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REVIEW

Pneumococcal vaccination in adults: rationale, state of the art and perspectives

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Key words

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Summary

Streptococcus pneumoniae (SP) is a leading cause of morbidity and mortality worldwide. Despite the availability, since the early 1980s, of a 23-valent pneumococcal polysaccharide vaccine (PPV23), its recommendation and increased use in the last decades, and the indirect benefits against invasive pneumococcal diseases following the pediatric immunization strategies with the 7-valent pneumococcal conjugate vaccine (PCV7), pneumoccal diseases, particularly Community Acquired Pneumonia (CAP), still remain a substantial burden among older adults in Western countries. The recent availability on the market of a second generation of pneumococcal conjugate vaccines, with an enlarged spectrum of protection against some serotypes not included in the PCV7 (i.e., the 13-valent pneumococcal conjugate vaccine – PCV13), opens new interesting perspectives for improving the control of this significant health-care issue among the entire population.
The most interesting and up-dated epidemiological data regarding the impact of SP in adults and the elderly in Western countries, together with the available evidence concerning the efficacy and effectiveness of the PPV23 in the same population, are reported and discussed below.

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Introduction

Streptococcus pneumoniae (SP) causes significant rates of morbidity and mortality around the world, since it is one of the main invasive disease aetiological agents (meningitis, bacteraemia/sepsis and bacteriemic pneumonia), as well as non-bacteriemic pneumonia, reaching the highest incidence rates and strongest clinical-health-care impact in both infants and older people [1, 2]. In relation to Community-Acquired Pneumonia (CAP), it has been estimated that on average this pathogen accounts for 30% of the cases, a percentage some studies have reported to be as high as 50%, which undoubtedly outline the SP clinical picture with the highest relative frequency and incidence in this population [2].
Despite universal immunisation programmes for children using the 7-valent pneumococcal conjugate vaccine (PCV7), available in the USA since 2000, and since 2001 in Europe, has determined a drastic reduction of invasive diseases and, even if to a lesser extent, also CAPs and Acute Otitis Media in the target population of the intervention [3, 4], the impact of the pneumococcal disease in the adult-older population still remains significant in the Western countries. All this notwithstanding:

(i) the availability, for several years, of a 23-valent anti-pneumococcal polysaccharide vaccine (PPV), currently recommended in many countries, including Italy, for the vaccination of over 65-year-old adults and patients >2 years of age affected by specific morbid conditions and immunosuppressed;
(ii) the indirect effect, known as *herd protection,* of the universal programmes of paediatric immunisation that has contributed, at least in part, to the reduction of invasive diseases even in non-immunised adults and older people, due to the direct effect of immunisation clearance of the oropharyngeal *carriage* of the paediatric infection *reservoir*, with a consequential reduced transmission of the microbial agent in the community [5, 6];
(iii) the well-known difficulty of conducting an aetiological assessment of the invasive disease cases and, even more, of non-bacteriemic pneumonia, which have certainly led to a significant underestimation of the global clinical impact of SP in the population [7].

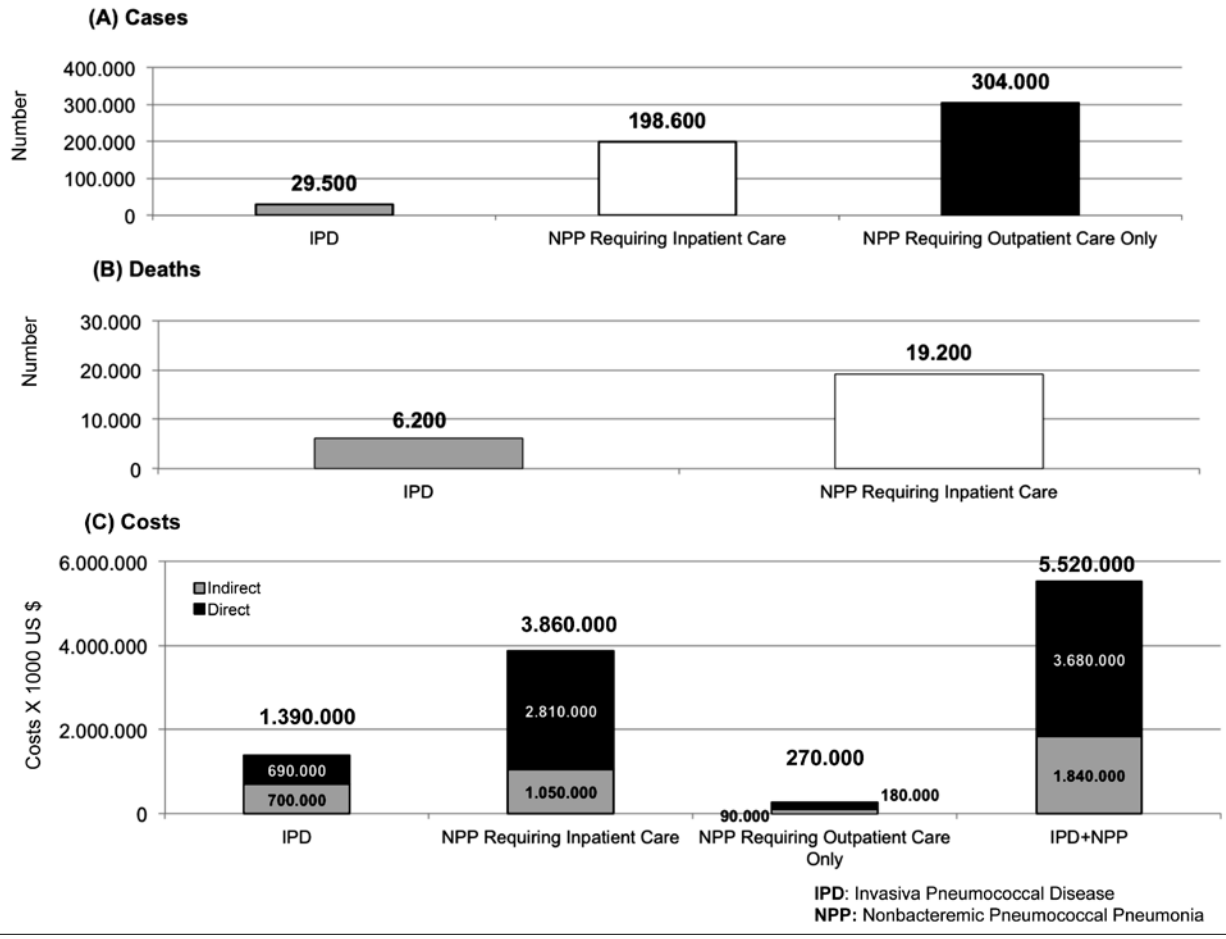
Although the universal immunization programs of new-borns have allowed, in the last decade, to obtain increasingly detailed scientific evidence on the epidemiology and burden of SP diseases in children, it would be appropriate to better focus on these aspects, in the adult-older age groups. In fact, in view of the clinical development of a second generation of pneumococcal conjugate vaccines (PCV13), with the possibility to be used on individuals aged >50 years, defining the epidemiology and the healthcare and economic impact of SP on this population group is particularly important for public health decision makers, in order to redefine in the short-to-medium term the appropriate vaccine prevention strategies.
Below, we shall briefly describe and discuss (i) some of the most interesting epidemiological data available in Western

countries regarding the health impact of SP in adults and the elderly, with a particular focus on CAPs, and (ii) the whole evidence about the efficacy/effectiveness profiles of PPV, which has been the only prevention tool available against SP for this age group during the last three decades.

Clinical and healthcare impact of pneumococcal disease in adults

If the estimation of the clinical impact of invasive diseases attributable to SP is well-known for its difficulty, it is even more difficult when the outcome to measure are the CAPs, due to (i) the heterogeneity of these clinical pictures, (ii) the poor tendency of physicians to obtain a diagnosis confirmed by laboratory tests, (iii) the sub-optimal sensitivity of blood culture, further accentuated by an early antibiotic therapy during the initial stages of illness, and finally, (iv) the difficulty of having data on incidence cases, particularly in the community setting (outpatients and domiciliary visits). This is indirectly confirmed by the great variability of incidence and mortality data reported in the literature regarding the adult population in relation to these pathological forms in the last 20 years.
Therefore, some interesting results recently published in the literature deserve to be mentioned, which have allowed to better define this important issue in the American, European and Italian context.
Weycker et al. developed a model capable of obtaining a detailed evaluation of the annual clinical and economic impact of SP diseases in the USA in adults aged ≥50 years, by analysing the incidence and mortality rates, and associated costs, both overall and divided according to age brackets and specific clinical risk profiles (e.g. patients suffering from chronic disease, immunosuppression, etc.). Therefore, it has been estimated that out of 91.5 million American adults aged ≥ 50 years, each year there are 29,500 cases of pneumococcal invasive disease (27,700 cases of bacteraemia and 1,800 cases of meningitis), 502,600 cases of non-bacteriemic pneumococcal pneumonia (198,600 cases requiring hospital care and 304,000 cases treated outside the hospital setting) and 25,400 deaths associated with pneumococcal disease (6,200 due to invasive disease and 19,200 due to pneumonia) [2]. In terms of direct and indirect costs, this important clinical impact has been translated into an annual estimation of 3.7 and 1.8 billion dollars respectively, most of which (81% direct and 62% indirect) are attributable to non-bacteriemic pneumococcal pneumonia [2] (Fig. 1).
Although the older elderly (i.e. those aged ≥ 85 years) accounted for only 6% of the study population, this was the group with the highest clinical burden, equal to 19% of

Fig. 1. Impact of pneumococcal diseases on adults aged ≥50 years in USA: cases, deaths and costs (from Weycker et al., 2012 [2], mod.).



all the cases, 33% of all deaths, and 21% of total direct costs. On the contrary, the population group aged between 50-64 years, accounting for 59% of the older American population, had the highest number of cases of pneumococcal disease (28%), as well as the highest total financial costs (39%) and the highest percentage of indirect financial costs (69%). Finally, in relation to the evaluation of outcomes in high-risk individuals (i.e. about 16% of adult Americans aged >50 years) accounted for the highest number of cases of pneumococcal disease (61%), pneumococcal-related deaths (67%) and the highest costs associated with this pathogenic agent (60%).

In relation to what has just been said, it is evident that the current healthcare and financial burden of SP in adult age is essentially attributable to non-bacteriemic pneumonia, as also recently reported by other American authors [8, 9].

In this respect, the impact of CAPs in adult age has been studied through several epidemiological surveys also within the European context, where the total annual rate ranged between 1.6 and 12/1000, including both hospitalized and non-hospitalized cases.

An interesting study conducted in Germany on a large national database including the entire adult population, based on the analysis of the hospital discharge chart including diagnoses for CAP (n = 388,406), related to 2005 and 2006, showed a high annual incidence of these morbid forms, equal to 2.75 and 2.96/1000 inhabitants respectively, with mean values equal to 7.65/1000 in patients aged > 60 years [13].

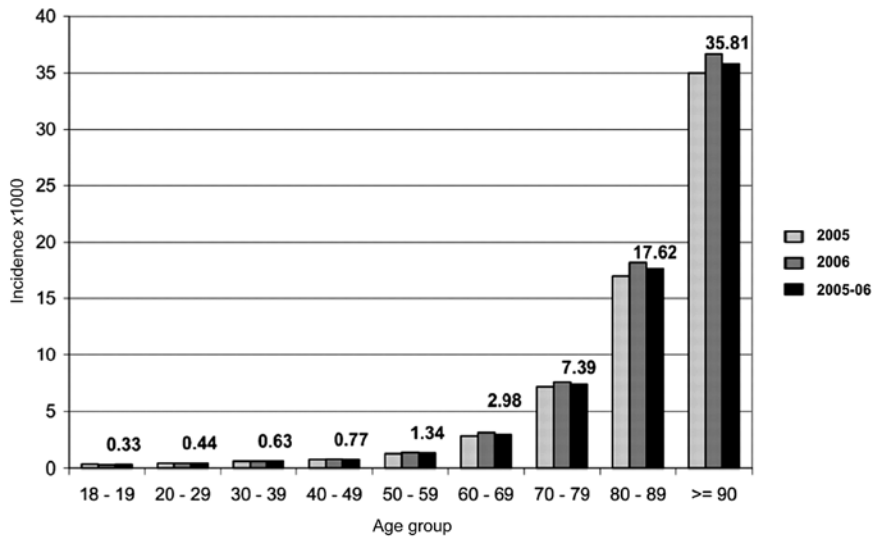
These data are exactly in line with those of a previous American study, which observed an annual CAP incidence in adult age equal to 2.67/1000 inhabitants [14]. In agreement with other previous investigations, CAP incidence was strongly age-dependent, with the highest values reported in the over-80 elderly population (Fig. 2). These data have a great relevance for public health, in terms of healthcare impact, especially in view of the ageing of the population expected to occur in the near future in various European countries and in the USA [15]. Further important information about this study involved mortality rates associated with CAPs, with a value of about 14%, this was found to be at a higher level than previously published (≤ 10%), since it could not be neglected even in low-risk subjects for their health conditions, already starting from the 50-59-year age group (Fig. 3). If, as we have already said, SP is considered the major CAP bacterial agent requiring hospitalisation of adults [16], these data clearly underline the need, from the view of public health, to improve prevention and control in the near future.

The significant impact of CAPs, and specifically of those caused by SP, was shown, in terms of hospitalisations and deaths, also by another study published in 2011 and conducted in Spain, where the hospital discharge charts (ICD9 CM codes 480-486) of hospitalised patients aged ≥ 50 years were retrospectively evaluated on a national basis for a period of 5 consecutive years (2003-2007) [17]. Of the 447,670 all cause pneumonias identified, the SP ones were 17%, with annual hospitalisation rates respectively equal to 6.27 and 1.09/1000, and deaths correlated to this were 75,932 and 9,062. Also this study showed that the highest clinical impact of SP was age-dependent, where the elderly were those mostly affected, with an incidence of 23.30 cases/1000 and 4.21 cases/1000 of all cause pneumonias and of SPs, in the population group aged ≥ 85 years. Similarly, the mortality and lethality rates increased with age, reaching peak values in those aged ≥ 85 years equal to 5.51 deaths/1000 and 23.6% for all cause CAPs and equal to 0.73 deaths/1000 and 17.4% for those due to SP.

Unfortunately, in Italy there is no nationwide surveillance system capable of producing an accurate estimation of the clinical and healthcare impact of invasive and non-invasive diseases caused by SP and in relation to this, very few studies are available in literature that focus on the burden caused by pneumonias in the adult-elderly population.

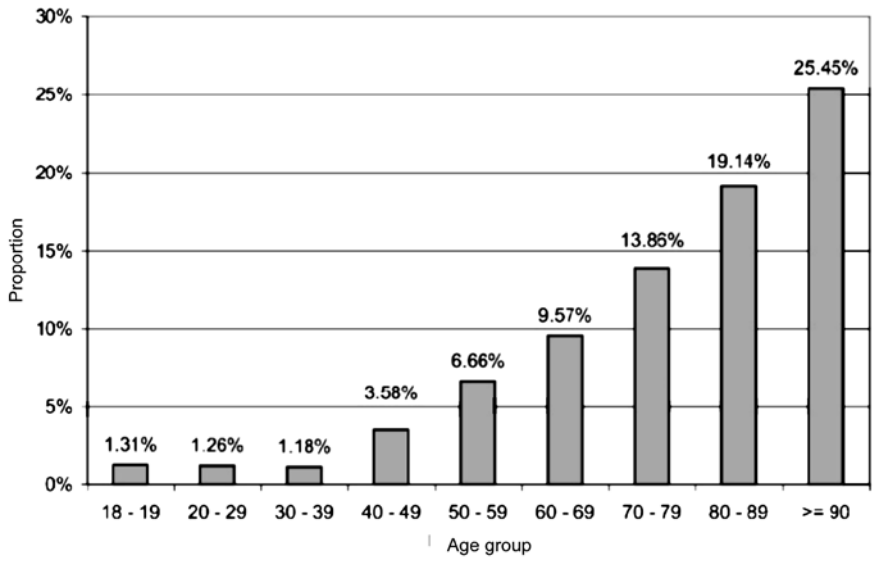
A particularly interesting study was the one conducted by Giorgi Rossi et al. between 1997-1999, by reviewing the hospital discharge charts, according to the ICD9-CM criteria, where the annual incidence of admissions for CAPs was 1.58/1000 in the adult population (lethality = 11.2%), rising up to 4.8/1000 in individuals aged ≥ 65 years (lethality = 13.8%), with an average age upon admission of 65 years (median = 70 years) [18]. Although in this study it was not possible to make an accurate es-

Fig. 2. Incidence of hospitalised Community Acquired Pneumonias (CAPs) in adults (per 1000), according to age groups, in a study based on the analysis of hospital discharge charts of a large European database (n= 388,406 cases monitored) (from Ewig et al., 2009 [13], mod.).



timation of the proportion of the invasive and non-invasive cases caused by SP, these results on the hospital admission rates per CAP were higher than those previously published regarding our national context [19], and perfectly matched those obtained by another study conducted in Spain, as previously discussed [10]. This evidence confirms that, in our country, CAPs are a morbid condition frequently found in the population, burdened by a significant healthcare impact, not only in terms of access to healthcare services, but also of lethality, especially in the elderly, thus stating the need to urgently address this issue as a public health priority.

Fig. 3. Distribution of in-patient mortality among adults admitted for Community Acquired Pneumonia (CAP), according to age groups, in a study based on the analysis of hospital discharge charts of a large European database (n = 388,406 cases monitored) (from Ewig et al., 2009 [13], mod.).



Capsular polysaccharide pneumococcal vaccine (PPV): state of the art

Since the early 1980s, a 23-valent PPV for the prevention of pneumococcal diseases has been available on the market. Current recommendations in Italy provide for its use in adults aged ≥ 65 years and in subjects, starting from the age of 2 years, affected by specific risk conditions (i.e. chronic diseases of the cardiovascular, respiratory and renal apparatus, anatomic and functional asplenia, conditions of immunosuppression, etc.) [20, 21]. The globally widespread use of PPV has been justified by the promising data obtained in terms of effectiveness against bacteremic pneumonias in clinical trials that had studied 13- and 14-valent polysaccharide vaccines, containing 50μg of each capsular antigen. In 1977, the results of these studies led to the commercialization in the USA of a 14-valent polysaccharide vaccine, substituted in 1983 by the current PPV containing 25μg of each capsule antigen, but without conducting new trials to evaluate its immunogenicity and effectiveness profile.
In this context, PPV has been widely used in vaccine practice, principally in the USA, where about 60% of the elderly and 30% of adults "at risk" between the age of 50 and 65 years received one dose in 2007. Although significantly higher than the results of vaccine coverage achieved in our country, these rates remain however sub-optimal, especially in consideration of the fact that the recommendation to use PPV dates back to the early 1980s. One of the reasons of the failure of PPV vaccination strategies in adults is surely linked to the doubts around the protective efficacy and effectiveness of PPV that emerged from the analysis of the results obtained from clinical trials conducted in the last few years, both for the invasive forms in chronic patients, and, principally, for non-bacteriemic pneumonias and deaths.

At least in part, these gaps have been ascribed to the proven sub-optimal ability of all non-conjugate polysaccharide vaccines of inducing an adequate immunological response and, above all, in maintaining it over time. In fact, it is renown that capsular polysaccharides contained in PPV are able to elicit, through a T-independent type mechanism, the simple differentiation of plasma cell populations with a short half-life, in charge of producing direct antibodies against capsular antigens of SP, principally of class IgG2 [22]. However, PPV is unable to trigger the creation of an immunological memory, because this is a T-dependent process. This has important implications in terms of duration of protection in that follow primary immunization and of the actual utility of vaccine boosters, although, for PPV, it has been shown how subsequent doses of vaccine are unable to achieve a better immune response, if not even worse, than the one obtained with priming [22]. In relation to this, the recommendations in force in Italy, in agreement with what was stated in a recent position paper of the WHO, provide for a single re-vaccination with PPV at a distance of 5 years from the administration of the first dose, whereas, a more recent recommendation in the USA by the *Advisory Committee on Immunization Practices* (ACIP) provides for re-vaccination only in high-risk subjects between the age of 19-64 years (e.g. affected by anatomic or functional asplenia and immunosuppressed) [23, 24].
As mentioned before, the interpretation of the results linked to the efficacy and effectiveness profile of PPV, in the light of the many studies conducted in the last 30 years, is still controversial today, even in consideration of some differences in terms of categories of enrolled subjects and clinical outcomes used by various research studies. This has been further complicated by some important methodological limitations of randomized controlled trials that evaluate effectiveness (e.g. randomi-

zation methods, study blindness), highlighted in recent meta-analyses, as well as selection bias and confounding factors that are integral to observational studies adopted to evaluate effectiveness. Moreover, it is renown that many factors contribute to make it difficult to evaluate the effectiveness of the vaccine concerned, in particular (i) the low frequency of the mostly specific outcome (the invasive pathology), (ii) the poor accuracy and non-uniqueness of the diagnostic criteria adopted for the CAP outcomes and finally (iii) the variability of the vaccine's effectiveness in relation to the age factor and to the severity of the pathological conditions associated with a higher risk of developing pneumococcal disease in the subjects being monitored.

Tables I and II illustrate the characteristics and the results of the efficacy of the main randomized controlled trials and non-randomized clinical studies conducted with PPV in adults.

With regard to this, two interesting meta-analyses conducted by the Cochrane Collaboration group have recently analysed the results reported in literature and considered them methodologically well designed [25, 26].

The first meta-analysis evaluated the results of 15 randomized controlled trials (n = 48,656 participants) and of 7 non-randomized controlled trials (n = 62,294 participants) on adults. In the randomized controlled trials, a strong evidence of PPV efficacy had been proven against invasive diseases (74%, 95% CI: 56-85; I-squared = 0%), whereas data analysed in relation to all cause pneumonias were found to be inconclusive, with a substantial heterogeneity from a statistical point of view (29%, 95% CI: 3-48; I-squared = 87.3%) [25]. In addition, the use of PPV did not determine any significant reduction of all cause mortality in the population included in the studies [25]. Those who benefited most of the positive effects of the vaccine were mainly the younger adults in good health conditions, yet [23]. Insufficient results were mainly found in the high risk populations, like adults affected by specific morbid conditions and immunosuppressed individuals of all ages, with PPV protective efficacy values equal to -56% (95% CI: -6.94 – 65) against invasive diseases and equal to 3% (95% CI: -1.46 – 35) versus pneumonias. With regard to the non-randomized trials, PPV efficacy in the prevention of invasive diseases ranged between 26-70% in immunocompetent adults and in subjects with underlying pathological conditions, but not immunocompromised, with a global value of 52% (95% CI: 39-63; I-squared = 31.4%) [25].

The second meta-analysis evaluated the efficacy of PPV in patients suffering from Chronic Obstructive Pulmonary Disease (COPD): only 7 randomized controlled trials published in the literature met the inclusion criteria for this review, that considered the prevention of pneumonia (n = 1372 patients examined) and COPD acute re-exacerbation (n = 216 patients examined) as the primary outcomes of analysis. Results did not allow

Tab. I. Characteristics and results of the main randomized controlled trials evaluating the efficacy of polysaccharide anti-pneumococcal vaccines in adults.

Authors	Year	Sample dimension	Characteristic of participants	Follow up (months)	Number of serotypes contained in the vaccine	Effectiveness (%)	
Austrian et al.	1976	4.500	Miners	24	6/13	55	45
Smit et al.	1977	4.694	Miners	24	6/12	na	38
Riley et al.	1977	11.958	Adults from Tari in Papua New Guinea Highlands	16	14	75*	15*
Austrian et al.	1980	1300	Patients of Mental Hospital	36	12	na	-5*
Austrian et al.	1980	13.600	Adults aged ≥ 45 years	30	12	na	11*
Gaillat et al.	1985	1.686	Adults aged ≥ 55 years	24	14	na	63
Klastersky et al.	1986	50	Patients with bronchogenic carcinoma	12	17	10*	na
Simberkoff et al.	1986	2.295	High risk patients aged ≥ 55 years	35	14	0	-28*
Davis et al.	1987	103	Adults with chronic obstructive pulmonary disease	24	14	na	13*
Koivula et al.	1997	2.837	Adults aged ≥ 60 years	36	14	na	-17*
Ortqvist et al.	1998	691	Non-immunocompromised adults aged 50 to 85 years who had been inpatients for community acquired pneumonia	32	23	65*	-17*
Alfageme et al.	2006	596	Adults with chronic obstructive pulmonary disease	36	23	na	24

na: data not available; IPD: Invasive Pneumococcal Disease; NPP: Nonbacteremic Pneumococcal Pneumonia; * no statistical significance

Tab. II. Characteristics and results of the main non-randomized trials evaluating the efficacy of polysaccharide anti-pneumococcal vaccines in adults.

Authors	Year	Sample dimension	Characteristic of participants	Study Method	Number of serotypes contained in the vaccine	IPD	NPP
Shapiro et al.	1984	90/90	Adults aged ≥ 18 years with indication for vaccination or aged ≥ 65 years	Case-control	14	67	na
Sims et al.	1988	122/244	Immunocompetent older adults aged ≥ 55 years	Case-control	Not specified	70 (37- 86)	na
Shapiro et al.	1991	1.054/1.054	Adults aged ≥ 18 years with indication for vaccination or aged ≥ 65 years	Case-control	14 o 23	47 (30-59)	na
Benin et al.	2003	108/330	Adults aged ≥ 18 years with indication for vaccination or aged ≥ 65 years	Case-control	23	26 (–29-58)	na
Jackson et al.	2003	47.365	Adults aged ≥ 65 years (follow-up 3 years)	Cohort	23	44 (7-67)	- 4 (-13- 4)
Dominguez et al.	2005	149/447	Adults hospitalised with invasive pneumococcal disease aged ≥65 years	Case-control	23	70 (48-82)	na
Vila-Corcoles et al.	2006	11.241	Adults aged ≥ 65 years (follow-up 3 years)	Cohort	23	40 (-65-88)	21 (2-36)

na: data not available; IPD: Invasive Pneumococcal Disease; NPP: Nonbacteremic Pneumococcal Pneumonia

to determine any benefit from PPV, because it was not possible to detect statistically significant differences between the intervention and control groups. In fact, the protective effectiveness of the vaccine was estimated to be equal to 28% (95% CI -1 – 49) and to 42% (95% CI -13 -70) against pneumonias and COPD acute re-exacerbations [26].

Conclusions and perspectives with the second generation of pneumococcal conjugate vaccines

In the light of what has been said, it is evident (i) on one hand, the still significant *burden* of SP disease in adults-elderly in Western countries, and (ii) on the other, some limits of PPV in terms of protection against invasive diseases, among adults affected with chronic diseases, non-bacteriemic pneumonias, the clinical picture with a higher incidence and healthcare impact on the population, and all-cause mortality.

The recent availability on the market, as well as PPV, of a second generation of pneumococcal conjugate vaccines for adults aged > 50 years [27], having an adequate safety and immunogenicity profile and, hopefully, determining a long-lasting protection against both invasive and non-invasive pneumococcal diseases, opens up new interesting perspectives to control this important health issue in the Western countries, especially in the elderly and high risk subjects of all ages. In the next future, further studies on pneumococcal vaccination efficacy and effectiveness are warranted in these target groups.

Furthermore, the availability of national data on the ecological scenario of SP and its clinical impact among adult and elderly population, in terms of admissions, mortality and lethality, as well as to estimate the subsequent burden for the society, in terms of costs and consumption of healthcare resources available, will offer better guidance to public health decision-makers when developing future vaccination strategies.

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