Pneumococcal vaccine in the elderly: a useful but forgotten vaccine

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ABSTRACT. Pneumococcal disease in the elderly is a major concern emphasizing the need for prevention. The review focuses on a literature-based analysis of the efficacy ("does the vaccine works?") and/or the effectiveness ("does vaccination help older population?") of pneumococcal vaccines 14- or 23-valent (PPV23) in the elderly.

In the setting of Streptococcus pneumoniae *pneumonia, there is still no conclusive evidence decisively confirming the efficacy of pneumococcal vaccine against pneumococcal pneumonia in the elderly populations. However, the efficacy of pneumococcal vaccination has been demonstrated in the prevention of invasive pneumococcal disease (IPD) such as bacteremia, which is the main complication of pneumonia.*

In the setting of IPD in the elderly, analysis of the current literature provides evidence for both the efficacy and effectiveness of PPV23, but most of the clinical studies failed to demonstrate a substantial reduction in all-cause mortality rate.

The community-acquired pneumonia guidelines in the industrialized countries include recommendations for pneumococcal vaccine by PPV23 for adults aged 65 years and over. Taking into account the preventive effect of PPV23 on IPD and the threat of a pandemic flu, the increase of PPV23 vaccination coverage in elderly patients should be strongly considered.

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INTRODUCTION

Pneumococcal disease is a major health threat. *Streptococcus pneumoniae* is responsible for non-invasive diseases such as acute otitis media and pneumonia, and invasive diseases like bacteremia and meningitis.

Invasive pneumococcal diseases (IPD) are serious and have a high risk of mortality; at-risk groups include elderly persons, persons with chronic diseases, asplenic patients and immunocompromised hosts.

The elderly represent an increased risk situation for severe pneumococcal diseases; such persons often have age-related impairment of the immune system and other defence mechanisms, decreased physical activity, chronic diseases, and poor nutrition and, in addition, are often in nursing homes and/or hospitals for elderly persons (1).

Pneumococcal pneumonia has an age-specific reporting rate, which is higher in young children and in the elderly. Case fatality rates are 20-40% among at-risk and alcoholic patients (and may exceed 50% in high-risk individuals) (2). It is an important cause of death in elderly persons. *S. pneumoniae* is responsible for a wide variety of disease manifestations. In the United States alone, it is estimated that pneumococci annually account for 3000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and 7 million cases of otitis media (3).

PPV23 vaccination coverage in the elderly is poorly documented. Vaccination rates may differ. Indeed, high coverage rates have been reported, such as 71% in USA (4, 5), 59% in USA (6) and 50% in Sweden (7), but low rates are reported in Israel (20.1-27.9%) (8), Belgium (29%) (9) and France (21.9%) (10). Thus, pneumococcal vaccination coverage may be improved where low.

DEVELOPMENT OF PNEUMOCOCCAL VACCINES

S. pneumoniae has 90 different serotypes (11, 12), each with a capsule of different chemical composition, and each stimulates the production of a specific immunity that may last for years. Only a minority of serotypes cause most cases of human disease, and 8 to 10 cause two-

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thirds of serious pneumococcal infections in adults (13).

14-valent vaccine was licensed in 1977 in the USA, followed by the 23-valent vaccine in 1983 (PPV23) (14).

PPV23 vaccines contains purified capsular polysaccharides derived from 23 *S. pneumoniae* serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F) (15). Thus, this vaccine covers 85-90% of serotypes responsible for all cases of invasive pneumococcal disease and includes major serotypes that have developed antimicrobial resistance (16, 17). Moreover, cross-protection within some serotypes exists, which protects for serotypes which are not in the vaccine (for example, antibody response to serotype 6B protects against serotype 6A).

PPV23 vaccine stimulates 23 type-specific anti-capsular antibodies (16) which aid the destruction of *S. pneumoniae* by white blood cells, but do not induce immunologic memory. The immune response in most elderly patients ≥65 years of age is as good as that in healthy younger adults, but is variable according to serotype (16, 18).

The response is decreased in immunosuppressed individuals (e.g., patients with leukemia, lymphoma, multiple myeloma, or AIDS (3). Antibody levels generally last 5 years or more (19).

At this time, conjugate pneumococcal vaccine elicits good antibody response and protection and is licensed for children, but not for adults or the elderly.

EFFICACY OF PPV23 IN ELDERLY

Results of clinical trials and meta-analyses are expressed as vaccine efficacy and/or vaccine effectiveness, which are two different concepts that are often confused. The question "Does the vaccine protect in ideal (experimental) conditions?" relates to efficacy. The question of whether an intervention works in routine clinical care relates to effectiveness ("does the vaccine protect in everyday life?").

Efficacy in pneumococcal pneumonia

The main clinical trials of pneumococcal vaccine in prevention of pneumococcal pneumonia are listed in Table 1.

Three of them were conducted with the 14-valent vaccine (Gaillat [20], Simberkoff [21] and Koivula [22]) and two with the 23-valent vaccine (Ortqvist [23], Honkanen [24]). Two of these studies suggest vaccine efficacy, but are not exempt from bias: the Gaillat (20) study was open, not double-blind. The Koivula (22) study was small and the predictive value of serologic diagnosis was unknown and, although all subjects received influenza vaccine, no analysis was performed in and out of the flu season; from multiple statistical comparisons, only one showed efficacy.

Three studies may be considered as inconclusive; for all of them the predictive value of serologic diagnosis is unknown. Simberkoff (21) studied an unusual serotype distribution, the study of Ortqvist (23) included an unrepresentative population and all three studies have an adequate sample size.

Recently, Fisman et al. (25) demonstrated (in an observational study) that prior vaccination against *S. pneumoniae* was associated with improved survival, reduction of respiratory failure or other complications, and length of stay in hospitalized patients with community-acquired pneumonia. Vaccine recipients were less likely to die of any cause during hospitalization than were individuals with no record of vaccination (adjusted odds ratio [OR] 0.50; 95% confidence interval [CI] 0.43-0.59), even after adjustment for the presence of comorbid illnesses, age, smoking, and influenza vaccination, and under varying assumptions about missing vaccination data. Vaccination also lowered the risk of respiratory failure (adjusted OR 0.67; 95% CI 0.59-0.76) and other complications, and reduced the median length of stay by 2 days, compared with non-vaccination ($p<0.001$).

The EVAN-65 study, published by Vila-Corcoles

Table 1 - *Prospective clinical trials of polysaccharide pneumococcal vaccine: prevention of pneumococcal pneumonia.*

Principal investigator	Vaccine	n	Characteristics	Protective efficacy	95% CI
Gaillat 1985 (20)	14-valent	1686	Geriatric hospitals and nursing homes	77%	51.2-89.3
Simberkoff[a] 1986 (21)	14-valent	2295	High-risk veterans ≥50 years	–32%	0.98-1.78
Koivula1997 (22)	14-valent	2837	Persons ≥60 years	15%	–43 - 50
	14-valent	886	Increased risk only	59%	6-82
Ortqvist 1998 (23)	23-valent	691	Persons ≥60 years discharged after hospitalization for pneumonia	–24%	–150 - –34
Honkanen 1999 (24)	23-valent	26,925	Persons ≥65 years	–20%	–90 - 20

[a] Patients ≥55 yr.

(26), is a prospective cohort study conducted in Tarragona, Spain. From January 2002 through April 2005, 11,241 subjects, all community-dwelling individuals aged ≥65 years who were assigned to 1 of 8 primary health care centers, were evaluated for PPV23 vaccination. The primary outcomes were IPD, pneumococcal pneumonia, overall pneumonia rate, and deaths due to pneumonia. All cases were validated by a check of clinical records. The authors demonstrated a significant reduction in the risk of hospitalization for pneumonia (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.59-0.92) and in the overall pneumonia rate (HR 0.79; 95% CI 0.64-0.98) related to vaccination. The protective effect against IPD was important, but did not reach statistical significance (HR 0.60; 95% CI 0.22-1.65) as the incidence of IPD was low (64 cases per 100,000 person-years). However, the vaccine showed a significant effectiveness of 45% in preventing pneumococcal pneumonia (HR 0.55; 95% CI 0.34-0.88) and a significant 59% reduction in the risk of death due to pneumonia among vaccinated subjects (HR 0.41; 95% CI 0.23-0.72).

Effectiveness in invasive pneumococcal disease (IPD)

An overview of effectiveness in IPD (case control studies and indirect cohort studies) is listed in Table 2 (19, 27-31). The evaluation criterion was IPD. When considering all serotypes, vaccine efficacy may vary from 47% (95% CI 30-59) to 81% (95% CI 34-94). When considering vaccine type plus or minus related vaccine type serotypes, vaccine efficacy varies from –21% (95% CI –221 - 55) to 79% (95% CI 49-92).

Shapiro's study (27) recruited patients over a 6-year period. Cases were subjects aged 18 years and over, hospitalized with confirmed IPD and eligible for pneumococcal vaccination. Controls were similar subjects to case patients, hospitalized for other causes and eligible for vaccination. Only written evidence was taken as proof of vaccination. Analyses were performed separately, both for immunocompetent healthy adults and immunocompromised patients, and vaccine effectiveness was assessed over time. The effectiveness of pneumococcal vaccination against IPD caused by vaccine serotypes in immunocompetent patients according to age and time since vaccination are listed in Table 3 (27). In brief, vaccine efficacy was fairly good in the age group 55-64 years, even more than 5 years after vaccination. Vaccine efficacy was good in 65-74-year-old patients, but protection declined with time since vaccination, as well as in all age groups.

A good protective efficacy of 75% (95% CI 57-85) was observed by Butler (19) in immunocompetent patients over 65 years old, but also in patients with diabetes mellitus (84%, 95% CI 50-95), coronary vascular disease (73%, 95% CI 23-90), chronic pulmonary disease 65%, 95% CI 26-83), anatomic asplenia (77%, 95% CI 14-95) and congestive heart failure (69%, 95% CI 17-88).

A recent observational study by Dominguez (32) assessed the effectiveness of PPV23 in preventing IPD in patients aged ≥65 years. In the adjusted analysis, the overall effectiveness of vaccination against infections due to all serotypes was 70% (95% CI 48-82). The effectiveness of vaccination was 76% (95% CI 51-88) in immunocompetent subjects with or without high-risk conditions, but it was 50% (95% CI –44 - 82) in immunocompromised subjects. For patients with infections due to vaccine or vaccine-related serotypes, the effectiveness of vaccination was 72% (95% CI 50-85) overall and 78% (95% CI 50-90) in immunocompetent patients, but it was only 46% (95% CI –54 - 81) in immunocompromised ones. The overall effectiveness of vaccination was 65% (95% CI 35-81) during the non-influenza period.

Spindler (33) analysed the impact of a three-year vaccination campaign with PPV23 in elderly persons by

Table 2 - *Pneumococcal vaccine: invasive disease overview of effectiveness.*

Source	Type of infection	Location (n. cases)	% Vaccine efficacy	95% CI
Shapiro 1991 (27)	All patients All serotypes	Connecticut (1054)	56%	42-67
Sims 1988 (28)	Clinical effectiveness patients >55 yr	Philadelphia (122)	70%	37-86
Farr 1995 (29)	High risk patients	Charlottesville (85)	81%	34-94
Davidson* 1994 (30)		Alaska (159)	64%	32-81
Shapiro 1991 (27)	Vaccine type ±	Connecticut (983)	56%	42-67
Forrester 1987 (31)	VT-related	Denver (89)	–21%	-221 - 55
Davidson* 1994 (30)		Alaska (87)	79%	49-92
Butler 1993 (19)	All patients Patients 65-74 yr Patients at least 75 yr	CDC	57% 70% 78%	45-66 30-87 54-89

Table 3 - *Effectiveness of pneumococcal vaccination against IPD caused by vaccine serotypes in immunocompetent patients according to age and time since vaccination.*

Age group (years)	n. case-control pairs	<3 years	3-5 years	>5 years
18-55	125	93 (82-97)	89 (74-96)	85 (62-94)
55-64	149	88 (70-95)	82 (57-93)	75 (38-90)
65-74	213	80 (51-92)	71 (30-88)	58 (–2 - 83)
75-84	188	67 (20-87)	53 (–15 - 81)	32 (–67 - 72)
>85	133	46 (–31 - 78)	22 (–90 - 68)	–13 (–174 - 54)

Aggregate effectiveness against vaccine-serotype invasive disease in immunocompetent persons (n=808) = 61%. n=1054 case patients and n=1054 matched controls. Adapted from (27).

comparing the incidence of IPD and serotype distribution in Stockholm county (36% coverage) *vs* Skane county (no vaccination campaign). The incidence of vaccine-type IPD in Stockholm declined significantly in elderly persons during the study period (1997-2001), from 50 to 28.9/100,000, but not in other age groups in Stockholm, nor in any age group in Skane.

Efficacy as shown by meta-analyses

The pneumococcal efficacy in three meta-analyses from Fine (34), Hutchinson (35) and Cornu (36) is described in Table 4. The fine study demonstrated good vaccine efficacy against IPD and pneumococcal pneumonia, toward all serotypes and vaccine serotypes. However, patients were under 55 years old, and no significant improvement could be demonstrated for pneumonia, or mortality. The Hutchinson study demonstrated a good efficacy against IPD, and a lower response for pneumococcal pneumonia, especially for all serotypes. The vaccine efficacy against pneumococcal pneumonia and mortality from pneumonia was 40% and 27% respectively in the Cornu study.

A recent meta-analysis by Melegaro (37) assessed the clinical efficacy of PPV23 in the elderly in IPD and pneumococcal pneumonia. The authors observed that PPV23 offers protection against IPD in the general elderly population (VE 65%; 95% CI –49 - 92) but it has a moderate effect in the high-risk elderly (VE 20%; 95% CI –188 - 78). The vaccine has little or no effect against pneumonia (VE 16% in the general elderly and –20% in the high-risk elderly group).

The recent meta-analysis by Moberley et al. (38) found strong evidence of PPV23 efficacy against IPD, but efficacy against all-cause pneumonia was inconclusive, and PPV23 was not associated with substantial reductions in all-cause mortality. Vaccine efficacy against primary outcomes appeared poorer in adults with chronic illnesses. Non-randomized clinical trials provided evidence for protection against IPD in populations for whom the vaccine is currently utilized.

The subgroup analysis for immunocompetent older adults included five studies. PPV reduced the risk of all IPD in immunocompetent older adults with a pooled estimated OR of 0.32 (95% CI 0.22-0.47; random-effects model). Statistical heterogeneity was absent (I2=0%, p=0.68).

Table 4 - *Pneumococcal vaccine: efficacy in meta-analysis (OR 95% CI).*

	Fine (34)	Hutchinson (35)	Cornu (36)
Invasive Pneumococcal Disease		0.27 (0.13-0.49)	
All serotypes			-
Vaccine serotypes		0.17 (0.09-0.31)	-
Pneumococcal Pneumonia			0.29 (0.20-0.421)[a]
All serotypes	0.34 (0.24-0.48)[a]	0.58 (0.47-0.72)	-
Vaccine serotypes	0.17 (0.09-0.33)[a]	0.25 (0.20-0.33)	-
Pneumonia Mortality			
All causes	ns	-	1.01 (0.91-1.12)
Pneumonia	ns	-	0.69 (0.51-0.93)
Pneumococcal Pneumonia	ns	-	-

[a] Definitive pneumococcal pneumonia.

PPV23 and Influenza

In the population aged ≥65 years in Sweden, Hedlund (39) assessed the effectiveness of combined vaccination against influenza and pneumococcal diseases: 100,242 persons were vaccinated with one or both vaccines during a one-year campaign. The incidence of hospital admissions during one year after the vaccination campaign, adjusted for sex and age, was significantly lower in the vaccinated than in the unvaccinated cohort for influenza (relative risk [RR] 0.68), pneumonia (RR 0.78) and IPD (RR 0.46). In the vaccinated cohort, the in-hospital mortality was lower for pneumonia (RR 0.55), COPD (RR 0.53) and cardiac failure (RR 0.72)

In summary, analysis of the current literature provides evidence for the efficacy and effectiveness of PPV23 against IPD in the elderly, but not against pneumococcal pneumonia or death.

Efficacy and effectiveness of PPV23; a critical approach

In a recent review paper, Fedson (40) analysed the efficacy and effectiveness of PPV23 in elderly and gave a new point of view of the results published over many years. The author discusses the results of several clinical trials of PPV23 among older adults which have failed to demonstrate protection against pneumococcal pneumonia (perceived as the most important manifestation of pneumococcal disease), and considers that the populations studied in these trials were too small to permit the expected efficacy of the vaccine to be demonstrated with statistical significance. Because these trials were underpowered, Fedson considered that they should not be considered as "negative", but inconclusive and uninformative.

Concerning the efficacy ("does the vaccine work?"), there is still no conclusive evidence for protection against pneumococcal pneumonia in these groups, but pneumococcal pneumonia is the leading cause of pneumococcal bacteremia (an invasive disease) and bacteremia can be prevented by vaccination.

Concerning effectiveness ("does vaccination help older people?"), many papers demonstrated the benefits of PPV23 in preventing IPD (case-control studies), and also prevention of pneumonia in COPD patients (retrospective cohort studies).

PNEUMOCOCCAL VACCINE IN THE ELDERLY: CURRENT GUIDELINES

Some discrepancies may be observed between professional societies' recommendations based on scientific data and experts' opinions and governmental public health recommendations, which also include cost-effectiveness at a population level. Most of the community-acquired pneumonia guidelines include recommendations for pneumococcal vaccine for the elderly:

The IDSA (41) recommends PPV23 for all persons aged ≥65 years of age. The committee of the CIDS/CTS (42) supports the use of the currently available pneumococcal vaccine in unvaccinated patients at risk of infection.

The ACIP (3) includes as target for pneumococcal vaccine patients aged ≥65 years.

The ERS (European Respiratory Society) (43) considers that the evidence for vaccination with PPV23 is not as strong as that for influenza, but recommends that the vaccine be given to all adult persons at risk of pneumococcal disease (≥65 years, institutionalization, etc.).

The SPILF (French Society for Infectious Diseases) (44) recommends PPV23 for persons aged ≥65 years. But the French health authorities (45) recommend the vaccine for at-risk adults and children aged ≥5 years, without specifically mentioning the elderly.

The BTS (46) recommends PPV23 for all those aged 2 years or older in whom pneumococcal infection is likely to be more common or serious. The UK Department of Health (13) recommends PPV23 for adults 65 years or over.

The position of the WHO (15) is quite mitigated. As many industrialized countries recommend PPV23 immunization of their elderly and other high-risk groups, WHO indicates that countries considering introducing PPV23 to the elderly will need to develop strategies for reaching this target. By contrast, in resource-limited settings where there are many competing health priorities, WHO considers that the evidence does not support routine immunization of the elderly with PPV23, and that higher priority should be given to introducing and maintaining high coverage of infants with PCV7.

Streptococcus pneumoniae has been indentified as the cause of around 50% of secondary bacterial pneumonia cases (and 20% of deaths) in the 1918 flu pandemic (47, 48). In preparation for a possible influenza pandemic, emphasis should be placed on increasing vaccination coverage among those for whom the vaccines are already recommended. Administering pneumococcal vaccines during a pandemic may be complicated by personnel shortages due to illness and vaccine shortages due to excessive demand. Therefore, ensuring that all persons with pneumococcal vaccine indications have been vaccinated before a pandemic occurs may be the best way of preventing pneumococcal disease during pandemics (49).

CONCLUSIONS

PPV23 is associated with a significant level of clinical protection against pneumococcal bacteremia. Considering the burden of illness of pneumococcal disease in the elderly and efficacy in preventing IPD, the protection against pneumococcal infection afforded by PPV23 may be useful and should be considered for older persons. The risk of a flu

pandemic emphasizes the need for protection in such persons. The limitations of this vaccine may be overcome in the future with new pneumococcal conjugate vaccines.

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