Cost effectiveness of adding 7-valent pneumococcal conjugate (PCV-7) vaccine to the
Norwegian childhood vaccination program

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined a childhood 7-valent pneumococcal conjugate vaccine (PCV-7) for the prevention of pneumococcal disease. The vaccination strategy consisted of PCV-7 added to the existing childhood vaccination schedule and administered at the age of 3, 5, 6 and 12 months, depending on whether 3 or 4 doses were given.

Type of intervention
Primary prevention (vaccination).

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a birth cohort of infants.

Setting
The setting was primary care. The economic study was carried out in Norway.

Dates to which data relate
The effectiveness data were derived from studies published between 1986 and 2005. No dates for resource use were reported. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A Markov model was constructed to simulate the strategies of PCV-7 versus no additional vaccination in a Norwegian cohort of infants (approximately 55,000 children). The model followed children from birth until death or age 100 years. The cycle length was one year. Each child was assumed to be initially well, but at risk of having various pneumococcal-related events and developing costly adverse health outcomes. All children were at risk of AOM, meningitis, septicaemia, or pneumonia caused by Streptococcus pneumoniae. The different events left the patient in one of several possible health states. Specifically, secretory otitis media with insertion of eardrum tubes, otitis sequelae (mechanically impaired hearing), hydrocephalus, epilepsy, neurological sequelae (severe or moderate), neurologically impaired hearing, empyema, dead from pneumococcal disease, dead from other causes, or well. The structure of the model was depicted graphically.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the epidemiological data on pneumococcal disease;
- the risk of AOM, meningitis, septicaemia or pneumonia;
- the case-fatality rate;
- vaccine coverage and efficacy (reported as relative risk reduction); and
- quality of life (QoL) data.

Study designs and other criteria for inclusion in the review
The primary studies appear to have been identified selectively. The risk of IPD was based on data derived from the Norwegian Surveillance System for Communicable Diseases (NSSCD), which is based on laboratory confirmed diagnoses. The risk of consolidated pneumonia in children was derived from a hospital database. Vaccine efficacy data were obtained from randomised controlled trials performed in the USA and in Finland. QoL data were derived from the database at the Harvard Center for Risk Analysis, choosing preference-based values.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The use of clinical trials to derive the effectiveness data was appropriate. The validity of the other sources was unclear.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Fourteen primary studies provided the clinical data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Effectiveness data obtained from studies performed in the USA were adjusted to Norway, according to the different serotype distribution.

Results of the review
The incidences per child per year were highest for the youngest age group of children in their first year of life (0.015% for meningitis and 0.009% for septicaemia), and decreased to 0.002% for both diseases in the fourth year of life.

The vaccine coverage was 51%, 75%, 70% and 56% for the first four years of life.

Sequelae occurred more often after meningitis than after septicaemia (these data were supported by the opinion of a panel of three paediatricians and three neurologists).
The risk of consolidated pneumonia in children was 16 per 100,000 per year.

The risk of AOM was 22 per 100 children during the first year of life, 23 during the second year, 22 during the third year, and 25 during the fourth year.

AOM developed into acute coalescent mastoiditis in 42 of 100,000 cases in the age group 0 to 4 years.

All patients with AOM developed secretory otitis media and impaired hearing for some time. About 5% would have persistent secretory otitis media.

Of children receiving ventilation tubes, about 20% would still have them after 12 months and, of these, 25% would have them for 2 years. At the age of 8 years, about 2% of those with ventilation tubes would still have them. In total, 5% of all children would have had a ventilation tube one or more times by the age of 5.

A number of patients would have reduced hearing after secretory otitis media, but most would have normal hearing at the age of 6. About 2% of all children would have permanent sequelae and impaired hearing by the age of 8 years.

The case-fatality rates for meningitis were 2.3% in the first year of life, 6.7% in the second year of life, and 12.5% in the third to fifth years.

The case-fatality rates for septicaemia were 4.2% in the first year of life, 11.1% in the second year of life, and 2.4% in the third to fifth years.

The risk of new events was equal after the age of 4 years, with no vaccine benefit after this age.

Vaccine reduced the risk of IPD among children by 93.9% (95% confidence interval, CI: 79.6 to 98.5) and pneumonia by 17.7% (95% CI: 4.8 to 28.9).

The relative risk reduction in the incidence of OAM was 6% (95% CI: -4 to 16).

The observed reduction of IPD due to vaccination was 8.9% for the age group 20 to 39 years, 12.9% for the age group 40 to 64 years, and 22.9% for individuals aged 65 years or older.

QoL values were not reported.

**Measure of benefits used in the economic analysis**

The summary benefit measures used were the total number of life-years (LYs) gained and quality-adjusted life-years (QALYs) gained with the PCV-7 vaccination strategy in comparison with no vaccination. Both measures were derived using the modelling approach. Other model outputs, such as the avoided number of meningitis cases and sequelae in children and adults, were also reported. An annual discount rate of 3% was applied.

**Direct costs**

The analysis of the costs was carried out from a societal perspective. It the direct costs of vaccination and sequelae such as meningitis, otitis media, pneumonia, septicaemia, epilepsy, hydrocephalus and neurological sequelae. The unit costs were not presented separately from the quantities of resources used, except for the cost of the vaccine. The estimation of resource use associated with the management of sequelae was based on the opinions of an expert panel. The costs were derived from fee schedules and diagnosis-related group price lists for Norwegian hospitals. The vaccine cost was derived from the official pharmacy sales price. Discounting was relevant, as a long-term time horizon was used, and an annual rate of 3% was used. The price year was 2004.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.
Indirect Costs
The indirect costs (i.e. productivity losses associated with sequelae) were included in the analysis. Days of work lost were based on authors’ opinions. The costs were obtained from average wage levels. Some information on the unit costs and quantities of resources used was provided. As in the analysis of the direct costs, an annual discount rate of 3% was applied and the price year was 2004.

Currency
Norwegian kroner (NOK). The average 2004 exchange rates from NOK to US dollars ($) and euros (EUR) were $1 = NOK 6.74 and EUR 1 = NOK 8.37. The costs were finally expressed in euros.

Sensitivity analysis
A univariate sensitivity analysis was performed to assess the robustness of model results to variations in several clinical and economic inputs, which were varied within reasonable ranges. The results were presented using a tornado diagram, which enables the most influential parameters to be identified. A probabilistic sensitivity analysis was also carried out by assigning probability distributions to all model inputs.

Estimated benefits used in the economic analysis
The total (undiscounted) gain from pneumococcal vaccination of 55,000 infants (a Norwegian birth cohort) was 69 LYs or 142 QALYs without HI, and 101 LYs or 175 QALYs when HI was taken into consideration.

The discounted values were 23.5 LYs saved or 52.1 QALYs without HI, and 47.9 LYs gained or 76.6 QALYs with HI.

Cost results
The acquisition of the vaccine for a birth cohort of 55,000 cost about EUR 14.8 million per year if 4 doses were given and EUR 11.1 million if 3 doses were given.

Pneumococcal-related disease cost EUR 2.7 million (undiscounted) less in a vaccinated cohort because of cost-savings from avoided pneumococcal disease among the vaccinated.

The estimated average lifetime treatment costs of pneumococcal disease were EUR 740 (undiscounted) per person without vaccination (EUR 1,910 including indirect costs) and EUR 790 with vaccination (EUR 1,850 including indirect costs).

The lifetime cost with vaccination was EUR 54 lower if 3 doses of the vaccine were given.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of pneumococcal vaccination versus no vaccination.

The cost per LY gained was above the Norwegian threshold of EUR 51,000 when 4 doses of the vaccine were given and when the indirect costs were not considered. Similarly, 3-dose vaccination was not cost-effective (at a threshold of EUR 51,000) when the indirect costs were not considered. On the other hand, with the inclusion of indirect costs and regardless of the HI scenario, pneumococcal vaccination with 3 doses was dominant (it produced more LYs and was cheaper than no pneumococcal vaccination).

When the cost per QALY gained was considered, pneumococcal vaccination was cost-effective in three scenarios. Specifically, with 4 doses but including the indirect costs and considering HI (EUR 37,000), with 3 doses and including the indirect costs, and regardless of the HI scenario (pneumococcal vaccination was dominant).

The univariate sensitivity analysis showed that the cost and effects of vaccination, costs of otitis sequelae and the probability of developing meningitis were the variables that had the greatest impact on the model results. For example,
at a vaccine price of EUR 20, the vaccination strategy was always cost-saving (regardless of the number of doses, perspective or HI).

The probabilistic sensitivity analysis suggested that the probability that the 4-dose pneumococcal vaccination strategy was cost-effective (cost per LY gained below the Norwegian threshold) at current price level was 0.19% without HI and 0.60% with HI.

Authors' conclusions
The inclusion of a 7-valent conjugate pneumococcal vaccine in the child health care programme in Norway may be cost-saving only from a societal perspective, and only if it is assumed that the vaccination scheme with 3 doses has the same effect as that with 4 doses. Further, the 4-dose scheme may only be cost-effective if both herd immunity (HI) and indirect costs are taken into consideration.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear as pneumococcal vaccination was compared with the current vaccination schedule in Norway. Both 4- and 3-dose vaccinations were considered. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published sources. The authors did not report the details of a systematic review of the literature, thus the primary studies might have been identified selectively. Data on the effectiveness of the vaccine schedule were derived from clinical trials, which should have ensured the validity of these primary estimates. Other data on the epidemiology of disease were obtained from multiple sources. When clinical data were not derived from Norwegian patients, local sources were used to reflect Norwegian patterns of disease. In some cases, the literature provided clinical estimates different from those observed in a local series of patients. These alternative estimates were used in the sensitivity analysis.

Validity of estimate of measure of benefit
LYs and QALYs were the most appropriate benefit measures because they express two relevant aspects of health (i.e. QoL and survival). The authors stated that the utility weights used to adjust survival were derived from a published database, but no information on this source of data was provided. Both benefit measures can be compared with the benefits of other health care interventions. Discounting was applied and the impact of using alternative discount rates or no discounting was investigated in the sensitivity analysis.

Validity of estimate of costs
The choice of the societal perspective was appropriate as all the relevant costs were included in the analysis, regardless of who paid for the services and for the economic consequences. The analysis also examined scenarios in which only the direct costs were considered, which might be of relevance to some decision-makers. Information on the unit costs and quantities of resources used was not presented separately, which could limit the possibility of replicating the analysis in other countries. However, the authors tested the use of alternative cost estimates as well as the possibility that the health authority might negotiate lower vaccine prices. Further, although the costs were treated deterministically in the base-case, probabilistic distributions were assigned to costs in the sensitivity analysis. Resource use associated with IPD was derived from expert opinion, but it was unclear whether the impact of these estimates on the total costs was tested. The price year was reported, thus replication in other time periods is possible. Key cost estimates were varied in the sensitivity analysis.

Other issues
The authors stated that several economic evaluations of pneumococcal vaccination had been published. Many of them used data from the same clinical trial but varied consistently in terms of the model structure and assumptions.
Conflicting results have also been published. In terms of the issue of the generalisability of the study results to other settings, it was noted that the conclusions of the current study could be extrapolated to other industrialised countries, although caution is required given the specific context of disease occurrence and costs. The authors noted that, although there was considerable uncertainty in some model inputs, the sensitivity analysis showed that the impact of the most uncertain model inputs did not substantially affect the results of the base-case analysis.

**Implications of the study**
The study results suggest that pneumococcal vaccination might be cost-effective, but only under specific conditions that would have to be explicitly considered by decision-makers.

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**Other publications of related interest**


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