Meta-analysis

Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials

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Abstract

The objective was to review the evidence of effectiveness of the polyvalent polysaccharide pneumococcal vaccine from prospective properly randomised controlled trials comparing pneumococcal vaccines with placebo in subjects who are immunocompetent and those likely to have an impaired immune system.

Databases searched included the Cochrane Library, (issue 2, 2000), MEDLINE (1966-August 2000), PubMed (to August 2000) and EMBASE (to August 2000). Reference lists of reports and reviews were also searched. To be included in the analysis, a study had to have been a prospective randomised comparison of a polysaccharide pneumococcal vaccine (any valency) and to have a placebo or no treatment comparison group. Papers had to report important clinical outcomes, such as rates of pneumonia, pneumococcal pneumonia, lower respiratory tract infections, pneumonia deaths or bacteraemia. Serological outcomes were not sought.

Thirteen randomised comparisons with over 45,000 subjects were identified in an extensive literature review. Eight studies had a quality score of 3 or more on a scale of 1 to 5. In three comparisons with 21,152 immunocompetent subjects (South African gold miners, New Guinea highlanders) pneumococcal vaccination was effective in reducing the incidence of all-cause pneumonia (relative risk 0.56, 95% confidence interval 0.47 to 0.66), pneumococcal pneumonia (0.16; 0.11 to 0.23), pneumonia deaths (0.70; 0.50 to 0.96) and bacteraemia (0.18; 0.09 to 0.34). In ten comparisons in over 24,000 people who were elderly or likely to have impaired immune systems, pneumococcal vaccination was without effect for any outcome.

Present guidelines recommend pneumococcal vaccination for "high-risk" groups. There is no evidence from randomised trials that this is of any benefit.

Introduction

Efforts to develop an effective pneumococcal vaccine date from the beginning of the last century. Polyvalent pneumococcal polysaccharide vaccine has now been available for many years, yet controversy persists as to its clinical efficacy [1,2]. At the time the vaccine was licensed there were only two published randomised trials, both carried out in unique populations of young, healthy people at extraordinarily high risk of pneumococcal disease. The dearth of randomised trials led to several retrospective studies using case-control and indirect cohort methods [3]. Although these types of studies can provide useful data on the efficacy of a vaccine, they are limited by the problems inherent in these methods. Furthermore, the available retrospective studies have examined different outcomes, by different methods, and reached

substantially different conclusions regarding the vaccine's efficacy for various subgroups of patients at risk for pneumococcal infection.

Since the current pneumococcal vaccine was licensed in 1979 several trials have been performed on populations more representative of those for whom the vaccine is recommended in the Western world. Thus an alternative way to examine the value of the vaccine is to conduct a meta-analysis of the available randomised trials. One such meta-analysis published in 1994 included nine randomised trials conducted in adults with vaccines of 12 to 17 valencies [4]. The authors concluded that pneumococcal vaccination significantly reduced the risk of definitive (or bacteraemic) pneumococcal pneumonia, but only in low-risk populations, i.e., those younger than 55 years old and without chronic medical or immunosuppressing conditions. Vaccination did not reduce the incidence of pneumonia of all causes, bronchitis, mortality due to pneumonia or pneumococcal infection, or mortality of all causes. The inconsistency between the lack of efficacy of the vaccine in elderly and high-risk patients and the nearly universal recommendations for its use in those populations is obvious. This conflict has important implications for both individual clinicians and health policy organisations. A subsequent meta-analysis [5] of 13 studies published up to 1986 included three quasi randomised studies. It concluded that pneumococcal vaccination was effective, but that 2520 people would have to be vaccinated to prevent one case of pneumococcal bacteraemia per year.

Although the price of an individual dose of vaccine is relatively low the aggregate financial and administrative costs of providing pneumococcal vaccination (and often re-vaccination) to the many subgroups of patients for whom it is currently recommended is substantial. Unlike in the United States, the UK Department of Health's recommendations for pneumococcal vaccination excludes those at risk through age alone [6]. Some advocate extending the policy to include universal vaccination of everyone aged 65 years and over [7]. Before additional efforts are made to encourage increased use of this vaccine it is crucial to try to determine its value. Several additional randomised trials, two with the newer 23-valent vaccine, have been conducted in elderly or high-risk populations. We therefore conducted another meta-analysis of all available randomised trials of polyvalent pneumococcal vaccine to evaluate its efficacy in populations that are immunocompetent and those that are likely to have an impaired immune system.

Methods

We attempted to locate all randomised comparisons of pneumococcal vaccines with placebo in any type of population. Databases searched included the Cochrane Library, (issue 2, 2000), MEDLINE (1966-August 2000), PubMed (to August 2000) and EMBASE (to August 2000) using "Pneumococcal", "vaccine", and variations on these as free text terms. Abstracts were examined and copies of qualifying papers (any language) were obtained and read by all authors. Reference lists from papers obtained and two previous overviews [4,5] were also examined.

To be included in the analysis, a study had to have been a prospective randomised comparison of a polysaccharide pneumococcal vaccine (any valency) and to have a placebo or no treatment comparison group. Because of the potential for bias, a prior decision was taken not to include studies with quasi-randomised design (alternate, date of birth etc). Papers had to report at least one clinical outcome of interest, such as rates of pneumonia, pneumococcal pneumonia, lower respiratory tract infections, pneumonia deaths or bacteraemia. The intention was to analyse outcomes according to whether vaccine recipients were likely to have healthy or impaired immune responses for whom pneumococcal vaccination is indicated in guidelines. Serological outcomes were not sought.

Each report was read independently by all authors and scored using a validated three-item quality scale [8]. Discussion and review achieved consensus. The maximum score for an included study was 5 and the minimum score was 1.

Relative benefit and relative risk estimates were calculated with 95% confidence intervals using a fixed effects model [9] because of the unreliability of statistical tests of heterogeneity [10]. Number-needed-to-treat with 95% confidence intervals was calculated by the method of Cook and Sackett [11]. A statistically significant difference from control was assumed when the 95% confidence interval of the relative risk did not include 1. Calculations were performed using Excel98 on a Power Macintosh G3.

Results

We found 12 reports of 13 randomised comparisons of polyvalent polysaccharide pneumococcal vaccines for inclusion with a total of 45,226 subjects ([12,13,14,15,16,17,18,19,20,21,22,23] Table 1). The report by Austrian et al, 1980 [15] comprised two separate trials. All but one [16] of the reports was in English. Eleven papers were published in scientific journals and one was available only as final report to the US National Institute of Health [15]. Four reports were excluded, three (with 54,863 patients) had a quasi-randomised design [24,25,26] and one [27] described the use of pneumococcal vaccine in children for protection against acute otitis media.

Three comparisons [12,13,14] reported outcomes in 21,152 healthy, mostly young, adults likely to have a normal immune system. Ten [15,16,17,18,19,20,21,22,23] reported outcomes on 24,074 people likely to have an impaired immune system because of age or ill health. Because of the potential importance of a competent immune system in determining the efficacy of pneumococcal vaccines, we divided the studies by this criterion.

The comparisons used a number of different pneumococcal polysaccharide vaccines. Five [12,13,14,15] administered vaccines that were not licensed. Vaccine valencies varied; one used a 6 or 12-valent vaccine, two a 12-valent, six a 14-valent, one a 15-valent, one a 17-valent and two a 23-valent vaccine. The follow-up period for outcomes was a minimum of one year and a maximum of five years; most were two or three years (Table 1). Quality of comparisons was mixed; one scored 5 points, three scored 4, four scored 3, four scored 2 and one scored 1. The major flaw was in lack of double blinding in six comparisons (Table 1).

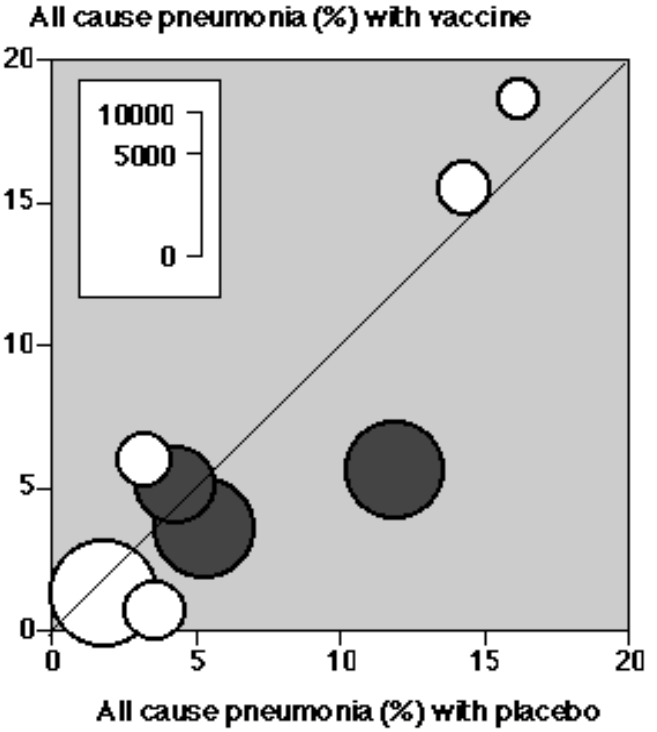

Figure 1

Effect of pneumoccocal vaccination on all cause pneumonia in people who were immunocompetent (filled circles) and immunocompromised or elderly (open circles). Size of symbol is proportional to number of people in the trial.

All pneumonias

Three comparisons had information on 14,567 immunocompetent persons [12,13,14]. The rate of pneumonia without vaccination was 6.5% (Figure 1; Table 2); in vaccinated people the relative risk of pneumonia was 0.56 (95%CI 0.47 to 0.66). The number-needed-to-treat in this population was 29 (24 to 36). This means that 29 African novice gold workers or Papua New Guinea highlanders would have had to have been vaccinated (in 1977) in order to prevent the occurrence of pneumonia in one of them. In five comparisons comprising 7,837 elderly or high-risk patients [15,16, 21,22,23] the rate of pneumonia without vaccination was 6.8%; pneumococcal vaccination had no effect, with a relative risk of 1.08 (0.92 to 1.27).

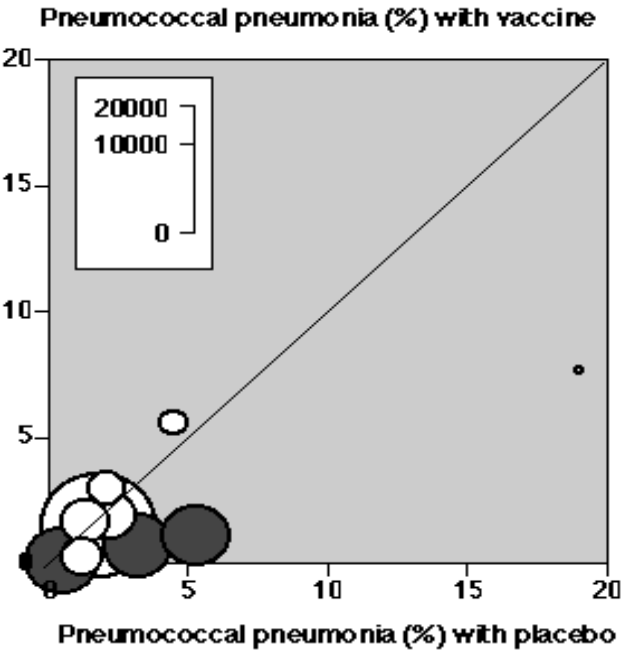

Figure 2

Effect of pneumoccocal vaccination on pneumoccocal pneumonia in people who were immunocompetent (filled circles) and immunocompromised or elderly (open circles). Size of symbol is proportional to number of people in the trial.

Pneumococcal pneumonia

Three comparisons had information on 14,567 immunocompetent persons [12,13,14]. The rate of pneumococcal pneumonia without vaccination was 3.1% (Figure 2; Table 2). In vaccinated people the relative risk of pneumococcal pneumonia was 0.16 (0.11 to 0.23) and the number needed to treat was 38 (33 to 45). In seven comparisons on 22,479 elderly or high-risk patients [15,16,17,18, 21,22,23] the rate of pneumococcal pneumonia without vaccination was 1.9%; pneumococcal vaccination had no effect, with a relative risk of 0.88 (0.72 to 1.07).

Lower respiratory tract infection

Two comparisons [13,14] had information on 10,067 immunocompetent persons. The rate of lower respiratory tract infection without vaccination was 5.6% (Figure 3; Table 2). For this endpoint the vaccine was without effect, with a relative risk for lower respiratory tract infection of 0.85 (0.71 to 1.02). In three [15,18] comparisons on 17,195 elderly or high-risk patients the rate of lower respiratory tract infection without vaccination was 9.4%; pneumococcal vaccination had no effect, with a relative risk of 1.06 (0.97 to 1.16).

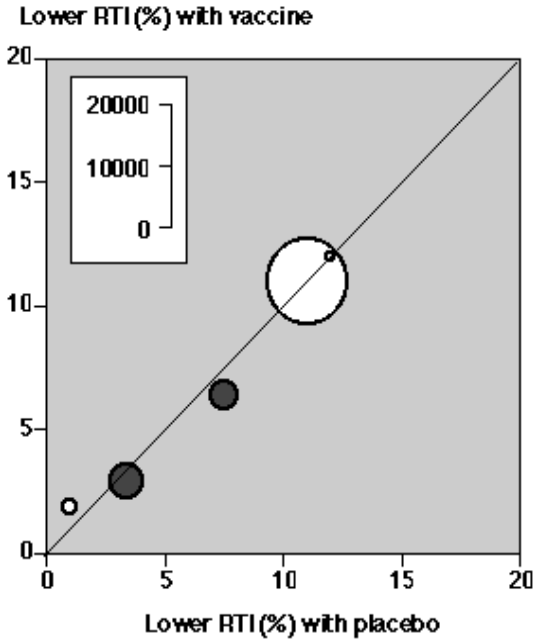

Figure 3
Effect of pneumoccocal vaccination on lower respiratory tract infection in people who were immunocompetent (filled circles) and immunocompromised or elderly (open circles). Size of symbol is proportional to number of people in the trial.

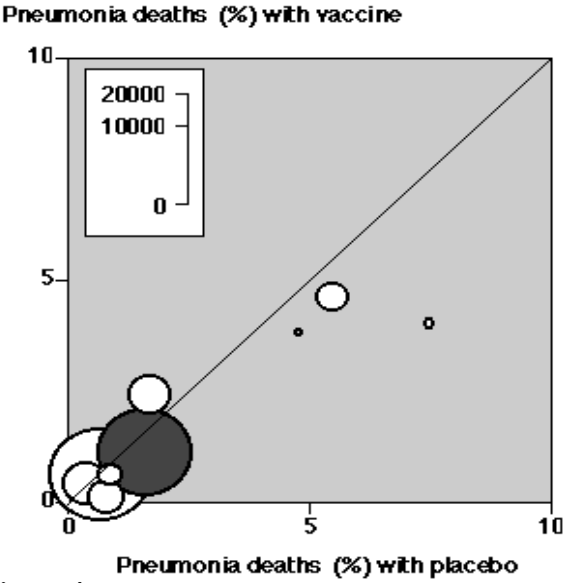

Figure 4
Effect of pneumoccocal vaccination on pneumonia deaths in people who were immunocompetent (filled circles) and immunocompromised or elderly (open circles). Size of symbol is proportional to number of people in the trial.

Pneumonia death

One comparison [14] had information on 11,958 immunocompetent persons. The rate of pneumonia death without vaccination was 1.6% (Figure 4; Table 2). In vaccinated people the relative risk of pneumonia death was 0.70 (0.50 to 0.96) with a number-needed-to-treat of 213 (114 to 1660). In seven comparisons on 22,559 elderly or high-risk patients [15,16,17,18,19, 21,22] the rate of pneumonia death without vaccination was 1.1%; pneumococcal vaccination had no effect, with a relative risk of 0.93 (0.72 to 1.20).

Bacteraemia

One comparison [12] had information on 5,427 immunocompetent persons. The rate of bacteraemia without vaccination was 3.8%. In vaccinated people the relative risk of bacteraemia was 0.18 (0.09 to 0.34). The number-needed-to-treat was 32 (26 to 44). In three comparisons on 927 elderly or high-risk [17,20,22] the rate of bacteraemia without vaccination was 1.4%; pneumococcal vaccination had no effect (Figure 5; Table 2), with a relative risk of 0.53 (0.14 to 1.94).

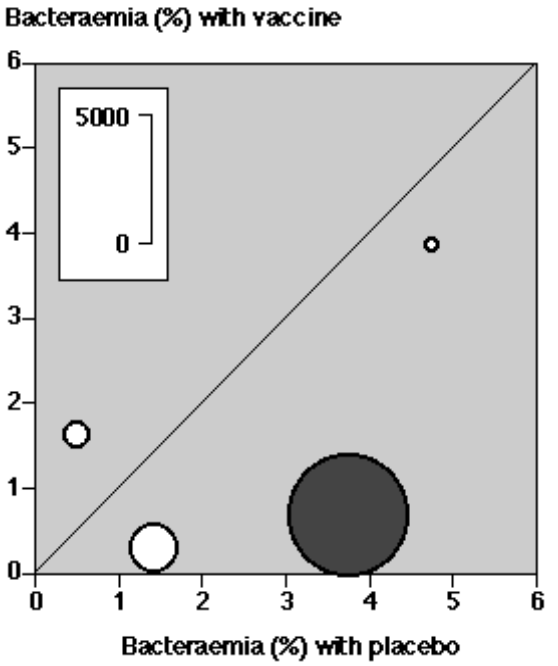

Figure 5
Effect of pneumoccocal vaccination on bacteraemia in people who were immunocompetent (filled circles) and immunocompromised or elderly (open circles). Size of symbol is proportional to number of people in the trial.

Adverse effects

Few studies reported adverse effects. Erythema and induration were reported almost 20 times more frequently with vaccine than with control in one study [15]. In another, higher rates of sore arm, swollen arm and fever were reported in vaccine recipients [14].

Randomised studies of pneumococcal vaccination

						Number affected/total							
Reference	Patient population	Number of patients	Vaccine type/Follow up	Diagnostic endpoints	Diagnostic criteria	All cause pneumonia	Pneumocccal pneumonia	Pneumococcal bacteraemia	LRTI	Pneumonia death	Adverse effects	Comments	Quality
Austrian, 1976	South African novice gold mine workers	4500	15 valent/placebo 2 years	1:Putative pneumococcal pneumonia and/or bacteraemia 2:Radiological pneumonia	1:Not given 2:X-ray	84/1493 358/3007	17/1493 160/3007	10/1493 113/3007				Meningococcal vaccine and placebo combined. Methods not presented.	R2 DB0 W0
Smit et al, 1977	South African novice gold mine workers	4694	6 or 12 valent/placebo about 2 years	1:Pneumonia 2:Bronchitis 3:Pneumococcal pneumonia	1:3 or more symptoms ' X-ray confirmation for pneumonia 2:Bronchitis not specifically defined ' X-ray 3:Culture	55/1523 169/3171	10/1523 103/3171		97/1523 238/3171		No clinically important reactions	Pneumonia occurring more than 14 days after vaccination.	R1 DB0 W0
Riley et al, 1977	Papua New Guinea highlanders	11958	14 valent/placebo 16 months	1:Pneumonia 2:LRTI 3:Respiratory death	1:Clinical ' X-ray 2:Sick, cough, pulmonaryinvolvement 3:Questioning of relatives for symptoms of pneumonia	36/2713 48/2660	2/2713 14/2660		78/2713 90/2660	68/5946 94/6012	3% with swollen arm 24% sore arm 7% fever in 131 patients	LRTI do not include pneumonia	R1 DB2 W0
Austrian, 1980 [1]	Institutionalised mentally ill patients	1300	12 valent/placebo 3 years	1:Respiratory illness 2:Clinical pneumonia 3:Radiological pneumonia 4:Pneumococcal pneumonia	1:Clinically diagnosed 2:Clinically diagnosed 3:X-ray positive 4:X-ray positive seropositive pneumonia	94/607 99/693			75/607 80/693	28/607 38/693	Erythema 213/607 12/693 Induration 79/607 4/693	LRTI do not include pneumonia	R1 DB2 W0
Austrian, 1980 [2]	Ambulatory population > 45 years in a health plan	13600	12 valent/placebo 30 months	1:Respiratory illness 2:Clinical pneumonia 3:Radiological pneumonia 4:Pneumococcal pneumonia	1:Clinically diagnosed 2:Clinically diagnosed 3:X-ray positive 4:X-ray positive seropositive pneumonia		99/6782 123/6818		749/6782 723/6818	44/6782 46/6818		Pneumococcal pneumonia here is more properly pneumococcal illness. LRTI includes pneumonia. Patients taken rather than number of ilnesses.	R2 DB0 W0
Gaillat et al, 1985	Persons >55 years living in residential homes and hospitals	1686	14 valent/untreated control 2 years	1:Pneumonia 2:Pneumococcal pneumonia 3:Mortality	1:Definitions of pneumonia varied	7/937 27/749	3/937 9/749			1/937 6/749		Study undertaken in 50 hospitals and homes in one district	R1 DB0 W1

Randomised studies of pneumococcal vaccination

Klastersky et al, 1986	Patients with bronchogenic carcinoma	50	17 valent/placebo Up to one year	1:Pneumococcal infection 2:Pneumococcal bacteraemia 3:Pneumococcal death	1:Febrile episodes with pneumococci + X-ray 2:as 1 plus blood culture		2/26 4/21	1/26 1/21		1/26 1/21	No adverse reactions noticed	Most patients receiving therapy likely to impair immunological responses.	R1 DB0 W1
Simberkoff et al, 1986	Persons >55 years and increased risk	2295	14 valent/placebo mean 2.9 years	1:Proved or probable pneumococcal pneumonia 2:Proved or probable pneumococcal bronchitis 3:Mortality	1:Pneumococcal infection is clinical infection and positive culture 2:Pneumococcal pneumonia is clinical infection, X-ray and positive culture 3:Bronchitis clinical plus negative chest X-ray plus positive culture		19/1145 15/1150		22/1145 12/1150	28/1145 20/1150		LRTI is bronchitis.	R2 DB2 W1
Davis et al, 1987	Patients with chronic obstructive pulmonary disease	103	14 valent/placebo up to 2 years	1:Pneumonia 2:Deaths from pneumonia	1:Clinical, X-ray and positive culture					2/50 4/53			R2 DB1 W1
Leech et al, 1987	Patients with chronic obstructive pulmonary disease	189	14 valent plus influenza vaccine/influenza vaccine plus placebo 2 years	1:LRTI 2:Pneumonia 3:Mortality	1:Fever, cough, sputum characteristics 2:LRTI plus positive X-ray			1/92 0/97				Information by illness episodes not by patients experiencing illness.	R1 DB1 W1
Koivula et al, 1997	People 60 years or older	2837	14 valent plus influenza vaccine/influenza vaccine alone	1:Pneumonia 2:Pneumococcal pneumonia 3:Pneumonia deaths	1:X-ray 2:Serological positive	69/1364 64/1473	26/1364 33/1473			5/1364 6/1473			R2 DB0 W1
Örtqvist et al, 1998	Non-immunocompromised patients aged 50 to 85 years with previous history of community acquired pneumonia	691	23-valent/placebo 5 years	1:Pneumonia 2:Pneumococcal pneumonia 3:Pneumonia deaths	1:Clinical plus X-ray 2:Pneumonia plus culture or serology	63/339 57/352	19/339 16/352	1/339 5/352		2/339 3/352	No serious adverse events		R2 DB1 W1
French et al, 2000	HIV-1 infected Ugandans <55 years (about 14% with previous history of pneumonia)	1323	23-valent/placebo 1 year	1:Invasive pneumococcal disease 2:Pneumococcal pneumonia 3:Allpneumonia	1:All definite and probable invasive pneumococcal disease events	40/667 21/656	20/667 14/656						R1 DB2 W1

Quality scores are R = randomised, DB = double-blinding, W = Withdrawals (Jadad et al, 1996)

Main outcomes of randomized trials of pneumococcal vaccines

Outcome	Patient group	Number of trials	Number of patients	Percent affected without vaccine	Percent affected with vaccine	Relative risk (95%CI)	Number-needed-to-treat (95%CI)
All pneumonias	Healthy immuno-competent	3	14 567	6.5	3.1	0.56 (0.47 to 0.66)	29 (24 to 36)
	Elderly or high risk	5	7 837	6.8	7	1.08 (0.92 to 1.27)	
Pneumococcal pneumonias	Healthy immuno-competent	3	14 567	3.1	0.5	0.16 (0.11 to 0.23)	38 (33 to 45)
	Elderly or high risk	7	22 479	1.9	1.7	0.88 (0.72 to 1.07)	
Lower respiratory tract infection	Healthy immuno-competent	2	10 067	5.6	4.1	0.85 (0.71 to 1.02)	
	Elderly or high risk	3	17 195	9.4	9.9	1.06 (0.97 to 1.16)	
Pneumonia-related death	Healthy immuno-competent	1	11 958	1.6	1.1	0.70 (0.50 to 0.96)	213 (114 to 1660)
	Elderly or high risk	8	22 559	1.1	1	0.93 (0.72 to 1.20)	
Pneumococcal bacteraemia	Healthy immuno-competent	1	5 427	3.8	0.7	0.18 (0.09 to 0.34)	32 (26 to 44)
	Elderly or high risk	3	927	1.4	0.8	0.53 (0.14 to 1.94)	

Note: Details of patient groups are given in the text Numbers-needed-to-treat are only given where there is a statistical benefit of treatment over control.

Discussion

In the Western world pneumococcal vaccine is almost universally recommended for adults who are at high risk for infections caused by *Streptococcus pneumoniae* because of an immuno-compromised state or certain diseases. Furthermore, in many of the nine countries in which it is used it is recommended for all elderly persons. This is in spite of the fact that most recent publications allow that "results of published controlled trials of pneumococcal vaccination in people with risk factors for pneumococcal infection are unclear" [7]. Several, but not all, retrospective studies suggest that it may be effective in preventing invasive pneumococcal disease, at least in immunocompetent people. In 1994 the results of prospective randomised trials suggested the lack of efficacy in most Western populations [4]. Despite this, another systematic review [5] using randomised and quasi-randomised studies, and making no distinction as to types of patients likely to be vaccinated in Western populations, concluded that pneumococcal vaccination was effective. Even so, 2520 older people would need to be vaccinated to prevent one case of bacteraemia at one year [5]. In their sensitivity analysis, excluding studies both quasi-randomised and unblinded studies, statistical significance was lost.

Three additional trials [21,22,23] have been published since 1996 (the date of the last search of the most recent review was November 1996 [5]), and we have included two studies missed by the previous review [19,20]. Improper randomisation has been shown consistently to lead to bias [28,29,30]. We chose not to include three large studies, both old [24,25] and new [26], that were quasi randomised. The two quasi-randomised studies from the 1930s and 1940s (26,000 patients) concluded the vaccine was effective. A recent quasi-randomised study in 27,000 over 65s in Finland found pneumococcal vaccination ineffective.

Though it is alleged that the vaccine is inexpensive, the cost to the NHS in England in 1999 was still a minimum of £5.4 million in prescription cost alone [31]. Additional expense, time and effort are required to implement vaccination policies. Obviously these costs would increase with expanded use of the vaccine. Much emphasis has been placed on the possible beneficial effects of pneumococcal vaccines in reducing pneumococcal bacteraemia. This is a rare event, occurring in about 7/100,000 of the general population [32]. Yet the data from prospective trials in high-risk patients show no statistically significant decrease in pneumococcal bacteraemia in vaccinated patients (0.8% versus 1.4%).

The modern pneumococcal vaccine has now been licensed for two decades, yet the debate over its efficacy persists [1,2]. Part of the reason for the controversy is that the current vaccines were not subjected to randomised controlled trials before their release. It is therefore crucial, despite assertions to the contrary [33] that

the new protein-conjugated pneumococcal vaccines are properly evaluated.

Some advocates of the vaccine argue that logistical difficulties, great expense, and ethical concerns make randomised trials unsuitable for resolving the pneumococcal vaccine controversy [34]. They suggest that properly conducted non-experimental studies offer attractive alternative strategies. But all observational designs are weakened by their reliance on allocation of vaccine by physician and patient preference. They also suffer from the potential for prognostic susceptibility bias, including inequalities of unknown risk factors, and the degree of reliability and availability of information on risk factors. Other sources of bias include those related to exposure-ascertainment, migration, and detection. Furthermore, all non-RCT designs require analytic assumptions to translate results into estimates of protective efficacy. The change from statistically significant results for pneumococcal vaccines when quasi-randomised trials were excluded [5] and the controversy over mammography trials [30] are reasons enough why properly conducted randomised trials are needed.

Even advocates of the pneumococcal vaccine agree, however, that randomised controlled trials are the most powerful design for preventing bias and estimating protection by the vaccine directly, without the need for assumptions [34]. They contend that the prospective controlled trials have been "inconclusive," and that failure to demonstrate efficacy should not be taken as evidence that the vaccine lacks efficacy [2]. There have been 13 RCTs of the multivalent pneumococcal vaccine, and the meta-analysis technique affords a means of combining the data on the 45,295 subjects enrolled in these studies. Our analysis of the available randomised suggests that the trials should be divided by the type of patients enrolled. Three studies have shown that the vaccine is effective (with low numbers needed to treat) in unique populations of healthy young adults at high risk for pneumococcal infection, such as South African gold miners and New Guinea highlanders. These subjects are capable of mounting a vigorous antibody response to the polysaccharide vaccine. They are also exposed to respiratory irritants (mining dust or fireplace smoke), which increases the risk of developing pneumonia. Finally, they share close living and sleeping quarters, which enables easy spread of a virulent strain of *Streptococcus pneumoniae* in the community [35]. This set of unusual circumstances is ideal for demonstrating the potential efficacy of the pneumococcal vaccine. Most pneumococcal infections are, however, sporadic; outbreaks in the antibiotic era caused by a single serotype are rare [36].

In more commonly encountered circumstances the vaccine is not effective. Adults with immunosuppressing conditions, and many with chronic medical disorders, are unable to mount an adequate antibody response to the vaccine [7]. Antibody response and vaccine efficacy are also reduced in the elderly [37],especially after age 75 [38], and wane more quickly [39]. Furthermore, since pneumonia in the elderly is usually caused by aspiration of oropharyngeal secretions, pneumococcal vaccine may prevent infection with *S. pneumoniae* but not pneumonia of other causes. Thus in non-epidemic situations the vaccine may be less effective in preventing pneumococcal infections. Even if the vaccine were effective, vaccinating millions of people in the UK in the hope of preventing perhaps 60% of the 7 cases of pneumococcal bacteraemia/100,000 [32] persons is of dubious value.

In the absence of strong data supporting the efficacy of pneumococcal vaccine, advocates have based their recommendations on the fact that the vaccine is relatively inexpensive and safe. Vaccination routinely causes discomfort at the injection site for a few days, and in perhaps 5-10% of patients this may be sufficient to interfere with daily activities [40]. The results of several of the RCTs, especially that in HIV-infected Ugandans [23] suggest that the vaccine may in fact have adverse effects. If all of the elderly persons and patients with various chronic medical conditions and immunosuppressing diseases that are targeted were to be vaccinated, the aggregate financial and administrative costs would be great. Moreover, since vaccine protection is thought to last only about five years (and perhaps 2-3 years in patients at highest risk), re-immunisation would be necessary for most recipients [35]. This has lead some to recommend monitoring vaccinees' antibody response a few weeks after administration, and annually thereafter, to ensure adequate response and to determine the appropriate time for revaccination [35]. This would greatly add to the cost of a vaccination program, and any potential benefits would have to be balanced against the known harm of vaccination and revaccination [40,41].

In the end it comes down to this: prospective randomised trials in the types of patients targeted in the Western world show the vaccines to be ineffective while retrospective studies show that it may be effective. If ten studies involving over 24,000 high-risk individuals fail to show any benefits, then programmes for mass pneumococcal vaccination need to be re-thought.

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