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REVIEW

Pneumococcal vaccination for the elderly in the Netherlands? Assessment of the quality and content of available comparative studies

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ABSTRACT

Background: A question that is currently topical in the Netherlands is whether it makes sense to introduce on a national scale vaccination against pneumococcal infections for elderly people who are at present receiving the influenza vaccination. We recently studied the scientific literature on the subject in an attempt to answer this question.

Methods: We searched for systematic reviews (SRs), randomised clinical trials (RCTs) and cohort studies in MEDLINE, EMBASE, the Cochrane Library, Current Controlled Trials and via Google (period 1966 to June 2002). The SRs and RCTs were assessed with a methodological checklist.

Results: We identified four SRs, two trials (of which one was pseudo-random) and one retrospective cohort study. The methodological quality of the SRs was reasonable and in this respect differed little among themselves. The SRs differed strongly with regard to subgroups, outcome measures, valency of vaccines, duration of follow-up and combination with influenza vaccination. The SRs showed that vaccination has more effect in low-risk groups, does not appear to be effective in high-risk patients and the elderly and is more effective in nonindustrialised countries. The outcomes based on the various outcome measures showed major differences. The three studies into the effectiveness of the pneumococcal vaccination in the elderly all showed major methodological shortcomings. For the majority of outcome measures the outcomes were negative.

Conclusion: There is insufficient convincing evidence in favour of the introduction of the pneumococcal vaccination as a supplement to influenza vaccination for the elderly. It seems as if (international) opinion had already been fully formed before published studies and systematic reviews become available in the last few years. It is perhaps worth considering setting up a prospective trial in the elderly Dutch population.

INTRODUCTION

A question that is currently topical in the Netherlands is whether it makes sense to introduce on a national scale vaccination against pneumococcal infections for elderly people who are at present receiving the influenza vaccination. We recently studied the scientific literature on the subject in an attempt to answer this question. At first sight it seemed difficult to give an unambiguous interpretation of the information uncovered, since a number of methodological problems were involved:

a) Most randomised clinical trials (RCTs) were performed on populations other than the target group under consideration here.[1,2]

b) Opinions on effectiveness were partly formulated before the RCTs focussing on elderly became available. And here, too, systematic reviews (SRs) played a part.
c) A great many different surrogate and end measures were applied in the RCTs.
d) The SRs available arrived at different conclusions and used a variety of methods.

This report gives a transparent analysis of systematic reviews currently available, RCTs and comparative cohort studies in order to investigate the extent to which these provide a valid and relevant answer to the question of whether the elderly in the Netherlands should receive the pneumococcal vaccination by way of supplement to the influenza vaccination.

METHOD

Literature search

The literature was searched and selected by the first author (period 1966 to June 2002). The search was conducted for the following.

Published SRs

Search carried out in MEDLINE and EMBASE [(Streptococcus infection (MeSH heading) or (pneumococc$ or streptococc$) (text word)] AND [vaccination (MeSH) or vaccin$ (text word)] in combination with the sensitive and specific search filter for SRs by Hunt and McKibbon;[3] Cochrane Database of Systematic Reviews;[4] Correspondence with authors.[5]

Published randomised and nonrandomised clinical trials

Search carried out in MEDLINE and EMBASE [(Streptococcus infection (MeSH heading) or (pneumococc$ or streptococc$) (text word)] AND [vaccination (MeSH) or vaccin$ (text word] in combination with the sensitive and specific search filter for RCTs from the Cochrane Collaboration.[6]
Search carried out in the Cochrane Controlled Trials Register.[7] Keywords as above.

Unpublished RCTs

Current Controlled Trials Register (http://www.controlled-trials.com).
General Internet browser (www.google.com). Keywords: pneumococcal vaccination.

Assessing the literature

Assessment of the quality of the SRs and their relevance to the question was carried out with the aid of a standard assessment list[8] and an algorithm for conflicting SRs,[9] by two researchers doing the assessment independently of one another (RJPMS and MO). Assessment of the (R)CTs was carried out with the aid of a standard assessment list[10] by two researchers working independently of one another (RJPMS and MO).

RESULTS

Search

Systematic reviews

The MEDLINE and EMBASE search came up with four SRs.[11-15] In addition there was a second Cochrane protocol on the subject[16] which, however, gave no further information with regard to the subject and thus fell outside the present assessment.

Clinical trials

The search provided two RCTs on the effectiveness of vaccination in the elderly people.[1,2] And an Internet search using the Google search engine (www.google.com) with the keywords 'pneumococcal vaccination' led to nothing extra, apart from the hits already known. Finally a (non-randomised) retrospective cohort study was found in which pneumococcal vaccination (partly combined with influenza vaccination) was evaluated.[17,18]

Systematic reviews

The methodological quality of the SRs was reasonable and in this respect differed little among themselves. Here it should be noted that the assessment list used mainly examines the correctness with which the various stages of an SR are implemented. But often there are several options for elaborating on a particular item. The four reviews therefore also differed from one another mainly with regard to method and outcomes. The algorithm of Jadad *et al.*[9] was used to investigate where the methodological differences between the SRs usually occur.

Clear differences were seen in the methods employed in the SRs. It is remarkable that three of the SRs were published within a relatively short period and that of the two trials in these SRs most relevant to our question, neither were,[12] both were[15] and only one[13,14] was included (*table 1*). The other (potentially) important differences between the SRs relate to the subgroups, outcomes, valency of the vaccines, duration of the follow-up in the trials and the combination with the influenza vaccination (*table 2*).

Subgroups

The subgroups formed differ greatly from review to review (*table 2*). In view of the question posed, there is a major issue here as to how aspects such as comorbidity and age are to be dealt with (>65 years sometimes not

Table 1
Characteristics of (pseudo-)randomised studies

STUDY	PARTICIPANTS, PRINCIPAL EXCLUSIONS – LENGTH OF FOLLOW-UP	INTERVENTION/CONTROL	REVIEWS (REFERENCES)			
Industrialised countries, high risk			**11**	**12**	**13,14**	**15**
Klastersky 1986	Bronchial carcinoma - unclear	17-valent/placebo	+	+	+	+
Simberkoff 1986	Chronic renal, hepatic, cardiac, pulmonary disease, alcoholism, diabetes. Excluded asplenia, recent hospitalisation, previous vaccination, haematological malignancy - 2.9 years	14-valent/placebo	+	+	+	+
Davis 1987	COPD. Excluded asthma, neoplasms, renal or hepatic impairment, sickle cell disease - 2 years	14-valent/placebo	+	+	+	+
Leech 1987	COPD. Excluded other lung disease, previous vaccination - 2 years	14-valent plus influenza/ placebo plus influenza	+	+	+	+
Industrialised countries, older age						
Koivula 1997	Elderly, community - 3 years	14-valent plus influenza/ influenza alone			+	+
Honkanen 1999	Elderly, community. Excluded terminally ill - 3 years	23-valent plus influenza/ influenza alone			O	+
Industrialised countries, other						
McLeod 1945	Young US military recruits	4-valent/placebo	O	+	O	O
Kaufman 1947	Long-term facility residents (80% aged >60 years)	2,3-valent vaccine	O	+	O	O
Austrian 1980*	Health plan members aged >45 - 2 years	12-valent/placebo	+	+	+	+
Austrian 1980*	Psychiatric inpatients - 3 years	12-valent/placebo	+	+	+	+
Gaillet 1985	Retirement home residents, geriatric inpatients. Excluded comorbidities, terminal illness, immunodeficiency - 2 years	14-valent/no placebo	+	+	+	+
Ortqvist 1998	Patients over 50 with previous pneumonia. Excluded immuno-suppression, low compliance - 4 years	23-valent/placebo			+	+
Less industrialised countries						
Austrian 1976*	Novice gold miners - 2 years	6 or 13-valent/ meningococcal vaccine/placebo	+	+	+	+
Riley 1977	Subsistence farmers - 3 years	14-valent/placebo	+	+	+	+
Smit 1977*	Novice gold miners - 2 years	6-valent/ meningococcal vaccine/placebo	+	+	+	+
Smit 1977*	Novice gold miners - 2 years	12-valent/ meningococcal vaccine/placebo	+	+	+	+

*Trials categorised according to Watson et al.[19] In the right-hand column inclusion of trial in question in the four systematic reviews. * Multiple trials presented in single report, + = trial included; o = trial excluded; blank = trial not available yet.*

specific as an inclusion criterion, while the average age is then quite high). To reach a conclusion it is important to determine whether a restriction should be imposed limiting the study to a particular trial dealing specifically with the question[1,2] or whether evidence from other trials (e.g. trials with a high average age of participants or trials with institutionalised patients with comorbidity) can be assessed as to its applicability to the question under examination.

Outcome measures
The outcome measures reported and analysed show major differences between the SRs. In addition, the conclusions of the various reviews contain a different hierarchy in the outcome measures.

Valency of vaccines
The vaccines used differ greatly in valency (*table 1*). None of the SRs pay any attention to this fact in separate subgroup analyses.

Duration of follow-up
This too differs greatly from trial to trial, which should not lead to any consequences if the relative risk/odds ratio remains constant over a shorter and longer period of follow-up. But in this area it is unclear as to whether such is the case.

Combination with influenza vaccination
Some studies report pneumococcal vaccination as being given supplementary to the influenza vaccination (as

Table 2
Subgroups, outcome measures and account taken of vaccine valency in SRs

STUDY (REFERENCE)	SUBGROUPS	OUTCOME MEASURES	ACCOUNT TAKEN OF VACCINE VALENCY	ACCOUNT TAKEN OF RANDOMISATION IN TRIALS	ACCOUNT TAKEN OF COMBINATION WITH INFLUENZA VACCINE
11	1. High risk: patients with comorbidity and institutionalised patients (n=5) 2. Low risk: miners, ambulant patients (n=7)	Confirmed pneumococcal pneumonia Confirmed pneumococcal pneumonia, vaccine type Possible pneumococcal pneumonia Possible pneumococcal pneumonia, vaccine type Pneumococcal disease Not pooled, but described: - Pneumonia (all causes) - Bronchitis - Mortality (all causes) - Mortality (pneumonia) - Mortality (pneumococcal infection)	No subgroup analysis with vaccines of different valencies	Restricted to genuine randomised studies	No
12	1. Elderly (n=7) 2. Chronically ill (n=3) 3. Institutionalised (n=3)	Vaccine-type systemic pneumococcal infection Systemic pneumococcal infection Pneumococcal pneumonia Non-vaccine type pneumococcal pneumonia	No subgroup analysis with vaccines of different valencies	Pseudo-random trials included	No
13,14	1. Normal immune system: young, healthy (n=3) 2. Weakened immune system or elderly (n=10)	Pneumonia (all causes) Pneumococcal pneumonia Lower airway infections Mortality (pneumonia) Bacteriaemia	Yes, two older trials excluded No subgroup analysis with vaccines of different valencies	Restricted to truly randomised studies; exclusion of pseudo-random trials: two older trials and one more recent one of the two specifically carried out on the elderly[2]	No
15	1. Nonindustrialised (n=4) 2. Industrialised a) All (n=10) b) Patients with comorbidity/ high risk (n=4) c) Elderly (>65 years) (n=2) d) 'Other' (n=4)	Mortality (all causes) Pneumonia (all causes) Pneumonia (pneumococci) Bacteraemia (pneumococci)	No subgroup analysis with vaccines of different valencies	Restricted to genuine randomised studies	No

would be the case in the Netherlands) (*table 1*). However in other studies only the pneumococcal vaccination is administered. None of the SRs include this fact in their conclusions.

Outcomes of systematic reviews

Table 3 shows the results of the four SRs in the same way as was presented in the original publications. It is immediately clear that subgroups, outcome measures and statistical heterogeneity have been dealt with in different ways.

The SRs deal with the 'elderly' category in different ways (*table 2*). In Fine *et al.*[11] the studies with a relatively large number of elderly people (often with comorbidity) come under the 'high-risk' category.

Hutchison *et al.*[12] deal separately with elderly people in the text of their SR. They state that seven of the 13 studies dealt predominantly with the elderly. In view of this numerical imbalance the authors believe that the results of overall poolings are also applicable to the elderly. It should be noted that this SR did not include the two studies carried out specifically on elderly people,[1,2] even though the SR appeared *after* publication of both studies, and that two major positively dated studies (from 1945 and 1947 respectively; with vaccine containing four and three pneumococcal types respectively) were included, whereas they had been omitted from the other SRs (*table 1*). In the SR by Moore *et al.*[13,14] the elderly are analysed together with the high-risk patients. Watson *et al.*[15] first separated the studies carried out in industrialised countries from

Table 3
Outcomes of systematic reviews

REFERENCE	OUTCOME MEASURES (NUMBER OF STUDIES)	POOLED OUTCOMES [95% CI], STATISTICAL HETEROGENEITY
11	Confirmed pneumococcal pneumonia (n=8)	OR_{fixed} 0.34 [0.24;0.48] RD_{random} 4 [0;7]*
	Low risk (n=3)	OR_{fixed} 0.32 [0.22;0.46] RD_{random} 11 [2;19]*
	High risk (n=5)	OR_{fixed} 1.23 [0.28;5.43] RD_{random} 0 [-1;2]
	Vaccine-type confirmed pneumococcal pneumonia (n=3)	OR_{fixed} 0.17 [0.09;0.33] RD_{random} 8 [1;16]*
	Low risk (n=2)	OR_{fixed} 0.16 [0.09;0.31] RD_{random} 15 [-14;45]*
	High risk (n=1)	OR_{fixed} 1.00 [0.06;16.06] RD_{random} 0 [-2;2]@
	Suspected pneumococcal pneumonia (n=4)	OR_{fixed} 0.47 [0.35;0.63] RD_{random} 13 [-21;47]*
	Low risk (n=1)	OR_{fixed} 0.40 [0.29;0.56] RD_{random} 41 [29;54]@
	High risk (n=3)	OR_{fixed} 0.98 [0.51;1.89] RD_{random} -3 [-21;15]
	Vaccine-type suspected pneumococcal pneumonia (n=3)	OR_{fixed} 0.39 [0.26;0.59] RD_{random} 16 [-3; 35]*
	Low risk (n=2)	OR_{fixed} 0.35 [0.23;0.55] RD_{random} 25 [15;35]
	High risk (n=1)	OR_{fixed} 0.86 [0.29;2.56] RD_{random} 1 [-5;7]@
	Pneumonia (all causes) (n=8)	OR_{fixed} 0.90 [0.77;1.04] RD_{random} 6 [-1;13]
	Low risk (n=5)	OR_{fixed} 0.89 [0.76;1.05] RD_{random} 6 [-2;14]
	High risk (n=3)	OR_{fixed} 0.92 [0.63;1.35] RD_{random} 5 [-16;26]*
	Bronchitis (n=3)	OR_{fixed} 0.84 [0.69;1.02] RD_{random} 8 [0;15]
	Low risk (n=3)	OR_{fixed} 0.84 [0.69;1.02] RD_{random} 8 [0;15]
	High risk (n=0)	-
	Mortality (all causes) (n=7)	OR_{fixed} 1.02 [0.90;1.14] RD_{random} 1 [-6;8]
	Low risk (n=3)	OR_{fixed} 0.84 [0.70;1.01] RD_{random} 2 [-2;7]
	High risk (n=4)	OR_{fixed} 1.16 [1.00;1.35] RD_{random} -18 [-47;11]
	Mortality (pneumonia) (n=4)	OR_{fixed} 0.78 [0.57;1.06] RD_{random} 2 [-2;5]
	Low risk (n=3)	OR_{fixed} 0.79 [0.57;1.0] RD_{random} 2 [-2;5]
	High risk (n=1)	OR_{fixed} 0.51 [0.09;2.92] RD_{random} 35 [-54;125]@
	Mortality (pneumococcal pneumonia) (n=3)	OR_{fixed} 4.59 [0.54;1.06] RD_{random} -3 [-6;0]
	Low risk (n=0)	-
	High risk (n=3)	OR_{fixed} 4.59 [0.54;38.81] RD_{random} -3 [-6;0]
12	Systemic pneumococcal infection	
	Vaccine type (n=4)	OR 0.17 [0.09;0.31]
	All infections (n=6)	OR 0.27 [0.13;0.49]
	Vaccine-type pneumococcal pneumonia (n=9)	Range ORs 0.08-1.17*
	Pneumococcal pneumonia	Range ORs 0.24-8*
	Non-vaccine-type pneumococcal pneumonia	Range ORs 0.40-1.13*
13,14	Pneumonia (all causes)	
	Healthy, immunocompetent (n=3)	RR_{fixed} 0.56 [0.47;0.66]§ NNT 29 [24;36]
	Elderly or high risk (n=5)	RR_{fixed} 1.08 [0.92;1.27]§
	Pneumococcal pneumonia	
	Healthy, immunocompetent (n=3)	RR_{fixed} 0.16 [0.11;0.23]§ NNT 38 [33;45]
	Elderly or high risk (n=7)	RR_{fixed} 0.88 [0.72;1.07]§
	Lower airway infections	
	Healthy, immunocompetent (n=2)	RR_{fixed} 0.85 [0.71;1.02]§
	Elderly or high risk (n=3)	RR_{fixed} 1.06 [0.97;1.16]§
	Pneumonia-related mortality	
	Healthy, immunocompetent (n=1)	RR_{fixed} 0.70 [0.50;0.96]§ NNT 213 [114;1660]
	Elderly or high risk (n=8)	RR_{fixed} 0.93 [0.72;1.20]§
	Pneumococcal bacteriaemia	
	Healthy, immunocompetent	RR_{fixed} 0.18 [0.09;0.34]§ NNT 32 [26;44]
	Elderly or high-risk	RR_{fixed} 0.53 [0.14;1.94]§
15	Mortality (all causes)	
	Industrialised (n=8)	RR_{fixed} 1.07 [0.97;1.18] R_{random} 1.07 [0.97;1.18]
	High risk (n=3)	RR_{fixed} 1.20 [1.00;1.42] R_{random} 1.15 [0.87;1.52]
	Elderly (1)	RR_{fixed} 0.99 [0.80;1.22] R_{random} 0.99 [0.80;1.22]
	Nonindustrialised (n=1)	RR_{fixed} 0.79 [0.63;0.99] R_{random} 0.79 [0.63;0.99]
	Pneumonia (all causes)	
	Industrialised (n=9)	RR_{fixed} 1.06 [0.97;1.17] R_{random} 1.03 [0.86;1.25]
	High risk (n=3)	*RR_{fixed} 1.17 [0.86;1.60] R_{random} 1.13 [0.79;1.62]
	Elderly (n=2)	RR_{fixed} 1.15 [0.95;1.40] R_{random} 1.15 [0.95;1.40]
	Nonindustrialised (n=3)	RR_{fixed} 0.67 [0.52;1.87] R_{random} 0.67 [0.52;1.87]

Table continued on the next page.

Table 3 continued
Outcomes of systematic reviews

REFERENCE	OUTCOME MEASURES (NUMBER OF STUDIES)	POOLED OUTCOMES [95% CI], STATISTICAL HETEROGENEITY
15	Pneumococcal pneumonia	
	Industrialised (n=5)	RR_{fixed} 1.06 [0.82;1.37] R_{random} 1.06 [0.82;1.38]
	High risk (n=2)	RR_{fixed} 1.07 [0.58;1.97] R_{random} 0.91 [0.33;2.53]*
	Elderly (n=2)	*RR_{fixed} 1.02 [0.75;1.40] R_{random} 1.01 [0.69;1.49]*
	Nonindustrialised (n=0)	-
	Bacteriaemia (pneumococci)	
	Industrialised (n=6)	RR_{fixed} 0.53 [0.22;1.29] R_{random} 0.53 [0.20;1.43]
	High risk (n=1)	RR_{fixed} 0.81 [0.05;12.16] R_{random} 0.81
	Nonindustrialised (n=1)	[0.05;12.16] RR_{fixed} 0.14 [0.02;1.14] R_{random} 0.14 [0.02;1.14]

OR = odds ratio; RR = relative risk; RD = risk difference (calculated as the difference in 'events' between intervention and control group per 1000 subjects); fixed = calculated according to the fixed effects model; random = calculated according to the random effects model.
** statistical heterogeneity between the studies; @ fewer than two studies: statistical heterogeneity not tested by authors; ∫ because of limited sensitivity of fixed-effects model the authors do not report on statistical heterogeneity; everything pooled with fixed-effects model.*

those performed in nonindustrialised countries. Subsequently the high-risk patients and the elderly are presented separately in subgroups.

The following tendencies can be seen:
- Vaccination is more effective in low-risk groups.[11,13,15]
- Vaccination does not appear to be effective in high-risk patients and the elderly.[11,13,15]
- Vaccination is more effective in nonindustrialised countries.[15]
- The outcomes based on the various outcome measures can show major differences.[11-15]

Randomised clinical trials and comparative cohort studies
There are two trials involving elderly people in Western countries that investigate the effectiveness of the pneumococcal vaccination as complementary to the influenza vaccination.[1,2] In addition there is one recent (non-randomised) retrospective cohort study.[17,18]

These three studies appeared relatively recently and are not included in all the SRs. For this reason we discuss them separately here (*tables 4* and *5*).

It is remarkable that the trial carried out by Koivula *et al.*[1] was not published until 12 years after completion of the study. The study performed by Honkanen *et al.*[2] is not truly randomised. The patients were divided up according to date of birth. It is known that pseudo-randomisation of this type can lead to bias (generally because of overestimation of the effect).[19,20]
Both studies are so badly described that some items regarding quality assessment could not be completed.

The outcomes of the trial carried out by Honkanen *et al.*[2] all point to the lack of an effect. In the trial by Koivula *et al.*[1] a large number of subgroup analyses are used to identify a single subgroup that runs a 'greater risk' of pneumococcal pneumonia and the summary of the trial seems to indicate that the study has been positive. The subgroup (30% of the total population) consists of elderly persons with 'risk factor for pneumococcal pneumonia': aged ≥70 years, cardiac diseases, lung diseases, asthma, alcoholism, institutionalised life or bed-ridden. It is unclear whether this subgroup was defined beforehand or subsequently assembled on the basis of the results of the study. If the latter is the case (certainly in view of the large number of analyses carried out) the result is not very convincing.[21] In addition, account should be taken of the fact that for all the pneumonias together (including pneumococcal pneumonia) no protective effect was observed (see figures in *table 4*).

The retrospective cohort study done by Nichol *et al.*[17,18] involved a selected population, namely elderly people with a chronic lung disease. With regard to many methodological aspects the study was described in an insufficiently detailed manner to permit adequate assessment of the methodological quality (see *table 5*). The study is particularly interesting (account taken of the limitations imposed by the study design and the population selection) for the comparison with the Dutch situation with regard to the added value of the pneumococcal vaccination as a supplement to the influenza vaccination.
The study was retrospective in nature and thus sensitive to selection bias. And, indeed, there were some major differences as regards baseline between the various groups. Those administered pneumococcal vaccine were generally younger, healthier, had had pneumonia less often and had previously been vaccinated more often against influenza prior to the study. Interpretation of these figures uncorrected for the differences[18] is therefore

Table 4
Trials carried out in the elderly in Western countries investigating the effectiveness of the pneumococcal vaccination as a supplement to the influenza vaccination

	REFERENCE 1	REFERENCE 2
Study design		
Country	Finland	Finland
Period of trial	1982-1985	1992-1994
Inclusion	Elderly people ≥60 years	Elderly people ≥65 years
Exclusion	Not described	Acute febrile illnesses, terminal illnesses
Intervention	14-valent pneumococcal vaccine plus influenza vaccine (valency not described) (n=1364) versus placebo and influenza vaccine (n=1473)	23-valent pneumococcal vaccine plus 3-valent influenza vaccine (n=13,980) versus placebo and influenza vaccine (n=12,945)
Outcome measures	Pneumonia	Pneumococcal pneumonia
Pneumonia	Pneumococcal pneumonia	Pneumococcal bacteriaemia
Follow-up	3 years	3 years
Methods		
Randomisation	Yes	Pseudo-random (allocation according to date of birth)
Allocation blinded	Yes	No
Complete follow-up	Information insufficiently detailed	Information insufficiently detailed
Intention-to-treat	Yes	Yes
Patients blinded	Yes	Information insufficiently detailed
Medical staff blinded	Yes	Information insufficiently detailed
Effect assessors blinded	Yes	Information insufficiently detailed
Comparability of groups at baseline	Yes	Yes
Prevention of co-interventions	Information insufficiently detailed	Information insufficiently detailed
Outcomes		
	Pneumonia RR 1.16 [95% CI 0.83-1.62]	Pneumonia RR 1.2 [95% CI 0.9-1.5]
	Pneumococcal pneumonia RR 0.85 [95% CI 0.51-1.42]	Pneumococcal pneumonia RR 1.2 [95% CI 0.8-1.9]
	The only statistically significant outcome from 15 analyses is the RR for pneumococcal pneumonia for the 'higher-risk group': RR 0.42 [95% CI 0.19-0.94]	Pneumococcal bacteriaemia RR 0.4 [95% CI 0.1-1.9]
	For the same 'higher-risk group' for the all pneumonias (including pneumococcal pneumonia) outcome RR 0.99 [95% CI 0.63-1.57]	

somewhat tricky. In the other article[17] baseline corrections were carried out. But correction is in no way a satisfactory solution to the problem of nonrandomisation[19] so that these figures should also be interpreted with caution. It is only in the article in which the baseline differences are corrected[17] that the added value of pneumococcal vaccination as a supplement to influenza vaccination is reported. But the reliability intervals are wide, making interpretation difficult.

DISCUSSION

A question currently topical in the Netherlands is whether pneumococcal vaccination should be introduced for (all) elderly people as a supplement to the influenza vaccination. This report takes a critical look at the available comparative studies into the effectiveness of the pneumococcal vaccination.

To this end, the available SRs[11-15] were first assessed as to quality and investigated as to mutual differences. This showed that there are major differences between the systematic reviews with regard to the selection of studies, the distinction made in the valency of the vaccines, the division into subgroups and the choice of the outcome measures accorded the greatest value. It is remarkable that three of the SRs[12-15] were published within a relatively short period and two trials that best matched up to the research question[1,2] were sometimes included and sometimes not.

Table 5
Comparative cohort studies in elderly people in Western countries investigating the effectiveness of pneumococcal vaccination as a supplement to influenza vaccination

	REFERENCE 17,18
Characteristics of study	
Country	United States
Research period	1993-1995
Inclusion	Elderly patients ≥65 years with a chronic lung disease
Exclusion	Not described
Intervention	Pneumococcal vaccine, perhaps in combination with influenza vaccine; vaccinated with pneumococcal vaccine n=1280; not vaccinated with pneumococcal vaccine n=618
Outcome measures	Admitted to hospital with pneumonia or influenza Mortality
Follow-up	Two years
Methods	
Randomisation	No (retrospective cohort study 1993-1996)
Allocation blinded	No
Complete follow-up	Information insufficiently detailed
Intention-to-treat analysis	Information insufficiently detailed
Patients blinded	No
Medical staff blinded	No
Effect assessors blinded	Information insufficiently detailed
Comparability groups on baseline	No; insufficiently corrected for in analyses (see also text)
Prevention of co-interventions	Information insufficiently detailed
Outcomes	*Corrected for baseline differences*[17] Admitted to hospital with pneumonia or influenza $RR_{\text{pneumococcal vaccine}}$ RR 0.57 [95% CI 0.38-0.84] $RR_{\text{pneumococcal and influenza vaccine}}$ RR 0.28 [95% CI 0.14-0.58] Mortality $RR_{\text{pneumococcal vaccine}}$ RR 0.71 [95% CI 0.56-0.91] $OR_{\text{pneumococcal and influenza vaccine}}$ (unclear why suddenly OR) = 0.18 [95% CI 0.11-0.31]
	Not corrected for baseline differences, pneumococcal and influenza vaccines reported on separately[18] Admitted to hospital with pneumonia or influenza $RR_{\text{pneumococcal vaccine}}$ RR 0.73 [95% CI 0.48-1.13] $RR_{\text{influenza vaccine}}$ RR 0.48 [95% CI 0.28-0.82] $RR_{\text{pneumococcal and influenza vaccine}}$ RR 0.37 [95% CI 0.20-0.71] Mortality $RR_{\text{pneumococcal vaccine}}$ RR 0.66 [95% CI 0.48-194] $RR_{\text{influenza vaccine}}$ RR 0.30 [95% CI 0.11-0.43] $RR_{\text{pneumococcal and influenza vaccine}}$ RR 0.11 [95% CI 0.12-0.32]

Analysis of the SRs shows that the pneumococcal vaccination has greater effect in low-risk groups, is not effective in high-risk patients and the elderly, is more effective in industrialised countries and that outcomes can differ greatly in the various outcome measures.

The studies into the effectiveness of the pneumococcal vaccination in the elderly (one RCT,[1] one pseudo-random study[2] and one retrospective study[17,18]) all showed major methodological shortcomings. For the majority of outcome measures the outcomes were negative.

It can be stated in conclusion that there is insufficient convincing evidence in favour of the introduction of the pneumococcal vaccination as a supplement to the influenza vaccination for the elderly. It seems as if (international) opinion had already been fully formed before published studies and systematic reviews became available in the last few years.

At present there is a lack of methodologically responsible randomised research into this specific indication. It is perhaps worth considering setting up a prospective trial in the elderly Dutch population. In calculating the size of the sample population required it should be realised that the above considerations indicate that the predicted effect will be limited. This applies in particular to the nonpneumococcal-related general outcomes such as 'all types of pneumonia' (thus not only pneumococcal-related), 'admission to hospital' and 'mortality'.

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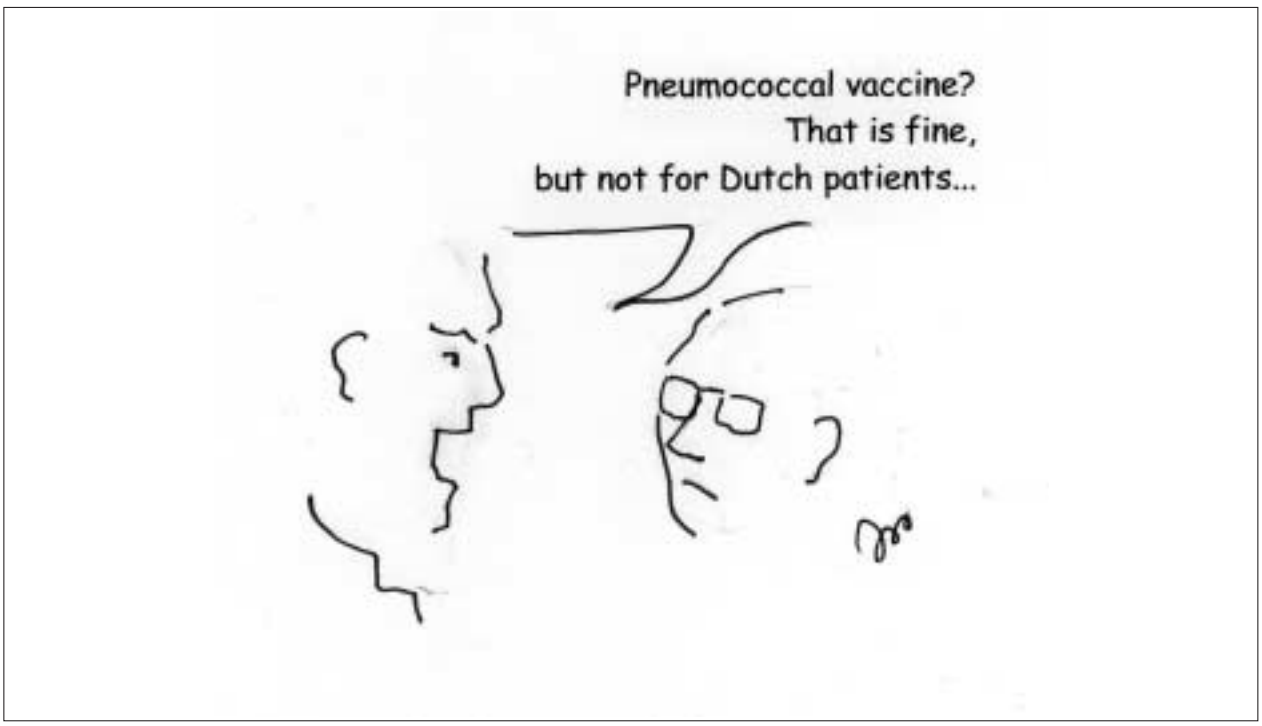

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