Center for Disease Control and Prevention (CDC) does from 1997, Italian Ministry of Health recommends a booster of pneumococcal vaccination every 5 years with the 23-valent vaccine (PPV23) in elderly and adult high risk groups (e.g. immunocompromised individuals) with the particular pur-

pose of preventing IPDs [10]. These diseases are in fact the cause of the highest rates of pneumococcal mortality among the elderly, with a rising trend observed over the last 20 years and intended to follow for the next years.
The efficacy of PPV23 in preventing IPDs in the elderly has been analyzed in many primary and secondary studies, with opposed results. For this reason we performed a review of the most recent meta-analyses available on this topic.

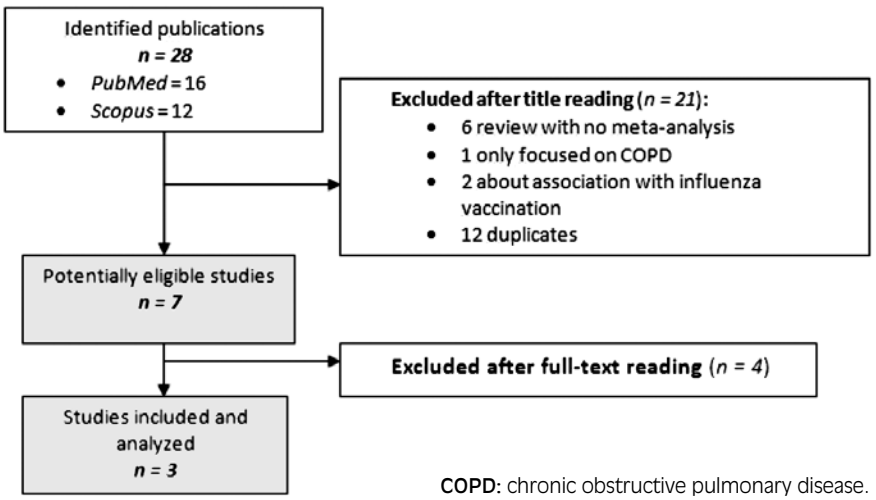
Methods

We conducted a literature search using PubMed and Scopus search engines using the following keywords: "pneumococcal", "polysaccharide", "vaccine", "efficacy", "elderly", "meta analysis". The search was updated until 30th September 2011 but only meta-analyses published in the last 7 years were selected.
The following step was the reading of selected studies and the analysis of results with respect to the IPDs. Finally, two assessors independently evaluated the quality of papers according to the PRISMA recommendations [11], with the consultation of a third researcher for solving disagreements.

Results

The search returned 16 results in PubMed and 12 in Scopus. Among them, the 3 following meta-analyses were selected: Huss et al. 2009, Moberley et al. 2008, Melegaro et al. 2004 (Fig. 1) [12-14].
According to our quality assessment, all meta-analyses showed positive results, and almost all items of the PRISMA checklist were respected. However, the research protocol and the registration number were absent in all the 3 revisions, and the flow-chart was not shown in Moberley's and Melegaro's works.
In all the 3 studies the efficacy of the different types of PPV was assessed, even if the most used and suggested for the adult in Italy, as well as in the rest of European and American countries, is PPV23.
In the study by Huss et al., 22 trials were included, 8 of which examined the efficacy of PPV23: three were focused on high risk subjects with chronic comorbidities (chronic obstructive pulmonary diseases, HIV), 3 on soldiers and 2 on adults and elderly. Among these trials, only the one by Alfageme et al. (2006) and the Swedish one from Örtqvist et al. (1998) were included in the Cochrane Review; the Swedish trial abovementioned, together with the study by Honkanen et al. (1999), were those about PPV23 analyzed in the Melegaro's review [13]. All the other trials included in the Cochrane and in the Melegaro et al. reviews were focused on polysaccharide antipneumococcal vaccines against less serogroups (i.e. PPV3, PPV12, PPV13, PPV14, and PPV17).
Fifteen Randomized Controlled Trials (RCT) were selected in the Cochrane Review, with a total number of 48,656 subjects recruited. Melegaro et al. analyzed 6 RCT and 3 quasi-randomized trials, 5 of which were conducted in European countries.
In the study by Huss et al. the relative risk of developing IPDs among vaccinated subjects was 0.90 (95%CI 0.46-1.77, I^2 4.9%), indicating a small benefit after vaccination. This contrasts with the results of the Cochrane Review by Moberley et al., in which the PPVs showed a protective efficacy in reducing the risk of IPDs of 74% (OR 0.26, 95%CI 0.15-0.46), with no statistical heterogeneity (I^2 0%). Six of the 8 trials included in the Melegaro et al. review assessed the efficacy of PPVs against IPDs only: two of them targeted the elderly and showed a reduction not statistically significant of the incidence of IPD of 65% (OR 0.35; 95%CI 0.08-1.49). In the other studies, focused on high risk elderly, the global estimate of vaccine efficacy against IPDs was minimal and not statistically significant (OR 0.80; 95%CI 0.22-2.88). The previous meta-analysis included in Melegaro et al. found a similar level of protection both among elderly, with a vaccine efficacy between 66% (52-76%) and 82% (66-91%), and among high risk elderly, with results of low efficacy not statistically significant.

Fig. 1. Flow-chart of selection process.



COPD: chronic obstructive pulmonary disease.

Discussion

The difference in efficacy estimates of PPVs has been widely debated, especially by Huss et al. and in the Cochrane Review, and not only in their two systematic reviews but also in following commentaries between these Authors.
The most important and evident difference regards the results about the efficacy of PPVs in preventing IPDs: this contrast is probably due to the exclusion by Huss et al. of 2 trials included in the Cochrane Review but considered by the first Authors inadequate in terms of quality of diagnostic procedures and randomization of patients, respectively [12].
In fact, the main problem in evaluating efficacy of PPVs in preventing IPDs, as well as pneumonia, stays actually in the comparison of results coming from available trials. As already stated by Huss et al., high heterogeneity can be found not only in the populations recruited in each trial (elderly, risk groups affected by different comorbidities, particular categories such as soldiers), but also in the blinding (open, controlled, double-blind), in the duration of follow-up (which sometimes is not even reported), and in the concealment of the allocation, often judged as unclear. Moreover, as already discussed by other Authors, there are no sufficient data useful to provide a systematic review and meta-analysis that could report robust results about the efficacy of PPV23, the vaccine most currently used in Western countries for the prevention of pneumococcal diseases in children older than 5 and in adults.

Conclusions

The heterogeneity of trials conducted until today on PPVs, which is reflected in different results, and the absence of a statistical significance in their findings do not allow definitive conclusions about the efficacy of PPVs in preventing pneumococcal diseases and their consequences.
Anyway, some studies suggest that PPVs confers very low protection against IPDs, in line with the conclusions of other observational studies about this topic [15, 16].
While waiting to see the results of the extension of the use of conjugate vaccine, especially the new 13-valent, among the population over 65, stakeholders should be aware of the results of meta-analyses discussed in this paper during the implementation of vaccination programmes for the elderly in Public Health.

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