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Effectiveness of pneumococcal vaccine in the elderly. Review of the literature and meta-analysis

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Aim. Estimate pneumococcal vaccine effectiveness in preventing *Streptococcus pneumoniae* illness in the elderly.
Design. Systematic review and meta-analysis.
Data source. MEDLINE, years 1964 to the 2000; EMBASE, from 1988 to the 2000; Cochrane Library, identified studies and previously published systematic reviews citations peruse, and contacts with field experts.
Study selection. Clinical trials, cohort and case-control studies, published in Spanish, English or French, that estimated pneumococcal disease rates in vaccinated or not vaccinated elderly.
Data extraction. The studies were valued independently by four investigators with predefined criteria of validity, such as results comparing rates of disease caused by serotypes included in the vaccine, random allocation, double blind design, included subjects pertaining to the same study base, and losses of less than 10% in clinical trials and 20% in observational studies.
Results. Eight clinical trials considered the relative risk (RR) of pneumococcal pneumonia, three did not make estimations on pneumonia originated by serotypes included in the vaccine and only one study fulfilled all the inclusion criteria. Vaccinated versus not vaccinated pneumococcal pneumonia RR was 0.86 (95% CI, 0.24 to 2.99). Vaccine effectiveness was 14% (95% CI, −199 to 76%).
Ten studies performed estimations on the effectiveness of the vaccine on invasive disease by vaccine serotypes. Of these, two clinical trials and two observational studies fulfilled the required quality criteria. RR of invasive disease was of 0.68 (95% CI, 0.39-1.18); vaccine effectiveness was 32% (95% CI, −1861%).
Conclusions. No evidence was found supporting pneumococcal vaccine effectiveness to reduce or avoid *S. pneumoniae* disease in the elderly.

Key words: Meta-analysis. Pneumococcal infection. Vaccination. Aged.

EFECTIVIDAD DE LA VACUNA FRENTE AL NEUMOCOCO EN EL ANCIANO. REVISIÓN SISTEMÁTICA Y METAANÁLISIS

Objetivo. Estimar la efectividad de la vacuna neumocócica para evitar enfermedad por *Streptococcus pneumoniae* en ancianos.
Diseño. Revisión sistemática y metaanálisis.
Fuentes de datos. MEDLINE, años 1964 a 2000; EMBASE, de 1988 a 2000; Cochrane Library, citas bibliográficas de estudios identificados, revisiones sistemáticas anteriores y contactos con otros autores.
Selección de los estudios. Ensayos clínicos, estudios de cohortes y de casos y controles, publicados en castellano, inglés o francés, que estimaron tasas de enfermedad neumocócica en ancianos vacunados y no vacunados.
Extracción de datos. Los estudios fueron valorados independientemente por 4 investigadores con criterios de validez predefinidos, tales como realizar estimaciones de tasas de enfermedad por serotipos incluidos en la vacuna, asignación aleatoria, doble enmascaramiento, pertenencia a una misma base del estudio de los sujetos incluidos y tasas de pérdida inferiores al 10% en ensayos clínicos y al 20% en los estudios observacionales.
Resultados. Ocho ensayos clínicos estimaron el riesgo relativo (RR) de neumonía neumocócica, tres no realizaron estimaciones sobre neumonía originada por serotipos incluidos en la vacuna y sólo uno de los 8 cumplió los criterios de inclusión. El RR de neumonía neumocócica de los vacunados, frente a los no vacunados, fue del 0,86 (intervalo de confianza [IC] del 95%, 0,24 a 2,99). La efectividad de la vacuna fue del 14% (IC del 95%, −199 al 76%).
Diez estudios llevaron a cabo estimaciones de la efectividad de la vacuna sobre enfermedad invasora por serotipos incluidos en la vacuna. De éstos, dos ensayos clínicos y dos estudios observacionales reunieron los criterios de calidad requeridos. El RR de enfermedad invasora fue de 0,68 (IC del 95%, 0,39 a 1,18). La efectividad de la vacuna fue del 32% (IC del 95%, −18 a 61%).
Conclusiones. No se encontraron pruebas de la efectividad de la vacuna neumocócica para reducir o evitar la enfermedad neumocócica en el anciano.

Palabras clave: Metaanálisis. Infección neumocócica. Vacunación. Anciano.

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A commentary follow this article (pág. 281)

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Introduction

The indications for pneumococcal vaccination in persons aged 65 years or more are controversial because of discordant results between different studies,[1-4] and important differences have been noted in international recommendations for vaccination in this age group.[2,5,6] The controversy first appeared at the beginning of the 1980s in the light of difficulties large clinical trials had in demonstrating the effectiveness of vaccination in older persons,[7] and it was argued that the large numbers of participants required to guarantee sufficient statistical power to prove the protective efficacy of vaccination made such clinical trials impracticable.[8] At the end of the 1980s, recommendations for vaccination in persons older than 65 years were based on the results of observational studies. It is therefore high time for a systematic, thorough review of the literature, which now includes clinical trials and observational studies. Methodological quality criteria can now be used to guarantee an unbiased estimate of the effectiveness of pneumococcal vaccination in older persons

Methodology

To estimate the effectiveness of 23-valent pneumococcal capsular polysaccharide vaccination in preventing the disease caused by pneumococcal organisms in persons older than 65 years, we systematically reviewed the literature, with attention to both clinical trials and observational studies. Bibliographic databases were searched for articles published in Spanish, English or French between the years 1964 and 2000 in MEDLINE, and between 1988 and 2000 in EMBASE. The CD-ROM edition of the Cochrane Library database[9] was searched up to and including the first disk issued in 2001. Previously unidentified items were searched for in the reference lists of retrieved articles and in those of four separate reviews (three of which were systematic) of the effectiveness of polysaccharide vaccines.[1-4] Researchers were contacted to request unpublished information and other unidentified items.

Two search strategies were used: the sensitive strategy was based on the terms *pneumoc* AND vaccin* AND elderly*, and the specific strategy used the terms *pneumoc* AND vaccin* AND elderly AND (effectiv* OR effica*)*. We retrieved clinical trials, cohort studies and case-control studies that reported results for the effect of vaccination on the risk of pneumococcal disease, defined as pneumococcal pneumonia or invasive disease caused by pneumococci of the serotypes included in the vaccine and identified by culture, in populations of adults aged 65 years or older. Invasive disease was defined by the isolation of pneumococcal organisms from a normally sterile anatomical site. [12].

Inclusion, exclusion and evaluation criteria for studies

Studies were evaluated independently by four researchers on the basis of predefined criteria for validity.[10-13] Differences were resolved by consensus between the researchers. The inclusion criteria used to select studies were: *a)* information included on the administration of the vaccine in adults aged 65 years or more; *b)* risk measured for pneumonia or invasive disease caused by pneumococci belonging to the serotypes included in the vaccine; *c)* information included on the comparability of cases and controls or exposed and unexposed persons, ie, information that both of the groups being compared belonged to the same study base;[14] *d)* random allocation according to an adequately concealed double-blind procedure in clinical trials;[15] *e)* response rates higher than 80% for observational studies, or drop-out rates lower than 10% for clinical trials;[16] *f)* absence of classification bias or serious violations of blinding;[15] *g)* suitable control of confounding variables, and *h)* sufficient information to be able to repeat the analysis.[17] Noncompliance with either of the first two criteria (*a* or *b*) led to exclusion of the study. The other criteria were used as parameters to evaluate the quality of the studies, which were classified according to the following matrix:[12]

BOX

Interpretation	According to the above criteria
A. Low likelihood of bias*	Does not violate any of the criteria
B. Moderate likelihood of bias*	Does not comply fully (partially complies) with one or more criteria
C. High likelihood of bias*	Does not meet one or more of the specified criteria

*Altered by uncontrolled confounding factors in the design or analysis

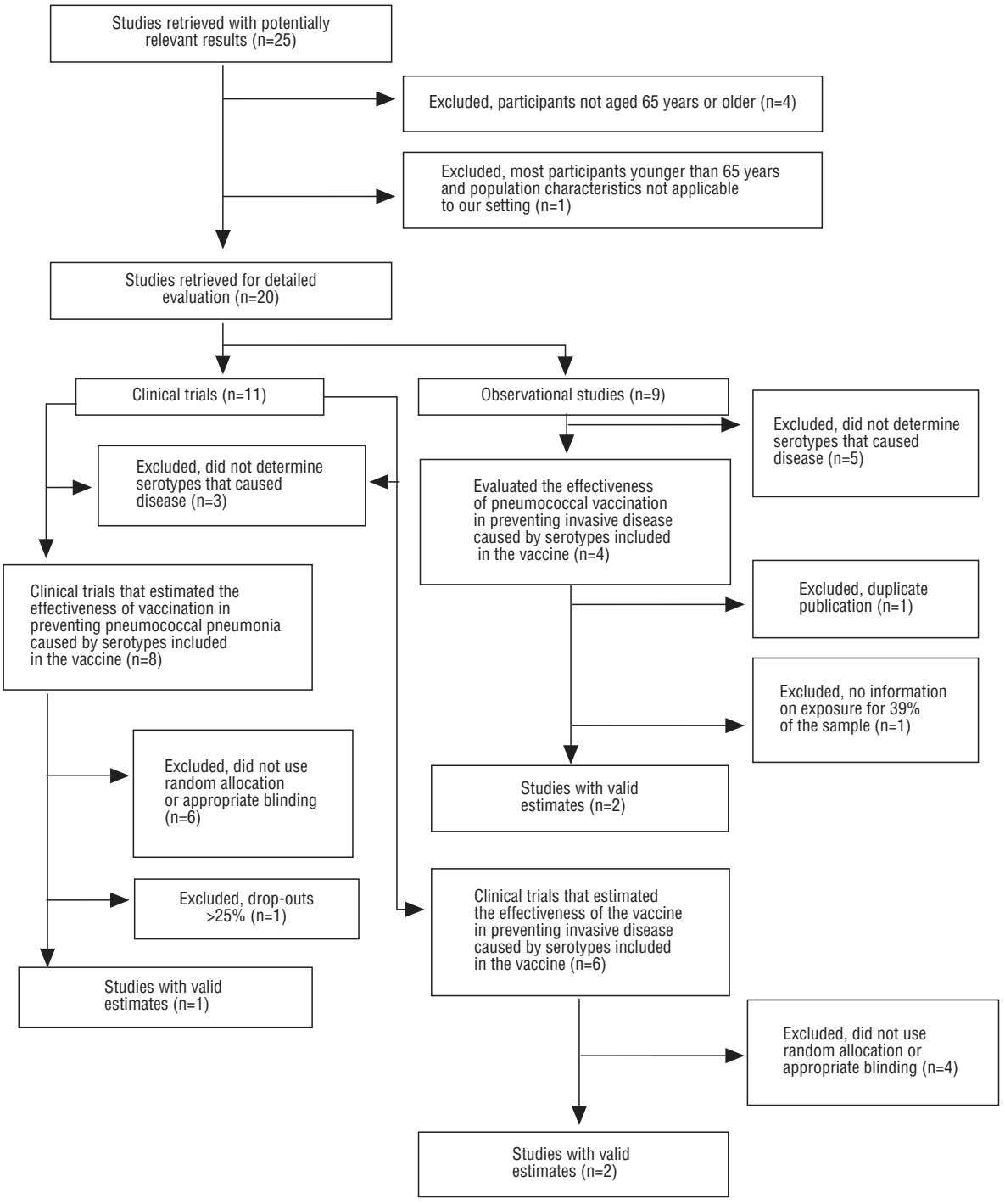
We excluded from the quantitative analysis all studies classified as C, and included all those classified as A or B.

Analysis

A descriptive analysis was prepared based on the year of publication, age groups included, type of population, study design, number of serotypes included in the vaccine, type of results studied and number of participants; relative risks (RR) were estimated and their confidence intervals (CI) calculated. Because of the low frequency of the events of interest, the odds ratio was considered an unbiased estimator of the RR. For each study we recorded factors that compromised the validity of the estimates and the likelihood that the results were biased.

Before estimating the protective effect of vaccination, we evaluated the homogeneity of the studies with graphs that illustrated point estimates of RR for pneumococcal disease and the CI, and their overlap or divergence. The hypothesis of homogeneity was tested by estimating the chi-squared value;[18] significant heterogeneity was considered to exist when $P<.10$. The possibility of publication bias was explored with the test of Egger et al.[19] The degree to which heterogeneity of the estimates was influenced by study characteristics such as design, number of serotypes in the vaccine, year and biases was studied by regression (metaregression analysis) of these characteristics on the logarithm of RR.[20] Only when the inclusion and validity criteria were satisfied and homogeneity could not be ruled out did we estimate the aggregate RR and its CI with the random effects method of DerSimonian and Laird[18] for a 95% confidence interval. When the confidence interval of the estimated RR included 1, we

Material and methods



General scheme of the study

Flow diagram showing items retrieved, evaluated and excluded, reasons for exclusion, type of study and results evaluated

TABLE 1 **Studies of the effectiveness and efficacy of 23-valent pneumococcal capsular polysaccharide vaccine in older persons**

Study	Age (years)	Type of study (design)	No. of serotypes included in vaccine	Type of pneumococcal disease	Exposed or cases	Cases observed in exposed individuals	Exposed or controls	Cases observed in control individuals	RR or OR	95% CI of the RR or OR
Kaufman, 1947[25]	≥50	Controlled clinical trial	3	Invasive disease by serotypes in the vaccine	5750	3	5153	33	0.08	0.16 to 0.26
				Death from pneumococcal disease (serotypes not specified)	5750	40	5153	98	0.37	0.25 to 0.53
				Pneumococcal pneumonia by serotypes in the vaccine	5750	3	5153	33	0.08	0.16 to 0.26
				Pneumonia of unspecified	5750	99	5153	227	0.39	0.3 to 0.5
Austrian, 1980[7]	≥45	Controlled clinical trial	12	Death associated with pneumococcal disease by serotypes in the vaccine	6782	4	6818	6	0.67	0.14 to 2.83
				Death from all causes	6782	45	6818	47	0.96	0.62 to 1.48
				Pneumonia of unspecified	6782	278	6818	265	1.05	0.89 to 1.25
				Pneumococcal pneumonia	6782	40	6818	42	0.96	0.60 to 1.51
				Pneumococcal pneumonia by serotypes in the vaccine	6782	24	6818	28	0.86	0.48 to 1.54
Bentley et al, 1981[29]	≥65	Controlled clinical trial	14	Invasive disease by serotypes in the vaccine	751	0	242	1	0	0 to 12.6
				Death associated with pneumococcal pneumonia by serotypes in the vaccine	751	3	242	0	1.28	0.13 to 63.48
				Pneumococcal pneumonia by serotypes in the vaccine	751	6	242	3	0.64	0.14 to 3.98
Shapiro y Clemens, 1984[30]	≥55	Case-control	14	Invasive disease	20	1	20	1	1	0.01 to 7737
Gaillat et al, 1985[31]	≥55	Controlled clinical trial	14	Pneumococcal pneumonia by serotypes in the vaccine	937	1	749	5	0.16	0.003 to 1.43
				Pneumonia of unspecified	937	9	749	31	0.23	0.1 to 0.5
Bolan et al, 1986[32]	≥65	Case-control	14	Invasive disease by serotypes in the vaccine	319	36	100	26	0.36	0.21 to 0.63
Klastersky et al, 1986[33]	40-78	Controlled clinical trial	17	Invasive disease by serotypes in the vaccine	26	1	21	1	0.81	0.01 to 63.39
				Pneumococcal respiratory infection	26	3	21	4	0.61	0.09 to 3.58
				Death from pneumococcal disease (serotypes not specified)	26	1	21	1	0.81	0.01 to 63.39
Simberkoff et al, 1986[35]	≥55	Controlled clinical trial	14	Invasive disease by serotypes in the vaccine	1145	1	1150	1	1	0.01 to 78.83
				Death associated with pneumococcal pneumonia by serotypes in the vaccine	1145	1	1150	0	2	0.1 to 118.53
				Death from all causes	1145	211	1150	171	1.24	1 to 1.52

This table continues in the next page

TABLE 1 **Studies of the effectiveness and efficacy of 23-valent pneumococcal capsular polysaccharide vaccine in older persons *(following)***

Study	Age (years)	Type of study (design)	No. of serotypes included in vaccine	Type of pneumococcal disease	Exposed or cases	Cases observed in exposed individuals	Exposed or controls	Cases observed in control individuals	RR or OR	95% CI of the RR or OR
				Pneumococcal pneumonia by serotypes in the vaccine	1145	6	1150	7	0.86	0.24 to 2.99
Davis et al, 1987[36]	40-80	Controlled clinical trial	14	Invasive disease	50	1	53	0	2.12	0.11 to 125.1
				Pneumococcal pneumonia	50	1	53	0	2.12	0.11 to 125.1
				Death from pneumococcal disease	50	1	53	0	2.12	0.11 to 125.1
Forrester et al, 1987[37]	≥50	Indirect cohor	14	Invasive disease by serotypes in the vaccine	26	18	63	43	1.05	0.39 to 2.81
				Death from pneumococcal disease (serotypes not specified)	26	13	63	23	0.98	0.42 to 2.28
Leech et al, 1987[38]	40-89	Controlled clinical trial	14	Invasive disease	92	1	97	0	2.11	0.11 to 124.43
				Death from all causes	92	6	97	11	0.57	0.17 to 1.70
Sims et al, 1988[39]	≥55	Case-control	23	Invasive disease	122	10	244	51	0.33	0.17 to 0.68
Gable et al, 1990[40]	≥50	Retrospective cohort	23	Pneumonia of unspecified	759	17	1159	19	1.37	0.71 to 2.61
Shapiro et al, 1991[41]	≥55	Indirect cohort	14 y 23	Invasive disease by serotypes in the vaccine	206		206	23	0.6	0.29 to 1.23
Butler et al, 1993[42]	≥65	Indirect cohort	14 y 23	Invasive disease by serotypes in the vaccine	443	70	82	35	0.25	0.15 to 0.42
Farr et al, 1995[43]	≥2 and ≥65	Case-control	14 y 23	Invasive disease	85	6	152	26	0.41	0.17 to 1.02
Koivula et al, 1997[44]	≥60	Controlled clinical trial	14	Pneumonia of unspecified	1364	27	1473	36	0.81	0.47 to 1.37
				Death from pneumococcal disease (serotypes not specified)	1364	1	1473	1	1.1	0.01 to 84.76
Ortqvist et al, 1998[45]	≥65	Controlled clinical trial	23	Invasive disease by serotypes in the vaccine	339	1	352	5	0.21	0.004 to 1.86
				Death associated with pneumococcal disease	339	2	352	3	0.69	0.06 to 6.04
				Death from all causes	339	29	352	28	1.07	0.62 to 1.88
				Pneumococcal pneumonia	339	19	352	16	1.23	0.6 to 2.56
				Pneumonia of unspecified	339	63	352	57	1.15	0.79 to 1.67
Honkanen et al, 1999[46]	≥65	Controlled clinical trial	23	Invasive disease by serotypes in the vaccine	13980	2	12945	5	0.37	0.03 to 2.26
				Pneumococcal pneumonia	13980	52	12945	40	1.2	0.78 to 1.87
				Pneumonia of unspecified	13980	145	12945	116	1.15	0.9 to 1.49
Nichol et al, 2000[47]	≥65	Retrospective cohort	23	Hospitalization for pneumonia or flu	1.280	90	618	82	0.53	0.39 to 0.72
				Death from all causes	1.280		618		0.71	0.56 to 0.91

RR: relative risk; OR: odds ratio; CI: confidence interval.

interpreted this to mean that vaccination did not confer significant protection against pneumococcal disease. The aggregate effectiveness of vaccination was calculated as (1–RR)×100.[21]

The number needed to treat (NNT) to avoid the outcomes of interest was also calculated.[22,23] All calculations were done with MS-Excel, MS-Access, Epi Info v. 6.04b and STATA v. 5 software.

Results

Twenty-five items were identified that compared the effectiveness of pneumococcal vaccination in preventing pneumococcal disease versus a control group.[7,24-47] Four articles were excluded because they dealt with young adults or children,[24,27,28,34] and a fifth item was excluded because it included individuals aged 10 years or more, did not supply information on age groups, and was done in a setting that made it difficult to extrapolate the results to western populations.[26] Of the remaining 20 articles (Table 1), 11 were clinical trials[7,25,29,31,33,35,36,38,44-46] and 9 were observational studies.[30,32,37,39-43,47]

Of the 11 clinical trials retrieved, eight analyzed the efficacy of the vaccine in preventing pneumococcal disease caused by serotypes included in the vaccine.[7,25,29,31,33,35,45,46] Six studies (Table 2) had one or both of the following problems: appropriate random allocation of the participants to the experimental or control group was not used, or the allocation procedure was not adequately concealed from the resear-

TABLE 2 **Characteristics and validity criteria for clinical trials retrieved**

Study	Population	Participants: Random allocation	Participants: Blinding	Participants: Investigators	Likelihood that estimates were biased	Observations
Kaufman, 1947[25]	Patients seen at two centers in New York (1937-1943)	Yes	No	No	High	Method of random allocation not specified. No allocation to placebo, no blinding. High likelihood of selection and classification bias. Analysis not adjusted for risk factors
Austrian, 1980[7]	Patients older than 40 years with insurance coverage from Kaiser Permanente	Yes	Yes	Yes	Moderate	37% of the participants included were 65 years of age or older; 33% were younger than 55 years
Bentley et al, 1981[29]	Patients institutionalized at an assisted care center	No	No	No	High	Drop-out rate >20%. Samples obtained from 74% of the patients with pneumonia; of these, 64% were sent for culture
Gaillat et al, 1985[31]	Patients institutionalized in retirement homes	Yes	No	No	High	No blinding or adequately concealed random allocation; participants drawn from 54 retirement homes of different characteristics; no information on characteristics or impact of drop-outs
Klastersky et al, 1986[33]	Patients with lung cancer	No	No	No	High	Included 50 patients aged 42 to 78 years
Simberkoff et al, 1986[35]	Patients at risk seen at Veterans Administration centers	Yes	Yes	Yes	Low	Patients at risk defined as those older than 55 years with one or more chronic diseases of cardiac, pulmonary, renal, hepatic, alcohol-related or diabetes-related origin
Davis et al, 1987[36]	Patients with chronic obstructive lung disease	Yes	Yes	Yes	Moderate	No information on age distribution or on serotypes
Leech et al, 1987[38]	Patients with chronic obstructive lung disease	Yes	Yes	Yes	Moderate	Method of random allocation not specified. No information on age distribution or serotypes
Koivula et al, 1997[44]	Persons older than 60 years living in the study area	Yes	No	No	High	Participants assigned to receive both flu and pneumococcal vaccination or flu vaccination only
Ortqvist et al, 1998[45]	Patients older than 50 years with antecedents of prior hospitalization for pneumonia	Yes	Yes	Yes	Moderate	Included 38 patients who did not fulfil protocol requirements
Honkanen et al, 1999[46]	Community-level study	Yes	No	No	High	Random allocation according. to year of birth. Flu vaccination alone compared to pneumococcal plus flu vaccination

TABLE 3 **Characteristics and validity criteria for observational studies retrieved**

Study	Population characteristics	Presence of biases: Seletion	Classification	Likelihood that estimates were biased	Observations
Shapiro y Clemens, 1984[30]	Patients hospitalized at the center where the study was done	No	No	Moderate	Two analyses were done: one paired, and one later unpaired analysis; the latter was considered inadequate. No information on serotypes
Bolan et al, 1986[32]	Isolation of pneumococcal organisms in samples received at the CDC (1978-1984)	No	No	Moderate	Results for the same series of patients were published in 1993
Forrester, 1987[37]	Patients hospitalized at the center where the study was done	No	No	Moderate	5% of the patients younger than 50 years with invasive disease were vaccinated, versus 15% who were not vaccinated
Sims, 1988[39]	Hospitalized patients	Yes	Yes	High	107 (46%) participants of 229 identified with invasive disease excluded because of insufficient data although they fulfilled all other inclusion criteria. Investigators not blinded
Gable et al, 1990[40]	Holders of Blue Cross/Blue Shield insurance	No	No	High	Bias introduced by inadequate analysis. However, the results allow the effect of vaccination to be estimated. Retrospective cohort study based on administrative data. No information on serotypes
Shapiro et al, 1991[41]	Pneumococcal organisms isolated at 11 hospitals (1984-1990)	Yes	Yes	Moderate or high	Uncertainty whether cases and controls were drawn from the sam e study base. 122 cases with disease caused by serotypes in the 23-valent vaccine but not in the 14-valent vaccine were excluded. The authors nonetheless provided an unbiased estimate of the effect of vaccination in persons older than 65 years
Butler et al, 1993[42]	Isolation of pneumococcal organisms in samples received at the CDC (1978-1984)	Yes	Yes	High	Of the 4624 cases of invasive disease identified, 1787 (39%) were not included in the analysis because of inadequate information about vaccination
Farr et al, 1995[43]	Patients hospitalized for invasive disease	No	No	Moderate	No information provided on serotypes
Nichol et al, 2000[47]	Persons older than 65 years with chronic obstructive lung disease enrolled at a health maintenance organization	Yes	Yes	High	Retrospective cohort study. Participants who were vaccinated differed in age, associated diseases, and access to flu vaccination. Observed and reported success rates rates were very high. No information on serotypes

chers and participants in the treatment group.[25,29,31,33,44,46] For the five remaining studies we estimated a low or moderate likelihood of bias, as participants were assigned randomly to one group or the other, and because researchers and participants were appropriately blinded to the procedure.[7,35,36,38,45]

Of the nine observational studies we retrieved, four analyzed the effectiveness of the vaccine in preventing pneumococcal disease caused by serotypes included in the vaccine,[32,37,41,42] and six were judged highly likely to be biased (Table 3). The patients described in the study by Bolan et al.[32] were included in the study by Butler et al.;[42] the former did not provide any indication of the thoroughness of the information regarding exposure, whereas the second lacked information about exposure for 39% of the participants eligible for inclusion. We therefore considered the validity of these estimates to be insufficient. In the study by Sims et al.,[39] 107 participants (46%) of a total of 229 were excluded because information about exposure was missing. The two studies by Shapiro et al. published in 1984[30] and 1991[41] had characteristics that met the criteria for estimates of moderate validity, and also presented estimates that changed direction when the analysis was repeated after ignoring the case-control matching[30] or af-

TABLE 4 **Effectiveness of pneumococcal vaccination in preventing *S. pneumoniae* disease in persons aged 65 years or older**

	Effectiveness (95% CI)*	Number needed to treat (95% CI)*		
		Estimated	Lower limit 95% CI	Upper limit 95% CI
Disease		Number of subjects needed to treat to prevent one case	Number of subjects needed to treat to cause one case	Number of subjects needed to treat to prevent one case
Pneumococcal pneumonia caused by serotypes in the vaccine	14% (–199 to 76%)	1.197	85 or more	242 or more
Invasive disease caused by pneumococcal serotypes in the vaccine	32% (–18 to 61%)	785	1.399 or more	412 or more

*Confidence interval.

ter information for 122 participants vaccinated with the 23-valent capsule polysaccharide vaccine was excluded.[41] The study by Gable et al.[40] was based on administrative data, and the analysis was inadequate. Lastly, in the study by Nichols et al.[47] exposed (vaccinated) and unexposed (unvaccinated) individuals could not be considered members of the same population at risk.

Effect of vaccination on pneumococcal pneumonia caused by serotypes included in the vaccine

Eight of the clinical trials retrieved (Table 1, Figure 1a) estimated the RR of pneumococcal pneumonia in vaccinated versus unvaccinated persons.[7,25,29,31,35,36,45,46] Three studies[36,45,46] did not estimate the number of cases of pneumococcal pneumonia caused by serotypes included in the vaccine (Table 2). Only the study by Kaufman et al.,[25] who investigated a vaccine composed of three capsular serotypes (Table 1), reported a favorable estimate of the vaccine´s protective efficacy. As shown in Figures 1a and 1b, this study cannot be considered similar to the others carried out between 1980 and 1998. None of the other clinical trials found a clinically significant protective effect (RR) for vaccination (Figure 1b). Figure 1c shows the estimates from those three trials (from among the original eight studies) that fulfilled the criteria for validity of the estimates (Table 2). The trial published by Austrian et al.[7] was excluded because samples for the identification of the serotype that caused pneumonia were obtained from fewer than 75% of the patients, although–as shown in Figure 1 and Table 1–none of their estimates showed vaccination to

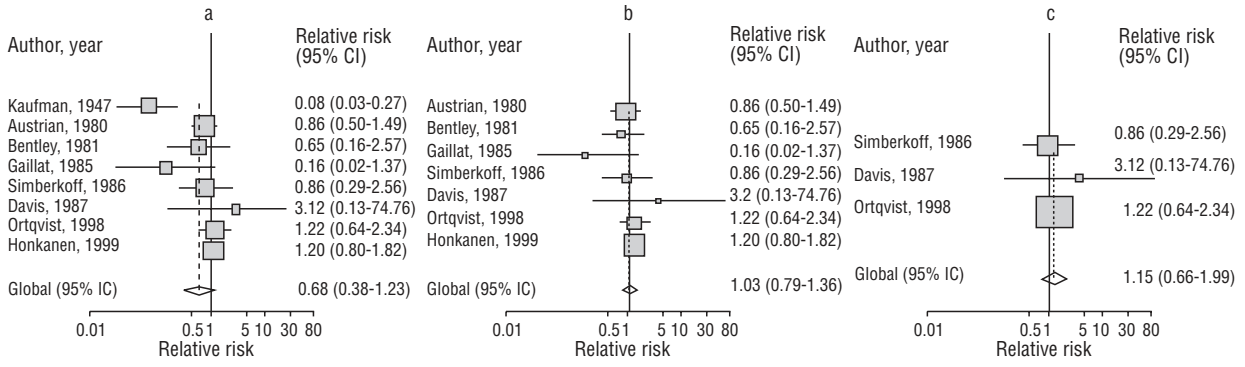


FIGURE 1 Relative risks of pneumococcal pneumonia. Part a shows all studies that measured the effectiveness of vaccination in preventing this disease; the test for homogeneity yielded a chi-squared value of 191.63 with 7 degrees of freedom and $P<.001$. Part b shows that after the study by Kaufman et al.[25] was excluded, the test for homogeneity yielded a chi-squared value of 2.69 with 7 degrees of freedom and $P<.85$. Part c shows the three studies that calculated the RR for pneumococcal pneumonia in vaccinated versus unvaccinated persons and that fulfilled our methodological quality criteria. However, two studies (Davis et al.[36] and Ortqvist et al.[45]) failed to investigate the serotypes that caused the disease. The areas of the boxes reflect the precision of the estimates obtained in different studies.

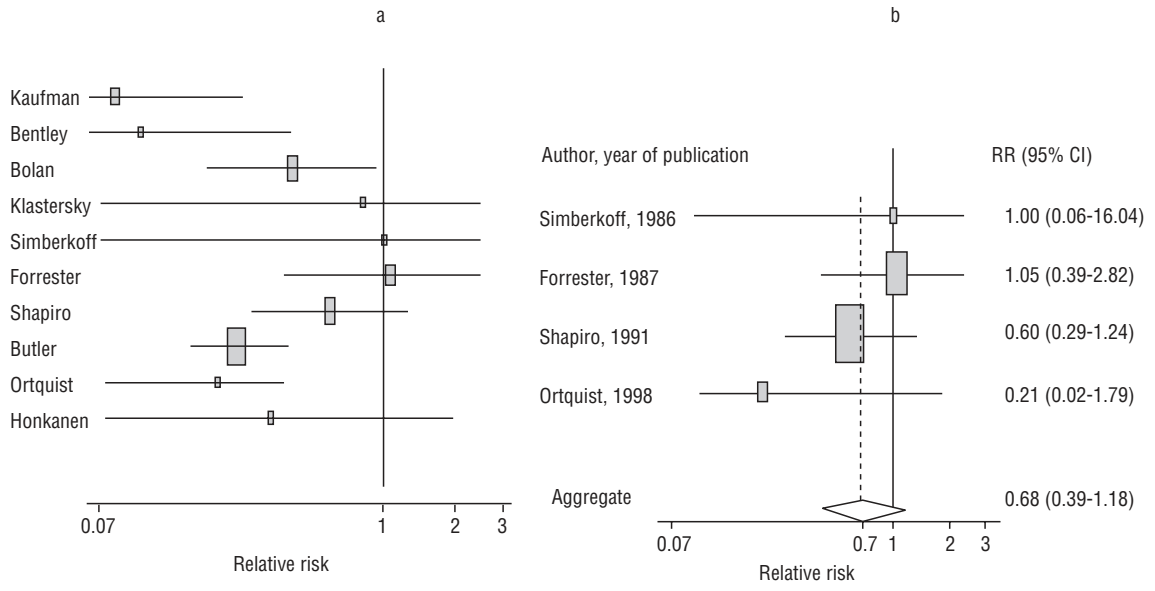


FIGURE 2

a) Estimates of relative risk (RR) of invasive disease caused by the pneumococcal serotypes included in the vaccine and the 95% confidence intervals (95% CI). For all studies retrieved, the test for homogeneity yielded a chi-squared value of 16.12 with 9 degrees of freedom and *P*=.06. The x axis scale has been truncated on both ends to improve legibility. b) Estimates of RR and 95% CI for the studies that fulfilled our inclusion criteria. Global RR was 0.68, 95% CI was 0.39 to 1.18; *P*=.17. The test for homogeneity yielded a chi-squared value of 2.09 with 3 degrees of freedom and *P*=.55. The areas of the boxes reflect the precision of the estimates obtained in different studies.

be protective. Lastly, only the clinical trial reported by Simberkoff et al.[35] in 1986 fulfilled the inclusion criteria for validity of the estimates and for our definition of a case: these authors provided estimates of the risk of pneumococcal pneumonia according to each serotype included in the vaccine.

The best available estimate placed the RR for pneumococcal pneumonia in vaccinated individuals compared to unvaccinated individuals at 0.86, with a 95% CI of 0.24 to 2.99. Effectiveness in preventing pneumococcal pneumonia caused by the serotypes in the vaccine was 14%, with a 95% CI of −199% to 76%. The number of individual needed to vaccinate (NNT) to prevent one case was 1197. The CI indicated the possibility that one case of pneumococcal pneumonia could be caused for every 85 or more persons vaccinated, and that one case could be prevented for every 242 or more persons vaccinated; this CI also included zero Table 4).

Effect of vaccination on invasive disease caused by serotypes included in the vaccine

Ten studied provided estimates of the effectiveness of vaccination against invasive disease caused by serotypes included in the vaccine (Figure 2a). Only three studies (Kaufman et al.,[25] Bolan et al.[32] and Butler et al.[42]) concluded that vaccination was significantly superior to the placebo (Figure 2a). The study by Kaufman et al.[25] had important limitations regarding random allocation of the participants and blinding of the investigators; the studies by Bolan et al.[32] and Butler et al.[42] reported results for the same series of patients and did not provide information on exposure for a large percentage of participants. The studies by Bentley et al.,[29] Klastersky et al.[33] and Honkanen et al.[46] did not satisfy the criteria because of problems with random allocation of the participants to different interventions, or problems with blinding the investigators or the participants (Table 2).

Of the 10 studies we examined, the clinical trials by Simberkoff et al.[35] and Ortqvist et al.,[45] and the observational studies by Forrester et al.[37] and Shapiro et al.[41] fulfilled our methodological quality criteria well enough so that we could trust the validity of their results (Tables 2 and 3). The aggregate RR for invasive disease was 0.68, with a 95% CI of 0.39 to 1.18 and a *P*=.17 (Figure 2b). The chi-squared test used to check the hypothesis of homogeneity of the different studies yielded a value of 2.09 with 3 degrees of freedom and a *P*=.55. The test of Egger et al. used to determine the possibility of publication bias yielded a nonsignificant value of *P*=.79. Effectiveness of vaccination was 32%, with a 95% CI of −18% to 51%, a

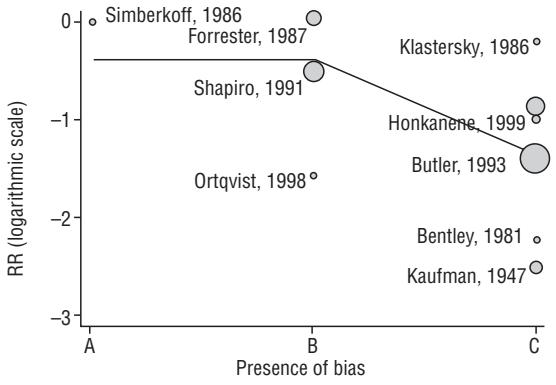


FIGURE 3

Results of metaregression analysis of the effect of publication bias on estimates of the effectiveness of vaccination in preventing invasive disease. Estimates for studies classified as A or B were significantly different (*P*=.004) from estimates obtained for studies classified as C. Interpretation of values along the x axis: A, A Low likelihood of bias; B, moderate likelihood of bias; C, high likelihood of bias (see Methods section).

result that implied that vaccination had no significant effect.

The estimated number of individuals needed to vaccinate (NNT) to prevent one case of invasive disease was 785, with a CI that showed that one case of invasive disease might be caused for every 1399 or more persons vaccinated, and that one case might be prevented for every 412 persons or more vaccinated. The CI again included zero (Table 4).

Sensitivity analysis

Figure 1a illustrates the effectiveness of vaccination in preventing pneumococcal pneumonia according to different studies. The results of the study by Kaufman et al.[25] explained the heterogeneity in the estimates of risk for pneumococcal pneumonia; this was further confirmed by metaregression analysis, which showed no significant alterations in the results according to the number of serotypes included in the vaccine, the year the study was done, or publication bias after the Kaufman et al. study was excluded.

Figure 2a shows that the results of studies that investigated the effectiveness of the vaccine in preventing invasive disease were markedly heterogeneous. Metaregression on the logarithm of RR and analysis of the influence of the year of the study, the study design, the serotypes included in the vaccine or publication bias showed that this last factor was the one that best explained (*P*=.009) the variability in our results (Figure 3). In fact, the point estimate of effectiveness of the vaccination was 2.6-fold greater in studies for which we considered validity of the estimates to be compromised than in studies we considered free from bias (classified as A or B). The RR increased from 0.26 to 0.68, and the CI for the latter value indicated that the effect of vaccination was null.

Discussion

Twenty-five years after vaccination with capsular polysaccharide vaccines for pneumococci was first authorized, uncertainty remains as to their effectiveness, and some authors have warned that recommendations in favor of systematic vaccination for all persons aged 65 years or more need to be reviewed in the light of current knowledge.[4] This situation has been fomented by proponents of vaccination who claimed that clinical trials would be impracticable and that observational studies were sufficient.[8] The present sytematic review of the literature and meta-analysis included both observational studies and clinical trials, and obtained estimates of the effectiveness of vaccination in which the lower limit of the CI was a negative value. In other words, we found no proof of the effectiveness of pneumococcal vaccine in reducing or preventing pneumococcal disease in older persons. These results are in agreement with the findings of Fine et al.[1] and Moore et al.,[4] who included in their reviews only clinical assays.

Several factors may compromise the results of a systematic review of the literature.[19] One possible source of bias is that studies eligible for inclusion may be overlooked because the predominance of publications in English makes studies in other languages less likely to be cited and retrieved. Another possible bias arises from the fact that the databases we used for our literature searches are selective in the references they include. Moreover, unpublished studies–most of which report negative findings–are not retrieved. In the present study we did not limit our searches to studies in English. We searched MEDLINE, EMBASE and the Cochrane Library, and made appropriate efforts to retrieve unpublished studies such as those by Austrian et al.,[7] a clinical trial with adequately concealed random allocation, double-blinding and a large number of participants (13 600). We contacted other researchers to obtain information on additional publications and scrutinized the reference lists of the items retrieved from database searches. In fact, the results of the test of Eggar et al., which we applied to studies that investigated invasive disease, supported our assumption that no bias was introduced by the noninclusion of studies that might have been overlooked.[19]

Another source of error is bias in the choice and application of inclusion and exclusion criteria, data extraction and quality control criteria. To avoid these pitfalls the aims and inclusion criteria were defined before the study was begun.[12] Moreover, we included both clinical trials and observational studies. All items were reviewed and assessed independently by the authors, who all used the same methods of analysis.

With regard to the studies we included, possible sources of heterogeneity were reduced by adapting our selection process to the question that formed the basis of the present analysis. The use of age as an inclusion criterion led us to exclude studies of children or young adults, in whom the response to vaccination differs from that in older persons;[1] in addition, we opted to include only those studies with unambiguous clinical outcomes that evaluated the protection conferred against pneumococcal pneumonia or invasive disease caused by *S. pneumonia* serotypes included in the vaccine.

A further potential source of heterogeneity between studies included in our analysis is the aggregation of results of clinical assays and observational studies. However, for studies designed and executed with adequate guarantees of methodological rigor, the results of clinical trials and observational studies concur.[48,49] Heterogeneity of the findings from included and excluded studies (Figure 2a) was explained mainly by the presence or absence of factors that compromised the validity of the estimates (Figure 3), as opposed to factors such as the type of study design, year of publication or number of serotypes in the vaccine, which had no significant influence on the results.

In comparison to fixed effect models, our random effects statistical model can be considered an appropriate method for aggregating data from different studies. The former approach assumes that differences in the estimates are caused only by sampling error, whereas the random effects model also takes into account the fact that because the characteristics of the participants were not homogeneous across the studies we included, the magnitude of the effects of vaccination differed between studies. This was in fact the case in the present review: the studies we retrieved involved populations that differed in their risk profiles, regardless of the participants´ age[18].

The discrepancy between our findings and the results of the systematic review by Hutchison et al.[3] can be explained by the fact that these authors pooled the results of studies involving different age groups. When we controlled for this factor, the statistical significance of the differences in the estimates disappeared.

In accordance with the terminology proposed by Altman,[23] we present our results as estimates of the number needed to treat (ie, to vaccinate) and the confidence interval. We extrapolated our figures to the most plausible incidence of cases of invasive disease in the community[50]–50 per 100 000 persons aged 65 years or older–assuming that 90% of the cases are caused by one of the serotypes included in the vaccine. The estimated NNT to prevent one case of invasive disease is 6947, with a CI that includes, on one extreme, the chance of causing one case of invasive disease per 12 352 persons or more vaccinated, and on the other extreme, the chances of preventing one case per every 3644 or more persons vaccinated. These estimates mean that we cannot claim to have sufficient evidence to support vaccination. The actual estimate lies somewhere on a continuum of values that includes, in addition to the null effect, the possibility that vaccination itself might contribute to cases of the disease it is intended to prevent.

In conclusion, our review provides no proof that pneumococcal vaccination with nonconjugate capsular polysaccharide vaccines of *S. pneumoniae* is effective in reducing or preventing pneumococcal disease in older persons. In the light of the results of the present review and meta-analysis, we can only conclude that the systematic recommendation for vaccination in the population of persons 65 years of age or older should not be made in the absence of results of clinical trials that unequivocally demonstrate a protective effect.

Discussion
Key points

What is known about the subject

- Several systematic reviews and meta-analyses of clinical assays have concluded that vaccination is no better than placebo in preventing pneumococcal disease in older persons.
- The recommendation to administer 23-valent pneumococcal capsule polysaccharide vaccination to older persons is based on results of observational studies of varying methodological rigor and occasionally inconsistent results.

What this study contributes

- A systematic review was undertaken of clinical trials and observational studies that investigated the effect of vaccination on rates of pneumococcal disease in older persons.
- The best available estimates of the effectiveness of vaccination in preventing pneumococcal disease in older persons is 32%, with a 95% confidence interval of −18% to 61%.
- The number of older persons that would need to be vaccinated to prevent one case of invasive disease caused by serotypes included in the vaccine is 7000, with a confidence interval that implies the possibility that one case would be caused for every 12 000 persons vaccinated.

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COMMENTARY

Pneumococcal disease: is prevention possible?

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The two strategies for dealing with pneumococcal infections are the rational use of antibiotics and vaccination. Effective prevention of *Streptococcus pneumoniae* infection has become a priority in the current era, when the emergence of antibiotic-resistant strains can compromise efforts to reduce mortality from invasive pneumococcal infection.

Despite the seriousness of pneumococcal disease, we do not yet have a vaccine that has been shown to be effective in all target groups. Polysaccharide vaccines are effective in preventing invasive disease in immunocompetent persons. However, studies in different groups of the immunodepressed population have shown their efficacy in these groups to be questionable. The is still little evidence of their usefulness in persons with asthma, patients with

- The two strategies for dealing with pneumococcal infection are the rational use of antibiotics and vaccination.
- Several meta-analyses have brought to light the controversy regarding the efficacy of pneumococcal polysaccharide vaccines.
- The usefulness of conjugate vaccines in adults, particularly in groups at greater risk, remains to be investigated.
- Whether smoking cessation decreases the incidence of the disease in older persons should be investigated.

HIV infection, and–as discussed in this editorial–in persons older than 65 years. Moreover, recommendations for vaccination have thus far not included other subgroups at high risk for the disease, such as smokers and African Americans.[1]

As regards the immunogenicity of the vaccine, the immune response induced is not the same in all patients or for all serotypes. Moreover, immunogenicity does not guarantee that opsonizing antibodies will be produced. One study showed a pneumococcal polysaccharide vaccine to be ineffective in older persons because of the lower production of opsonizing antibodies regardless of the titer of antibodies achieved.[2]

Several meta-analyses have brought to light the controversy regarding the efficacy of pneumococcal polysaccharide vaccines. The analysis by Moore et al. confused circumstances with populations, and as noted in an earlier commentary, the effectiveness of the vaccine was compared in the general population, immunocompromised patients and older persons.[3] The authors of the meta-analysis published in this issue of ATENCIÓN PRIMARIA are to be commended for responding to the challenge of undertaking a study of high quality in the setting of their primary care activities. However, the study is also remarkable for its rigor in the exhaustive search methods used and in its effort to examine a particular subpopulation characterized by immunodepression.

The authors found no proof that pneumococcal polysaccharide vaccination was effective in older persons. As the authors note in their article, the meta-analysis by Hutchinson et al. yielded findings that contradicted those of Puig et al. because the former combined results for different age groups. When this fact was taken into account, the statistical significance of the estimates disappeared. The review by Cornu et al. likewise failed to find any preventive effect, a result the authors attributed to weak statistical power.[4]

However, questions have been raised with regard to the indication for vaccination. Is it ineffective but nonetheless cost-effective? Does a combined strategy of vaccination during the flu vaccination campaign improve performance by extending coverage? Some clinical studies suggested an additive effect of double vaccination in preventing community-acquired pneumonia, particularly in older persons at greater risk for this disease and for hospitalization.[5] Is pneumococcal vaccination advisable for older institutionalized patients to prevent outbreaks of the disease? Are there any subgroups among older persons for which the indication for vaccination has been clearly established, such as persons with chronic obstructive lung disease? Some indications seem to reserve a role for this controversial vaccination.

The recent appearance of conjugate pneumococcal vaccines, which are currently useful in pediatrics, appears to disrupt the transmission of antibiotic-resistant pneumococci, and thereby reduce the rate of resistance in the immunized population and persons who come in contact with immunized individuals, as a result of the «herd effect». One question worth examining is whether a joint strategy of child vaccination with the conjugate vaccine and the simultaneous administration of flu and pneumococcal polysaccharide vaccination in older persons would lead to a significant decrease in the disease, particularly in cases caused by resistant germs. The effectiveness of conjugate vaccines for adults, especially for groups at greatest risk, also remains to be investigated.

A fundamental consideration is immunological memory. Experience to date is limited to *Haemophilus influenza* type B vaccination, whose epidemiological impact was evident when a conjugate vaccine was used but not with a vaccine prepared from a panel of polysaccharides. Even with the limited information available, the theoretical superiority of conjugate pneumococcal vaccines does not guarantee clinical efficacy.[6] The availability of these vaccines makes additional in-depth epidemiologic studies even more necessary to determine the mortality and morbidity associated with the disease, the serogroups that cause invasive and noninvasive disease, and the serogroups linked to higher rates of resistance. In addition, information is still needed on the existence of carriers and the possible shift of the ecological niche toward other, previously less pathogenic serogroups. The geographic variability of invasive pneumococcal disease supports the need for such studies, and should favor the development of vaccines with shared antigens such as *Pneumococcus* surface protein A (PspA) or *Pneumococcus* surface adhesin (Psa A).[3]

As important factor in health care management is cost-effectiveness. In Spain, studies of the type suggested above should be done to determine whether or not vaccination is indicated for older persons, and scientific evidence should be used to try to avoid inequities in the health care system.

In conclusion, these are the main issues awaiting resolution:

– The population of older persons who respond poorly to 23-valent pneumococcal capsular polysaccharide vaccination can be identified as a target population for improved vaccines (conjugate and DNA, currently in the experimental phase).
– Efforts are needed to determine whether treatment of a correctable nutritional deficit would improve the immune response to the polysaccharide vaccine in this group.
– Whether the adult population responds more uniformly to new (ie, conjugate and DNA) pneumococcal vaccines should be determined.
– Whether smoking cessation decreases the incidence of invasive pneumococcal disease in older persons should be investigated.[7]

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