Clinical effectiveness of pneumococcal vaccine

Meta-analysis

Brian G. Hutchison, MD, MSC, CCFP Andrew D. Oxman, MD, MSC Harry S. Shannon, PHD
Stephen Lloyd, MD, MSC Christopher A. Altmayer Kurien Thomas, MD, MSC

ABSTRACT

OBJECTIVE To determine the clinical effectiveness of pneumococcal vaccine.

DATA SOURCES Computerized searches of MEDLINE, EMBASE, and SCISEARCH databases were performed, reference lists of retrieved articles were reviewed, and first authors of published studies were contacted.

STUDY SELECTION Studies of use of pneumococcal vaccines in adults were included if the study design was a randomized or quasi-randomized controlled trial and at least one of the following clinical outcomes was reported: vaccine-type systemic pneumococcal infection, systemic pneumococcal infection, vaccine-type pneumococcal pneumonia, pneumococcal pneumonia, non–vaccine-type pneumococcal pneumonia.

SYNTHESIS Study quality was assessed and descriptive information concerning the study populations, interventions, and outcome measurements was extracted for 13 trials involving more than 65000 patients. Estimates of vaccine efficacy, based on a meta-analysis of randomized and quasi-randomized trials, were determined for clinical outcomes.

CONCLUSIONS Vaccination with pneumococcal polysaccharide vaccine can be expected to reduce the risk of systemic infection due to pneumococcal types included in the vaccine by 83% and systemic infection due to all pneumococci by 73%. We found no evidence that the vaccine was less efficacious for the elderly, institutionalized people, or those with chronic disease.

RÉSUMÉ

OBJECTIF Déterminer l'efficacité clinique du vaccin antipneumococcique.

SOURCES DES DONNÉES Des recensions par ordinateur ont été réalisées dans les bases de données MEDLINE, EMBASE et SCISEARCH, les listes de références des articles extraits ont été analysées et on a communiqué avec le premier auteur des études publiées.

SÉLECTION DES ÉTUDES Pour être incluses, les études sur le recours au vaccin antipneumococcique chez les adultes devait être conçues sous forme d'essai contrôlé aléatoire ou quasi-aléatoire et au moins une des issues cliniques rapportées devaient être au nombre des suivantes: une infection systémique à pneumocoques du type du vaccin; une infection systémique à pneumocoques; une pneumonie à pneumocoques du type du vaccin; une pneumonie à pneumocoques; une pneumonie à pneumocoques de type différent du vaccin.

SYNTHÈSE La qualité des études a fait l'objet d'une évaluation. Des renseignements descriptifs concernant les populations étudiées, les interventions et la mesure des résultats ont été extraits de 13 études portant sur plus de 65000 patients. Une estimation de l'efficacité du vaccin, fondée sur une méta-analyse des études aléatoires et quasi-aléatoires, a été faite en fonction des issues cliniques.

CONCLUSIONS On peut s'attendre à ce que le vaccin polysaccharide antipneumococcique réduise de 83% le risque d'infection systémique due aux types de pneumocoques que comporte le vaccin et de 73% le risque d'infection systémique causée par tous les types de pneumocoques. Aucune donnée probante n'a été relevée à l'effet que le vaccin serait moins efficace chez les personnes âgées ou en établissement, ou les malades chroniques.

This article has been peer reviewed.
Cet article a fait l'objet d'une évaluation externe.
Can Fam Physician 1999;45:2381-2393.

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Uncertainty about the usefulness of pneumococcal vaccine is reflected in the low levels of vaccine use, the discrepant conclusions of review articles, and conflicting recommendations from authoritative bodies regarding its use. The 1995 United States Behavioral Risk Factor Surveillance System revealed that 35.6% of people older than 65 years had ever received pneumococcal vaccine.[1] This is a substantial increase from 1993 when coverage was 28.7%.[2] This level of vaccination contrasts, however, with a US national health objective to increase pneumococcal vaccination levels to at least 60% among noninstitutionalized, high-risk populations by the year 2000.[3]

In 1996, the Centre d'épidémiologie d'intervention du Québec conducted a survey to determine the level of pneumococcal vaccine coverage among all noninstitutionalized people 18 years or older residing in Quebec.[4] Self-reported vaccination coverage levels were 1.2% (95% confidence interval [CI] 0.5 to 1.9) for the whole population, 1.8% (95% CI 0.0 to 3.8) for people 65 years or older, and 1.9% (95% CI 0.0 to 3.9) for people aged 18 to 64 years with high-risk conditions. Coverage in Canada also appears low based on pneumococcal vaccine distribution data from 1980 to 1993. Distribution levels in Canada were less than eight doses per 10 000 population each year from 1980 to 1989 and increased to 10 to 12 doses per 10 000 population annually from 1990 to 1993.[5]

Among authors of recent editorials, review articles, and policy statements on the subject, there is a distinct lack of consensus regarding vaccine efficacy, disease incidence, cost effectiveness, and appropriateness of immunizing specific target populations.[6-22] Given this background of uncertainty and disagreement regarding the evidence, we undertook a systematic overview of randomized and quasi-randomized (a method of group assignment, such as alternation or allocation based on odd-even birth dates or identification numbers, that falls short of strict randomization) clinical trials of pneumococcal vaccine effectiveness to provide quantitative summary measures of vaccine efficacy.

Dr Hutchison *teaches in the Department of Family Medicine, the Department of Clinical Epidemiology and Biostatistics, and the Centre for Health Economics and Policy Analysis at McMaster University in Hamilton, Ont.* **Dr Oxman** *is on staff in the Department of Health Services Research at the National Institute of Public Health in Oslo, Norway.* **Dr Shannon** *teaches and* **Mr Altmayer** *is a student in the Department of Clinical Epidemiology and Biostatistics at McMaster University.* **Dr Lloyd** *teaches in the Department of Family Medicine at McMaster University.* **Dr Thomas** *teaches in the Clinical Epidemiology Unit at the Christian Medical College and Hospital in Vellore, India.*

Method

Data sources. We searched MEDLINE for reports of primary research published from January 1966 to November 1996. *Index Medicus* was searched manually back to 1938, 2 years before publication of the earliest trial of which we are aware. EMBASE and SCISEARCH were also searched, and the reference lists of all retrieved articles were reviewed. To ensure that all relevant literature was obtained, we wrote to first authors of clinical studies of pneumococcal vaccine effectiveness and to organizations producing immunization guidelines and asked them to identify any other published or unpublished data of which they were aware.

The computer searches and reference lists of all the retrieved articles were reviewed by two of the investigators for studies of clinical effectiveness. Complete texts of all potentially relevant articles were obtained and reviewed by B.G.H. and S.L. using the following inclusion criteria: the target population was adults; the intervention was a pneumococcal (*Streptococcus pneumoniae*) vaccine; at least one clinical outcome was reported; and the study design was a randomized controlled trial or a prospective cohort or case-control study. We report here on randomized or quasi-randomized controlled studies in which one or more of the following clinical outcomes was assessed: vaccine-type systemic pneumococcal infection, systemic pneumococcal infection, vaccine-type pneumococcal pneumonia, pneumococcal pneumonia, and non–vaccine-type pneumococcal pneumonia.

We chose to focus on pneumococcal disease outcomes because they provide a more sensitive and accurate measure of vaccine effectiveness than nonspecific outcomes, such as clinically or radiologically diagnosed pneumonia, which involve dilution of any protective effect of the vaccine by the presence of an unknown number of cases of non-pneumococcal disease. We included the outcome non–vaccine-type pneumococcal pneumonia to assess the possibility that a reduction in pneumococcal infections due to vaccine serotypes might be offset by an increase in infections due to serotypes not included in the vaccine.

Table 1. Methodologic criteria for prospective studies

ALLOCATION	
***	Random
**	Quasi-random (ie, alternate)
FOLLOW UP	
**	Active
*	Passive
?	Cannot tell
COMPLETENESS OF FOLLOW UP	
***	≥90%
**	≥80% and <90%
*	<80%
?	Cannot tell
OUTCOME ASSESSMENT	
****	Blinded or all-cause mortality
***	Death or illness with isolation of *S pneumoniae* from normally sterile tissues or body fluids without blinding, or radiologically confirmed pneumonia without blinding
**	Hospitalization with respiratory illness or clinical illness associated with isolation of *S pneumoniae* without blinding
*	Clinical illness with no blinding
BLINDING OF PROVIDERS AND SUBJECTS	
***	Placebo controlled with blinding of providers and subjects
**	Blinding of subjects only or providers only
*	No blinding
?	Cannot tell

Study selection. The methodologic rigour of each study included was assessed using the criteria shown in **Table 1**. The methodologic quality of each study was independently appraised by three investigators. Disagreements among reviewers regarding assessments of study quality were resolved by consensus.

Age and other characteristics of the study populations, type of vaccine, and raw data on the incidence of clinical outcomes were extracted independently from each study by two investigators. For studies where outcomes were not reported as proportions, rates were used. In the few cases where this occurred, the duration of follow up was short enough that few patients would have experienced more than one episode of disease. Therefore, little, if any, difference would be expected between reported rates and the proportion of patients who experienced one or more events.

Analysis. Common odds ratios (OR) were estimated for each outcome using exact methods with EGRET Statistical Software (prerelease version, Statistics in Epidemiology Research Corp, Seattle, Wash, 1989). In some circumstances, the data set was too large for this procedure and the package was used to calculate an asymptotic (large-sample) combined OR. For both methods, a 95% CI was estimated and the homogeneity of the individual studies' ORs was examined. Statistically significant heterogeneity ($P<.05$) indicates a low probability that differences in results among individual studies are due to chance alone.

When results of studies were statistically significantly heterogeneous for an outcome, logistic regression (using EGRET) was used to test for possible sources of variability in the results. In these analyses, possible explanatory variables were dichotomized, and the following factors were considered: whether the study was a randomized controlled trial, whether the vaccine was ≥12 valent, and whether subjects were exclusively elderly, chronically ill, or institutionalized. Interactions with vaccination status were assessed. A significance level of 5% was used in these analyses.

Although ORs are not identical to relative risks, they provide a good approximation when outcomes are comparatively rare, as in this study. Odds ratios, which are common in meta-analyses, have desirable statistical properties when combining results across studies.[23] In this study, they represent the ratio of the odds of a clinical outcome occurring in those vaccinated with the odds of a clinical outcome occurring in those not vaccinated. Therefore, an OR of less than 1.0 represents beneficial treatment. We treat the OR as equivalent to relative risk in our presentation of results. Relative risk reductions, which are commonly reported measures of dichotomous treatment effects, are also presented as a complement of the ORs.

Our evaluation of study quality was not used to weight studies during aggregation of data. Studies were weighted according to their size, with larger studies receiving more weight. Recognizing that lack of blinding might introduce bias, we conducted a sensitivity analysis in which we excluded the three unblinded trials, thereby assigning zero weight to these trials, to determine if inclusion of these studies had an important effect on overall results.

Synthesis

The MEDLINE search yielded more than 1000 citations; we retrieved more than 250 articles. Among these, 45 reports of 37 independent studies were identified. Twenty independent studies reported in 20 papers referred to adult populations.[24-43] These included 15 prospective studies published between 1945 and 1987,[24-39] one unpublished prospective study (personal communication from P. Helena Mäkelä), and four case-control studies.[40-43] Thirteen were randomized or quasi-randomized controlled studies in which one or more of the five clinical outcomes of interest were assessed.[24-33,35-39]

Descriptive details regarding these 13 studies are presented in **Table 2,**[24-33,35-39] and our methodologic assessment of the studies is summarized in **Table 3.**[24-32,35-39] Only one of these studies fully met all our methodologic criteria.[36] Eleven were randomized trials. The method of allocating patients to vaccine or control groups was mixed (non-random and quasi-random)[24,25] or quasi-random[26] in the other two studies. For more than half the studies, we could not ascertain how complete follow up had been or whether subjects had been actively followed up or investigators had relied on routinely collected data. Main results are summarized in **Table 4,** and results for each clinical outcome are presented in **Tables 5** to **9.**

Systemic pneumococcal disease. Four studies contributed data on systemic infection (positive culture of blood[24,25,28-31] or any normally sterile body fluid[39]) due to pneumococcal types included in the vaccine (**Table 5**[24,25,28-31,39]). The common OR derived from results of all four studies was 0.17 (95% CI 0.09 to 0.31), a risk reduction of 83%.

Six studies assessed systemic infection caused by any pneumococcus, vaccine-type or non–vaccine-type (**Table 6**[24,25,27,36-39]). The common OR derived from all six prospective studies was 0.27 (95% CI 0.13 to 0.49), showing a reduction in risk of systemic pneumococcal infection of 73% with use of pneumococcal vaccine.

Pneumococcal pneumonia. Nine studies contributed data on pneumonia (diagnosed either clinically or radiologically) associated with growth of vaccine-type pneumococci from blood or, more commonly, respiratory secretions (**Table 7**[24-26,28-33,37,39]). In all but one study,[39] pneumococcal vaccination was associated with a reduction in vaccine-type pneumonia, with ORs ranging from 0.08 to 0.85. In six studies, the reduction was statistically significant. Differences in results across studies were greater than would be expected by chance alone ($P<.0001$).

Seven studies assessed pneumococcal pneumonia (defined as clinically or radiologically diagnosed pneumonia associated with growth of pneumococci, either vaccine-type or non–vaccine-type, from blood or respiratory secretions or, in one study,[37] with pneumococcal antigen in the urine) as an outcome (**Table 8**[24-26,33,35-37,39]). In three of these studies[24-26,37] the reduction in pneumococcal pneumonia was statistically significant with ORs ranging from 0.24 to 0.69. Heterogeneity of study results was significant ($P<.0001$).

Non–vaccine-type pneumococcal infection. Five studies contributed data on pneumonia caused by non–vaccine-type pneumococci (**Table 9**[24-26,33,37,39]). In four of the five studies, the observed effect of pneumococcal vaccine on non–vaccine-type pneumonia was not statistically significant, with ORs ranging from 0.40 to 1.13.[26,33,37,39] In Kaufman's cohort quasi-random study[24,25] among institutionalized, mainly elderly subjects, using vaccines containing either two or three pneumococcal serotypes, there was a statistically significant reduction in pneumonia caused by non–vaccine-type pneumococci, with an OR of 0.44 (95% CI 0.27 to 0.68). Heterogeneity of results across the five studies was greater than would be expected by chance ($P=.036$).

Special populations

Elderly people: Seven of the 13 studies included in this overview had substantial numbers of elderly subjects.[24,25,33,35-39] Two of the four studies contributing data on vaccine-type systemic pneumococcal infection[24,25,39] and five of the six studies in which systemic pneumococcal infection was reported as an outcome[24,25,36-39] had study populations that were substantially or exclusively elderly. Therefore, the overall common ORs for vaccine-type systemic pneumococcal infection (common OR 0.17, 95% CI 0.09 to 0.31) and systemic pneumococcal infection (common OR 0.27, 95% CI 0.13 to 0.51) can be assumed to apply to the elderly. Four studies providing data on vaccine-type pneumococcal pneumonia[24,25,33,37,39] and six studies reporting pneumococcal pneumonia as an outcome[24,25,33,35-37,39] had mostly or exclusively elderly subjects. In stepwise logistic regression analysis, there was no significant interaction between vaccination and presence or absence of exclusively elderly or near-elderly study populations for these outcomes.

Chronically ill people: Three studies had populations composed entirely of people with chronic illness,[35,36,38] and two additional studies[37,39] included substantial numbers of chronically ill subjects (27% in one case[37] and at least 69% in the other[39]). Only one of

Table 2. Studies included

FIRST AUTHOR	COUNTRY WHERE STUDY CONDUCTED	DATA COLLECTION PERIOD	DESIGN	SAMPLE SIZE	LIVING SITUATION	CHRONIC DISEASE	% OF ELDERLY	VACCINE VALENCE	DURATION OF FOLLOW UP (MO)			OUTCOME MEASURES				
									LOW	HIGH	MEAN	VACCINE-TYPE SYSTEMIC PNEUMOCOCCAL INFECTION	SYSTEMIC PNEUMOCOCCAL INFECTION	VACCINE-TYPE PNEUMOCOCCAL PNEUMONIA	PNEUMOCOCCAL PNEUMONIA	NON-VACCINE-TYPE PNEUMOCOCCAL PNEUMONIA
Kaufman[24,25] (1947)	US	1937-1943	QCT/NCT*	10 903	INS	NR	79% > 60 y	2,3	NR	NR	18	X	X	X	X	X
MacLeod et al[26] (1945)	US	1944-1945	QCT	17 035	OCL	NO	0	4	NR	7	NR			X	X	X
Riley et al[27] (1977)	NG	NR	RCT	5373	COM	NO	NR	14	16	16	16		X			
Austrian et al (a)[28,29] (1975-1976)	SA	1972-1974	RCT	4497	OCL	NO	0	6	9	NR	NR	X		X		
Austrian et al (b)[29-31] (1975-1977)	SA	1974-1976	RCT	4495†	OCL	MIX	0	13	NR	NR	NR	X		X		
Smit et al (a)[32] (1977)	SA	1973-1975	RCT	3019	OCL	NO	0	6	11	15	NR			X		
Smit et al (b)[32] (1978)	SA	1974-1976	RCT	1675	OCL	NO	0	12	0.1	19	NR			X		
Austrian (c)[33] (1980)	US	1974-1976	RCT	13 690	COM	NO	32% > 65 y	12	21	33	NR			X	X	X
Davis et al[35] (1988)	US	1978-1982	RCT	103	COM	YES	(mean 63 y)	14	1	48	32				X	
Klastersky et al[36] (1986)	BE	NR	RCT	47	COM	YES	(mean 61 y)	17	NR	NR	NR		X		X	
Gaillat et al[37] (1985)	FR	1980-1982	RCT	1686	INS	MIX	100% > 55 y	14	24	24	24		X	X	X	X
Leech et al[38] (1987)	CA	1981-1983	RCT	189	COM	YES	(mean 67 y)	14	24	24	24		X			
Simberkoff et al[39] (1986)	US	1981-1985	RCT	2295	COM	MIX	82% > 55 y	14	NR	NR	35	X	X	X	X	X

BE—*Belgium;* CA—*Canada;* COM—*community dwelling;* FI—*Finland;* FR—*France;* INS—*institutionalized;* MIX—*mixed;* NCT—*non-randomized controlled trial;* NG—*New Guinea;* NO—*none;* NR—*not reported;* OCL—*other communal living;* QCT—*quasi-randomized controlled trial;* RCT—*randomized controlled trial;* SA—*South Africa;* US—*United States;* YES—*all patients had chronic disease.*

* *This study used non-random allocation in the first year and quasi-random allocation in the subsequent 5 years.*

† *7495 for vaccine-type pneumococcal bacteremia.*

Table 3. Methodologic assessments: *Studies are listed in order of methodologic rigour (strongest to weakest) from top to bottom.*

STUDY	ALLOCATION	FOLLOW UP	COMPLETENESS OF FOLLOW UP	OUTCOME ASSESSMENT	BLINDING
Klastersky et al[36] (1986)	***	**	***	****	***
Leech et al[38] (1987)	***	**	Mortality**, morbidity*	****	***
Simberkoff et al[39] (1986)	***	**	?	****	***
Davis et al[35] (1987)	***	?	?	****	***
Riley et al[27] (1977)	***	?	?	****	***
Smit et al (a,b)[32] (1977)	***	?	?	****	***
Austrian (b)[29-31] (1975-1977)	***	?	?	****	***
Austrian (a)[28,29] (1975-1976)	***	?	?	****	***
Gaillat et al[37] (1985)	***	*	***	Systemic pneumococcal infection***, other outcomes**	*
MacLeod et al[26] (1945)	**	?	?	**	?
Kaufman[24,25] (1947)	First year*; after**	?	?	Systemic pneumococcal infection***, other outcomes**	*

For scoring criteria, see **Table 1**.

the four studies in which vaccine-type systemic pneumococcal infection was assessed had a study population of largely chronically ill people.[39] No effect of vaccination was apparent in this study (OR 1.15, 95% CI 0.36 to 3.74). Four of the six prospective studies contributing data on systemic pneumococcal infection had study populations that were exclusively[36,38] or substantially[37,39] chronically ill. Pneumococcal vaccination was not associated with a statistically significant protective effect in any of these studies. Four of the seven studies contributing data on pneumococcal pneumonia had populations composed entirely[35,36] or substantially[37,39] of chronically ill people. In logistic regression analysis, there was no significant interaction between vaccination and presence or absence of subjects who were exclusively chronically ill for this outcome.

Institutionalized people: Three of the 13 studies were conducted in chronic care institutions.[24,25,33,37] Of the four studies contributing data on vaccine-type systemic pneumococcal infection, one[24,25] had an institutionalized study population. Results of that study indicated that vaccination protected against vaccine-type systemic pneumococcal infection (OR 0.07, 95% CI 0.00 to 0.50). Two of the six studies in which systemic pneumococcal infection was reported as an outcome were set in chronic care institutions.[24,25,37] In both these studies, pneumococcal vaccination was associated with a reduction in infection, which in one study[24,25] was statistically significant. Three of nine studies contributing data on vaccine-type pneumococcal pneumonia[24,25,33,37] and three of seven studies contributing data on pneumococcal pneumonia[24,25,33,37] had institutionalized populations. In all three studies, both outcomes were less frequent among those vaccinated. In logistic regression analysis, the vaccine was more effective for institutionalized populations for both vaccine-type pneumococcal pneumonia and pneumococcal pneumonia.

Sensitivity analysis. In our sensitivity analysis, we excluded the three unblinded studies[24-26,38] and, in the process, excluded all studies that involved quasi-random allocation, used vaccines containing less than six pneumococcal serotypes, and were conducted before 1970.[24-26] Exclusion of non-blinded studies had little effect on the common OR for vaccine-type systemic pneumococcal infection (common OR 0.19, 95% CI 0.09 to 0.36 for the sensitivity analysis vs 0.17, 95% CI 0.09 to 0.31 for the main analysis, which included all eligible studies).

Table 4. Main results

OUTCOME	NUMBER OF STUDIES	TOTAL SAMPLE SIZE	RANGE OF ODDS RATIOS	AVERAGE BASELINE RISK/1000 *	TEST FOR HOMOGENEITY (*P* VALUE)†	COMMON ODDS RATIO‡	95% CI‡ LOW	95% CI‡ HIGH
Vaccine-type systemic pneumococcal infection	4	25 190	0.07-1.00	8.8	.25	0.17	0.0	90.31
Systemic pneumococcal infection	6	20 493	0.14 - ∞	4.5	.08	0.27	0.13	0.49
Vaccine-type pneumococcal pneumonia	9	59 295	0.08-1.17	15.7	<.0001			
Pneumococcal pneumonia	7	45 759	0.24 - ∞	11.3	<.0001			
Non–vaccine-type pneumococcal pneumonia	5	45 609	0.40-1.13	6.6	.04			

**Average baseline risk—Total number of events in control groups divided by total number of patients in control groups. Numbers in table represent a weighted average of number of events per 1000 patients for all studies reporting each outcome.*

†P values for χ^2 test for homogeneity of the odds ratios (ORs) calculated using exact method (ie, probability of the observed differences between the ORs from individual studies occurring due to chance alone).

‡The common OR is a weighted average of the ORs from all the studies reporting the outcome where the OR from each study is weighted by the precision of the estimate (1/variance). The 95% confidence intervals are calculated using a fixed effects model. For outcomes with statistically significant heterogeneity, the common OR has not been presented.

For the outcome systemic pneumococcal infection, the common OR increased to 0.53 (from 0.27) in the sensitivity analysis, and the effect of vaccination was no longer statistically significant (95% CI for common OR 0.14 to 1.78). Because there was statistically significant heterogeneity of results across studies for the outcomes vaccine-type pneumococcal pneumonia and pneumococcal pneumonia in both the main analysis and the sensitivity analysis, comparison of common ORs with and without the non-blinded studies is not possible. After excluding the non-blinded studies, the common OR for non–vaccine-type pneumococcal pneumonia was 1.14 (95% CI 0.61 to 2.15) and the statistical heterogeneity of results across studies, which had been present in the main analysis, was eliminated (*P* [heterogeneity] = 1.00).

Effectiveness of the vaccine

Based on available results of randomized and quasi-randomized controlled studies, there is little doubt that pneumococcal vaccine substantially reduces the risk of systemic pneumococcal infection. Risk reduction for systemic pneumococcal infection due to pneumococcal serotypes included in the vaccine was more than 80%. Vaccine-type systemic pneumococcal infection provides the most sensitive measure of the efficacy of pneumococcal vaccine because outcome is based on retrieval of pneumococcal serotypes included in the vaccine from normally sterile body fluids. Risk reduction for systemic pneumococcal infection due to any pneumococcus, vaccine-type or non–vaccine-type, was about 73%.

The vaccine is expected to be less effective against all-type systemic pneumococcal infection than against vaccine-type systemic pneumococcal infection. While pneumococcal vaccine might have some protective effect against pneumococcal serotypes antigenically related to serotypes included in the vaccine, it would not offer protection against other non-vaccine serotypes. Studies by the US Centers for Disease Control (CDC) covering the period May 1978 to April 1992 showed that 67% of unvaccinated patients with systemic pneumococcal infections were infected with serotypes included in the 14-valent vaccine and 88% were infected with serotypes included in the 23-valent vaccine.[44]

Our pooled results from clinical trials for vaccine-type systemic pneumococcal infection are broadly consistent with those obtained in retrospective studies conducted by the CDC comparing serotype distributions of pneumococcal isolates obtained from vaccinated and unvaccinated people,[44] the single case-control study which assessed this outcome,[43] and a prospective cohort study among chronically ill institutionalized elderly people.[34] Our estimate of overall vaccine effectiveness for preventing vaccine-type systemic pneumococcal disease (83% risk reduction), however, which is derived from the combined results of randomized and quasi-randomized studies, is substantially

Table 5. Vaccine-type systemic pneumococcal infection: *Test of heterogeneity* P=.25

STUDY	EXPERIMENTAL EVENTS (N)	CONTROL EVENTS (N)	ODDS RATIO	95% CI
Kaufman[24,25]	1 (5750)	12 (5153)	0.07	0.00-0.50
Austrian (a)[28,29]	2 (1490)	42 (3007)	0.09	0.01-0.37
Austrian (b)[29-31]	8 (2467)	71 (5028)	0.23	0.09-0.47
Simberkoff et al[39]	1 (1145)	1 (1150)	1.00	0.01-78.88
Common odds ratio and 95% CI			0.17	0.09-0.31

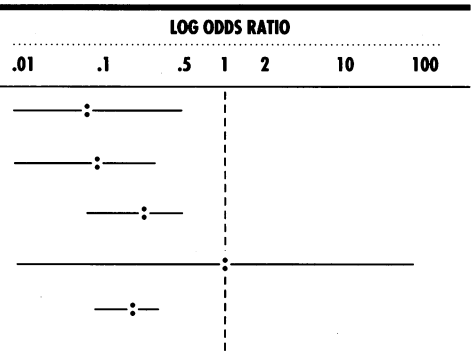


Table 6. Systemic pneumococcal infection: *Test of heterogeneity* P =.08

STUDY	EXPERIMENTAL EVENTS (N)	CONTROL EVENTS (N)	ODDS RATIO	95% CI
Kaufman[24,25]	8 (5750)	34 (5153)	0.21	0.08-0.46
Riley et al[27]	1 (2713)	7 (2660)	0.14	0.00-1.09
Klastersky et al[36]	1 (26)	1 (21)	0.80	0.01-65.90
Gaillat et al[37]	0 (937)	1 (749)	0.00	0.00-31.17
Leech et al[38]	1 (92)	0 (97)	∞	0.03-∞
Simberkoff et al[39]	2 (1145)	1 (1150)	2.01	0.10-118.69
Common odds ratio			0.27	0.13-0.49

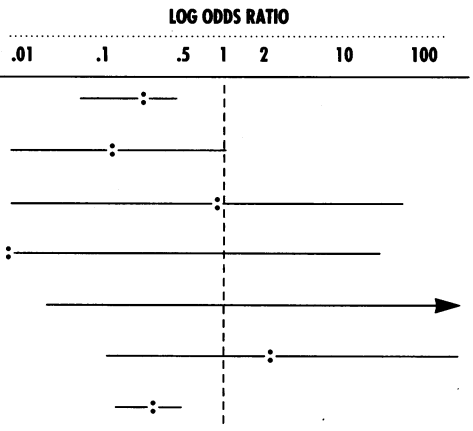


Table 7. Vaccine-type pneumococcal pneumonia: *Test of heterogeneity* P <.0001

AUTHOR	EXPERIMENTAL EVENTS (N)	CONTROL EVENTS (N)	ODDS RATIO	95% CI
Kaufman[24,25]	3 (5750)	33 (5153)	0.08	0.02-0.26
MacLeod et al[26]	4 (8586)	26 (8449)	0.15	0.04-0.44
Austrian (a)[28,29]	14 (1490)	132 (3007)	0.21	0.11-0.36
Austrian (b)[29-31]	17 (1493)	160 (3002)	0.21	0.12-0.34
Smit et al (a)[32]	9 (983)	78 (2036)	0.23	0.10-0.47
Smit et al (b)[32]	1 (540)	25 (1135)	0.08	0.00-0.51
Austrian (c)[33]	24 (6872)	28 (6818)	0.85	0.47-1.52
Gaillat et al[37]	1 (937)	5 (749)	0.16	0.00-1.43
Simberkoff et al[39]	7 (1145)	6 (1150)	1.17	0.34-4.24
Common odds ratio			0.25	0.20-0.33

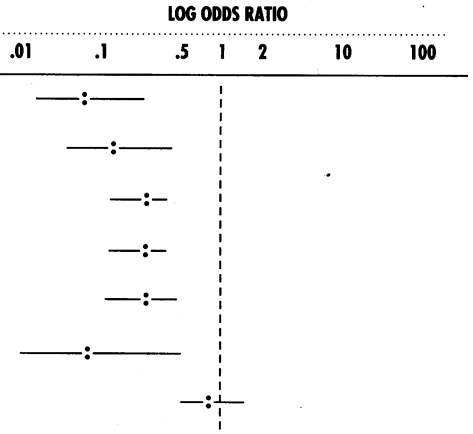


Table 8. Pneumococcal pneumonia: *Test of heterogeneity* P <.0001

STUDY	EXPERIMENTAL EVENTS (N)	CONTROL EVENTS (N)	ODDS RATIO	95% CI
Kaufman[24,25]	34 (5750)	96 (5153)	0.31	0.20-0.47
MacLeod et al[26]	60 (8586)	85 (8449)	0.69	0.49-0.98
Austrian (c)[33]	40 (6872)	42 (6818)	0.94	0.60-1.49
Davis et al[35]	1 (50)	0 (53)	∞	0.03-∞
Klastersky et al[36]	2 (26)	4 (21)	0.36	0.03-2.86
Gaillat et al[37]	3 (937)	10 (749)	0.24	0.04-0.93
Simberkoff et al[39]	16 (1145)	15 (1150)	1.07	0.49-2.34
Common odds ratio			0.58	0.47-0.72

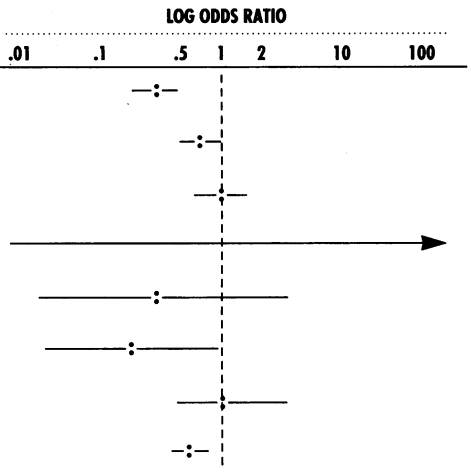
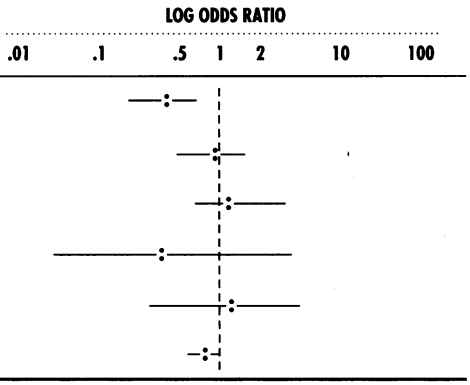


Table 9. Non–vaccine-type pneumococcal pneumonia: *Test of heterogeneity* P <.036

STUDY	EXPERIMENTAL EVENTS (N)	CONTROL EVENTS (N)	ODDS RATIO	95% CI
Kaufman[24,25]	31 (5750)	63 (5153)	0.44	0.27-0.68
MacLeod et al[26]	56 (8586)	59 (8449)	0.93	0.63-1.37
Austrian (c)[33]	16 (6872)	14 (6818)	1.13	0.52-2.51
Gaillat et al[37]	2 (937)	4 (749)	0.40	0.04-2.79
Simberkoff et al[39]	8 (1145)	7 (1150)	1.15	0.36-3.74
Common odds ratio			0.73	0.56-0.94



higher than that obtained in the two retrospective studies: 57%[44] and 56%,[43] respectively. Similarly, for systemic pneumococcal infection due to any pneumococcus (vaccine type or non–vaccine-type), the common estimate of effect derived from clinical trials (73% risk reduction) is greater than estimates of vaccine efficacy obtained in recent case-control studies[40-43] (range 0 to 67%).

Because the vaccines assessed in the 13 prospective studies included in our analysis contained from two to 17 pneumococcal serotypes, our results might underestimate the effect of the current 23-valent vaccine on this outcome. The basis for the lower estimates of vaccine effectiveness from case-control studies is not clear. Possibilities include overmatching and ascertainment bias.

Heterogeneity of results

The heterogeneity of results across studies for the outcomes pneumococcal pneumonia and vaccine-type pneumococcal pneumonia might be related in part to unreliability and variability of outcome measurement. Diagnosis of pneumococcal pneumonia is usually made on the basis of clinical or x-ray examination findings in combination with the growth of pneumococci on sputum culture. Unfortunately, sputum culture results often fail to accurately identify the causative organism in pneumonia.[45,46] More accurate diagnosis requires invasive procedures that are rarely clinically justified.

Given the statistically significant heterogeneity of results for these outcomes, we are unable to estimate the overall magnitude of the protective effect of pneumococcal vaccine against either pneumococcal

Key points

- Antipneumococcal vaccination is effective in preventing vaccine-type pneumonia and systemic pneumococcal infections; risk is reduced by at least 73%.
- The vaccine can be expected to protect institutionalized patients and elderly people.
- For people older than 65 years, where the incidence of pneumococcal bacteremia is about 50 cases per 100 000 people, 2520 elderly people would need to be vaccinated to prevent one case of pneumococcal bacteremia per year.

Points de repère

- L'immunisation antipneumococcique est efficace dans la prévention des infections systémiques à pneumocoques et des pneumonies dues au type couvert par le vaccin; le risque est réduit d'au moins 73%.
- On peut s'attendre à ce que le vaccin protège les patients souffrant de maladies chroniques, les patients en établissement et les personnes âgées.
- Pour les personnes de plus de 65 ans, chez qui l'incidence des bactériémies pneumococciques est d'environ 50 cas par 100 000 personnes, il faudrait vacciner 2 520 personnes âgées pour prévenir un cas par année de bactériémie pneumococcique.

pneumonia or vaccine-type pneumococcal pneumonia. It should not be forgotten, however, that, of the nine studies providing data on vaccine-type pneumococcal pneumonia, all but one showed a reduction in vaccine-type pneumonia among vaccine recipients. In six studies this was statistically significant.

Special populations

From a clinical and health-policy viewpoint, the overall effectiveness of pneumococcal vaccination is perhaps less important than its effectiveness in particular subgroups considered to be at increased risk of pneumococcal disease or more vulnerable to its effects: elderly, institutionalized, and chronically ill people.

Two of four studies for vaccine-type systemic pneumococcal infection and five of six studies for systemic pneumococcal infection as the clinical outcome had study populations that included a substantial proportion of elderly subjects. Pneumococcal vaccine can, therefore, be expected to reduce the risk of vaccine-type systemic pneumococcal infection and systemic pneumococcal infection by about 83% and 73%, respectively, among elderly people. This compares with an estimated vaccine efficacy of 75% (95% CI 57% to 85%) against vaccine-type pneumococcal bacteremia among immunocompetent patients 65 years old or older in Butler and colleagues' retrospective study of pneumococcal serotype distributions among blood isolates from vaccinated and unvaccinated people.[44]

Similarly, because five of six studies contributing data on systemic pneumococcal infection had study populations that were partly or exclusively elderly, the overall common OR for this outcome (common OR 0.27, 95% CI 0.13 to 0.51), corresponding to a risk reduction of 73%, can be assumed to apply to the elderly.

Based on studies during the 1980s of pneumococcal bacteremia in two communities, Charleston County, SC,[47] and Oklahoma City, Okla,[48] the CDC estimate the annual incidence of pneumococcal bacteremia to be 50 cases per 100 000 people 65 years old or older.[12] Allowing for the fact that about 11% of elderly people had received pneumococcal vaccine at the time of those studies,[49] we estimate that approximately 2520 elderly people would need to be vaccinated to prevent one case of pneumococcal bacteremia per year based on our estimate of vaccine effectiveness from the results of controlled clinical trials.

Data from clinical trials in which the outcomes pneumococcal pneumonia and vaccine-type pneumococcal pneumonia were assessed give no indication of reduced vaccine effectiveness in the elderly. For example, in stepwise logistic regression analysis, there was no significant interaction between vaccination and an exclusively elderly study population for the outcome vaccine-type pneumococcal pneumonia.

Our results do not provide either evidence of reduced vaccine effectiveness or definitive evidence of equivalent vaccine effectiveness for people with chronic illnesses.

Because our meta-analyses for the outcomes vaccine-type systemic pneumococcal infection and systemic pneumococcal infection included studies set in chronic-care institutions, and because the results of those individual studies were consistent with the overall results, we believe that our overall estimates of the protective effect of pneumococcal vaccination against those outcomes are applicable to institutionalized populations.

For the outcomes pneumococcal pneumonia and vaccine-type pneumococcal pneumonia, an institutionalized study population was associated with *increased* vaccine effectiveness in stepwise logistic regression analysis.

The results of both our main analysis and the sensitivity analysis do not support the concern that, among recipients of pneumococcal vaccine, pneumococcal infections due to vaccine serotypes might be replaced by infections due to non-vaccine pneumococcal serotypes.

Our stepwise logistic regression analysis has features that limit its usefulness. Our dichotomous categorization of study populations as exclusively elderly, exclusively chronically ill, or exclusively institutionalized vs "other" compromises our ability to assess the interaction between vaccine effectiveness and these variables. Many of the studies with "other" study populations included a substantial proportion of subjects (sometimes a majority) with the characteristic of interest. For many studies, however, insufficient detail was available on the distribution of these characteristics to allow a more sophisticated analysis.

Recent meta-analysis

During preparation of this manuscript, Fine and colleagues reported results of a meta-analysis of randomized controlled trials of pneumococcal vaccine in adults.[50] Their inclusion criteria differed from ours because they excluded trials of pneumococcal vaccines less than 5-valent. They also did not include data from Austrian's randomized controlled trial of 6-valent vaccine among South African gold miners,[29-31] even though this study appears to meet their inclusion criteria.

They assessed somewhat different outcomes than we did, but, for the outcome that corresponded most closely to the outcome vaccine-type systemic pneumococcal infection in our study (definitive vaccine-type pneumococcal pneumonia [defined as clinically and radiographically confirmed pneumonia with vaccine-type *S pneumoniae* isolated from a culture of blood, a transthoracic lung puncture specimen, or a sample from a usually sterile body fluid]), the summary OR was 0.17, which is the same as our common OR for vaccine-type systemic pneumococcal infection. For the outcome definitive pneumococcal pneumonia (defined as clinically and radiographically confirmed pneumonia with *S pneumoniae* isolated from a culture of blood, a transthoracic lung puncture specimen, or a sample from a usually sterile body fluid), the summary OR was 0.34, compared with 0.27 for systemic pneumococcal infection in our study. In contrast to our results, however, Fine and colleagues found significant heterogeneity of results among studies for both of these outcomes.

Conclusion

Based on a meta-analysis of controlled clinical trials, vaccination with pneumococcal polysaccharide vaccine can be expected to reduce the risk of systemic infection due to pneumococcal types included in the vaccine by 83% (95% CI 69% to 91%) and systemic infection due to all pneumococci (vaccine type or non–vaccine-type) by 73% (95% CI 51% to 87%). These estimates of vaccine efficacy are higher than those reported in recent retrospective studies.[40-44] Our analyses do not indicate that the vaccine has less efficacy among the elderly, institutionalized people, or those with chronic illness. Finally, we found no evidence that pneumococcal infections due to vaccine serotypes are replaced in those vaccinated by infections due to other pneumococcal serotypes.

Correspondence to: *Dr B.G. Hutchison, Centre for Health Economics and Policy Analysis, Health Sciences Centre, Room 3H3, McMaster University, Hamilton, ON L8N 3Z5; telephone (905) 525-9140, extension 22123; fax (905) 546-5211; e-mail* **hutchb@fhs.mcmaster.ca**

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