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Assessing the Potential Cost Effectiveness of Pneumococcal Vaccines in the US

Methodological Issues and Current Evidence

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Abstract

Pneumococcal disease imposes a notable burden on society, particularly in the elderly and those at high risk of complications. Preventive strategies, especially vaccines, are possibly the best way to minimise such a burden. We report on the conduct and results of a preliminary exploratory review of the economics of pneumococcal vaccines in the elderly population in the US. After extensive electronic and manual searches, we identified 5 economic evaluations that fulfilled our study criteria. From these we extracted key economic variables and assessed the quality of the studies against the criteria in the checklist for authors and peer reviewers of economic submissions to the *British Medical Journal*. We found variation of quality of study design such as a lack of clarity in the treatment of indirect costs and a failure to present the data on resource use and costs separately. We carried out supplementary searches to assess the quality of the epidemiological and efficacy evidence upon which the economic models were based and found contradictory evidence of effects of the vaccines, which included the results of 2 meta-analyses. One of these meta-analyses reported that retrospective studies, especially case-control studies, tended to underestimate the protective efficacy of the vaccine by as much as 20%. We believe that a well resourced Cochrane review of the clinical evidence of the effects of the vaccines should be carried out before any further economic studies. No more economic modelling should take place before such a review is undertaken.

Streptococcus pneumoniae (pneumococcus) is an important cause of morbidity and mortality worldwide. Despite the availability of specific antibiotic therapies, the case-fatality rates for bacteraemic pneumococcal pneumonia have remained high. Globally, pneumococcus accounts for over 1 million deaths each year in children under 5 years of age[1,2] and is the most commonly identifiable cause of community-acquired pneumonia.[3] In the US, the associated mortality rate has remained unchanged over the last 30 years.[4] Pneumococcus is responsible for 30 to 50% of community-acquired pneumonia and 8% of nosocomial pneumonia in the UK[4] and might be the cause of most cases of pneumonia with no identifiable causative organism.[4] In developing countries the attack rate of pneumococcal disease is high, particularly in children, and an estimated 60 to 90% of lower respiratory tract infections in children under 5 years of age are caused by *S. pneumoniae*. Similar or even

higher attack rates have been observed in crowded communities of adults.[4]

S. pneumoniae causes a wide variety of other disorders, from meningitis and infection of other serous cavities, endocarditis, otitis media and sinusitis to infrequent but comparatively benign soft tissue infections. It is also one of the leading causes of acute bacterial meningitis with bacteraemia, which is often more severe in elderly people, preschool children, alcoholic patients, and asplenic patients. Even with appropriate antimicrobial therapy and intensive care support, mortality approaches 25 to 30% in patients with pneumococcal bacteraemia.[2,3] Given concerns over growing antibiotic resistance and the potentially heavy burden of pneumococcal disease in the community,[5] preventive measures are of considerable importance in controlling the spread of infection.

Modern vaccines contain the capsular polysaccharides of 23 different pneumococcal serotypes and are known as 23-valent vaccines. At present, three 23-valent pneumococcal vaccines are available: Pneumovax II (Pasteur Merieux Connaught), Pneumovax 23 (Merck) and Pnu-Immune (Wyeth-Lederle Vaccines). Renewed interest has led to the development of conjugate vaccines (at present undergoing trials) and to an evaluation of the relative cost effectiveness of preventing pneumococcal disease, especially compared with other preventive interventions.

The aim of this study was to assess the current state of knowledge with regard to the cost effectiveness of pneumococcal vaccines in the elderly in the US.

1. Methods

We carried out a preliminary exploratory review of the topic by electronically searching Medline and EMBASE, using a search strategy with the following Medical Subject Headings (MeSH) terms or combined sets, from 1981 to 1998, in any language: pneumococcal vaccine, efficacy, adults, elderly, cost, effectiveness, cost effectiveness, cost utility, cost-benefit.

The bibliography of retrieved articles was reviewed to identify further studies. We also searched the Bath Information and Data Services (BIDS) database.

Further searches were carried out by the Cochrane Vaccines Field using the Cochrane Controlled Trials Register (CCTR), part of the Cochrane Library.

In view of the findings of our review and the importance of clinical effectiveness in the economic assessment of the vaccines, further preliminary searches were carried out to identify meta-analyses of randomised, controlled trials and evaluative vaccine studies of different design. These were identified initially from the bibliographies of economic evaluation papers retrieved and from a further electronic search of Medline, BIDS and CCTR.

Studies identified by our search and retrieved were considered for inclusion according to the following criteria:

- Centred on the use of pneumococcal vaccines
- Economic (i.e. addressed technical and/or allocative efficiency aspects of the introduction of pneumococcal vaccines or presented some relevant cost data)
- Original (i.e. reported data not previously available)
- Analytical (i.e. appeared to compare the relevant intervention with other interventions or against do-nothing option)
- Either self-standing or part of a larger study (such as a randomised controlled trial)
- Specific study population (elderly)
- Specific country (US).

Studies satisfying all criteria were included in our exploratory review. Thus, we excluded studies with no economic content, or those that referred to earlier vaccines. We kept a list of the excluded studies with the reason for exclusion made clear. This list is available on request from the authors. We extracted the following data from each paper included in our exploratory review:

- Study aim or aims (these were divided into the issue that the study was addressing, the compa-

rator selected and the study perspective, whether data had been collected prospectively, retrospectively or to construct a model)
- Economic viewpoint
- Year of publication
- Study population (general or at-risk groups)
- Study design (as indicated by comparison with the design indicated in the title, charts, or text and the standard definitions of economic evaluation types)
- Estimated incidence of the disease in the reference general population or in at-risk groups
- Direct and indirect cost of pneumococcal pneumonia cases
- Cost of vaccination
- Currency in which the costs were expressed
- Benefit-to-cost ratio (BCR)
- Cost-to-effect ratio (CER)
- Time horizon to calculate cost
- Use of discount rate
- Discount rate used
- Conclusions (favourable, favourable with caveat, unfavourable, unfavourable with caveat, equivocal)
- Presence of sensitivity analysis.

Direct costs were defined as costs borne by the health service, such as diagnosis, treatment, hospitalisation and follow-up. Indirect tangible costs were defined as those borne by society (such as loss of output).

The quality of the economic studies was assessed using the *British Medical Journal* checklist for authors, reviewers and editors.[6] The results and conclusions of the studies were assessed for consistency and reliability by applying the checklist. Important gaps in knowledge were then identified and the appropriate design of economic and clinical studies to fill these gaps was considered.

2. Results

2.1 Economic Aspects

A search of the economic literature identified 1 unpublished and 73 published articles dealing with the economics of pneumococcal vaccines. Of these, 16 were epidemiological studies and 49 contained no economic analysis and were excluded. Of the remaining 9 articles, one was an update of a previous study,[7] two (including the unpublished paper) were review articles[8] and one study was conducted in Spain.[9]

The 5 included studies were those by Willems et al.[10] (published in 1980), Patrick and Woolley[11] (1981), Gable et al.[12] (1990), Rose et al. [13] (1993) and Sisk et al.[14] (1997).

The results (from a health-service perspective) of the included studies are in table I.

The *British Medical Journal* checklist has 3 main sections, covering study design, data collection and analysis, and interpretation of results. While the research question was always well stated and the alternatives being compared were clearly described, the most common weakness in study design was the lack of clear justification for the

Table I. Results and conclusions of the studies included in the review. The viewpoint of the studies is that of the health service; costs are in US dollars

Study	Measure	Population category	Economic outcome	Conclusion
Willems et al.[10]	Cost per QALY	All ages 65+y 2-4y	$4800 $1000 $77 200	Consider vaccination of elderly
Patrick & Woolley[11]	Benefit-to-cost ratio	Adults High risk	0.130 0.338	Vaccinate 50+y and high risk population
Gable et al.[12]	Cost savings	50+y	$141/person/year	Vaccinate 50+y and high risk population
Rose et al.[13]	Cost savings Cost per life-year gained	Low risk High risk	$187/patient/lifetime $2910	Vaccinate HIV-infected patients
Sisk et al.[14]	Cost savings Cost per QALY	65+y	$8.27/vaccinated person $35 per QALY (age 65-74y)	Vaccinate to prevent pneumococcal bacteraemia

QALY = quality-adjusted life-year.

Table II. Cost data (in US dollars) used in the studies included in the review. Time horizon of evaluation 2 to 72 years

Item	Year of valuation	Cost
Cost of vaccination	1978	$9.00-$11.37
	1987	$18.53
	1990	$19.80
	1997	$12-$24
Cost per case of pneumonia		
hospitalised	1987	$1454-$2723
	1990	$5111
outpatient	1987	$122-$638
	1990	$295
Cost per case of bacteraemia		
hospitalised	1997	$8991

choice of comparators (e.g. other vaccines, do nothing option). In data collection, the main concern was the failure to give details of the studies from which effectiveness data were drawn. There was a lack of clarity in the treatment of indirect costs, and a failure to present the data on resource use and costs separately.

In the analysis and interpretation of results, although discounting was carried out appropriately, the choice of discount rate was rarely justified and there was a wide variation in time horizons (table II). The majority of studies did not justify the ranges of values used in sensitivity analysis and there was a general failure to report confidence intervals whenever stochastic data were presented. Additionally, when we analysed the distribution of cost data in the included studies, we found considerable variability in the estimates used (table II). Although we did not adjust the estimates for inflation and purchasing power variations, the observed variability is only partly explained by the differences in year of valuation.

2.2 Efficacy Assumptions

We analysed some of the epidemiological and vaccine efficacy assumptions used as the basis of the economic studies. Pneumococcal disease estimates varied between 2.3 and 6 per 1000 in the control groups of the studies, efficacy estimates varied between 66 and 88% for vaccines, and the duration of efficacy was estimated to be between 3 and 8 years.

Some examples of the conflicting evidence on the effectiveness of the vaccines are summarised in table III. Variability of effect estimates for the pneumococcal vaccines can partly help to explain the variability of cost estimates and conclusions found in the economic literature.

We identified 2 meta-analyses. The first, published by Fine et al.,[15] consisted of data from 9 randomised, controlled trials, pooling data from 25 000 individuals. The authors concluded that pneumococcal vaccination is protective against different forms of pneumococcal pneumonia in low risk adults, but failed to show an equivalent effect in high risk adults.

The second meta-analysis, by Hutchison et al.,[16] was carried out a year later, in 1995. They reviewed and pooled data on nearly 30 000 individuals from randomised and quasi-randomised studies and found evidence of a high protective effect (73%) of vaccination against all types of pneumococcal infections in elderly and high risk individuals. In a later published version[17] of their review, the authors drew attention to the incomplete nature

Table III. Examples of evidence of clinical effectiveness of pneumococcal vaccines by population and study design

Outcome	Population	Study design	Conclusions
Invasive pneumococcal infection	All ages	Meta-analyses of randomised controlled trials	Protective
	Elderly and high risk		Conflicting
Pneumonia (all causes)	Adults	Case-control studies	
	Elderly and high risk	Case-control studies	
Death from pneumonia/pneumococcal infection	All ages, high risk	Randomised controlled trials and case-control studies	Equivocal
Pneumococcal bacteraemia	Elderly	Case-control studies	Favourable

of the reporting of results of pneumococcal vaccine trials in the 17 review articles analysed in their review. An additional point is the finding that retrospective studies, especially of case-control design, tended to underestimate the protective efficacy of the vaccine by as much as 20%.

3. Discussion

We carried out a review that was limited in scope by the resources at our disposal and can only be considered to be exploratory in nature. For instance, we were unable to write to all authors and interrogate private databases, which could have yielded further economic studies. Nevertheless, our preliminary look at the economics of the effects of pneumococcal vaccines in the elderly revealed that evidence is currently limited. What evidence exists is of variable quality, a finding in keeping with that of other reviews of vaccine economics. However, a major cause of such variability is the uncertainty regarding the effects of the 23-valent pneumococcal vaccines and the prevalence of disease in the community. The finding of incompleteness and bias in reporting results of effectiveness studies of pneumococcal vaccine[17] and the different clinical outcomes reported in such studies could further explain the apparently contradictory nature of the evidence. We believe that a well resourced Cochrane review[18] of the clinical evidence of the effects of the vaccines should be carried out before any further economic studies. We also do not believe that any more economic modelling should take place before such a review is undertaken. The following evidence should be sought from properly powered and conducted prospective studies:

- Controlled evidence of the impact of vaccines on mortality in elderly and high risk individuals
- Controlled evidence of the impact of vaccines on morbidity in elderly and high risk individuals
- Better evidence of infection rates and disease in the general population.

From the limited evidence in our possession, we conclude that vaccines appear to be most efficacious in those at lowest risk of disease, but the cost of vaccination for this group would be greater because of the numbers involved. Although vaccination of high risk groups may be the most cost-effective solution, the effectiveness of the vaccines has not been clearly demonstrated in these groups. Application of the best possible economic evaluation methods, as in Sisk et al.,[14] cannot overcome this problem.

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