The cost-effectiveness of pneumococcal conjugate vaccination in Australia
Butler J R, McIntyre P, MacIntyre C R, Gilmour R, Howarth A L, Sander B

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 use of the heptavalent pneumococcal conjugate vaccine (PCV7) in children aged 0 - 4 years was examined. Four doses of vaccine were given at ages 2, 4, 6 and 12 - 15 months.

Type of intervention
Primary prevention.

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

Study population
The study population comprised a hypothetical cohort of children aged 0 to 4 years.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1989 and 2002. No dates for the resource use data were explicitly reported. Some cost data were derived from studies published between 1992 and 2001. The prices used referred to 1997-98.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A decision tree model was constructed to examine the economic and clinical consequences of PCV7 vaccination against no vaccination in a hypothetical birth cohort of 250,000 children. Over the 5-year time horizon, cohort members could experience invasive pneumococcal disease (IPD) of vaccine serotypes confirmed with positive blood culture, or a clinical diagnosis of pneumonia or otitis media. IPD of non-vaccine serotype was not considered. IPD could manifest as meningitis, bacteraemia, or other focal infections including pneumonia. Children who survived meningitis could experience no sequelae, hearing deficits, or neurological deficits. Mortality from causes other than those included in the model was ignored. The model structure was depicted graphically.

Outcomes assessed in the review
The outcome measures used in the decision model were:
the proportions of children who received only one, two, three, or four doses of vaccine;

the duration of vaccine efficacy;

the incidence rates for IPD and the proportion of IPD manifesting as meningitis, bacteraemia, or other focal infection;

the case-fatality rates for meningitis, bacteraemia, or other focal infection;

the rates of pneumonia;

the proportion of children with at least one episode of otitis media and episodes of otitis media per case;

the rates of IPD - proportion of vaccine serotype, proportion with meningitis (with hearing deficit and without sequelae), proportion with neurological deficit (mild, moderate, or severe), bacteraemia (moderate or severe), other focal infections (mild, moderate, or severe), incidence rate of pneumonia (moderate or severe), rate of otitis media (moderate or severe);

vaccine efficacy; and

the disability weights.

Sex-weighted life expectancy was also estimated.

**Study designs and other criteria for inclusion in the review**

It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. No information on the design and characteristics of the studies was provided, except for a double-blinded, randomised, controlled clinical trial that was used for vaccine efficacy. Some data were derived from Australian datasets. Sex-weighted life expectancy was obtained from Australian life tables.

**Sources searched to identify primary studies**

Not stated.

**Criteria used to ensure the validity of primary studies**

Not stated.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

Eleven primary studies provided evidence.

**Methods of combining primary studies**

Not stated.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**
The proportions of children who received only one, two, three, or four doses of vaccine were 9% (1 dose), 9% (2 doses), 24% (3 doses) and 58% (4 doses), respectively.

The duration of vaccine efficacy was 5 years.

The incidence rates of IPD per 100,000 were 105.6 for children aged 0 - 1 year and 35.2 for children aged 2 - 4 years.

The proportion of IPD manifesting as meningitis was 0.13 for age group 0 - 1 and 0.06 for age group 2 - 4. The proportions of IPD manifesting as bacteraemia were 0.64 (age 0 - 1) and 0.65 (age 2 - 4), respectively, and the proportions of IPD manifesting as other focal infection were 0.23 (age 0 - 1) and 0.29 (age 2 - 4).

The case-fatality rates for age 0 - 1 year and age 2 - 4 years were, respectively, 0.115 and 0.071 for meningitis, 0.004 and 0.014 for bacteraemia, 0.015, and 0.005 for other focal infection.

The rate of pneumonia was 0.0065 for age 0, 0.0015 for age 1, and 0.0003 for age 2 - 4 years.

In the case of otitis media, the proportion of children with at least one episode was 0.63 at age 0, 0.59 at age 1, 0.41 at age 2, 0.43 at age 3, and 0.43 at age 4 years.

The episodes of otitis media per case were 1.98 at age 0, 1.80 at age 1, 1.76 at age 2, 1.86 at age 3, and 1.74 at age 4 years.

The rate of IPD was 0.83.

Among children with meningitis, the proportion of those without sequelae was 0.54, the proportion of those with hearing deficit was 0.30 (0.29 moderate, 0.72 severe, 0.27 without cochlear implant, 0.73 with cochlear implant), and the proportion with neurological deficit was 0.16 (0.20 mild, 0.40 moderate, 0.40 severe).

The rates of moderate and severe bacteraemia were 0.12 (moderate) and 0.88 (severe), respectively.

The rates of moderate and severe cases of other focal infections were 0.06 (moderate) and 0.94 (severe), respectively.

The incidence rate of pneumonia (per 1,000 persons) was 0.49 for moderate disease and 0.51 for severe disease.

The rates of moderate and severe otitis media were 0.9925 (moderate) and 0.0075 (severe), respectively.

Among children with severe otitis media, the proportion without tympanostomy was 0.39 and the proportion with tympanostomy was 0.61.

Vaccine efficacy was 93.9% (95% confidence interval, CI: 79.6 - 98.5) against IPD of vaccine serotype, 6.4% (95% CI: 3.9 - 8.7) against episodes of clinically diagnosed otitis media, 6% (95% CI: -1.15 - 1.1) against all clinically diagnosed pneumonia, 8.9% (95% CI: 0.9 - 16.3) against clinical pneumonia with a radiograph obtained.

The disability weights for meningitis, bacteraemia, other focal infections, pneumonia and otitis media were also reported.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions to derive data on disability weights that were not found in the literature.

**Estimates of effectiveness and key assumptions**
Estimated disability weights were reported alongside published data.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the number of deaths, number of life-years lost and disability-adjusted life-years.
years (DALYs). All measures were estimated using the modelling approach. DALYs were calculated by combining disability weights and expected survival, all obtained from the literature. An annual discount rate of 5% was applied.

**Direct costs**
Discounting was relevant as the costs were incurred over a long time horizon. An annual discount rate of 5% was applied. The unit costs were presented separately from the quantities of resources used for vaccine costs only. Other costs were presented as macro-categories. A detailed breakdown of the items was not provided. The economic evaluation considered all items related to the treatment of meningitis, bacteraemia, other focal infections, pneumonia and otitis media. The cost/resource boundary of the study was not stated clearly. Resource use was estimated using authors' assumptions. The costs came from published sources and authors' opinions. The costs were estimated using 1997-98 prices.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
Australian dollars (Aus$).

**Sensitivity analysis**
Sensitivity analyses were carried out to examine the robustness of the cost-effectiveness ratios to variations in some key inputs. One-way sensitivity analyses were performed on the discount rate, vaccine price, pneumonia incidence and vaccine efficacy. Two-way sensitivity analyses were conducted on vaccine efficacy, vaccine price and pneumonia incidence. CIs were used when available, otherwise the authors set the ranges.

**Estimated benefits used in the economic analysis**
In a cohort of 250,000 children and assuming 100% participation, the total discounted number of deaths was 36.6 (undiscounted 39.7) without vaccination and 24.2 (undiscounted 26) with vaccination. The difference was 12.4 (undiscounted 13.7).

The total discounted number of life-years lost was 790 (undiscounted 3,094) without vaccination and 522 (undiscounted 2,031) with vaccination. The difference was 268 (undiscounted 1,064).

The total discounted number of DALYs was 2,426 (undiscounted 5,261) without vaccination and 1,917 (undiscounted 3,570) with vaccination. The difference was 509 (undiscounted 1,691).

**Cost results**
In a cohort of 250,000 children and assuming 100% participation, the total costs of vaccination were Aus$78.6 million.

The total discounted treatment costs were Aus$144.2 million (undiscounted Aus$170.5 million) without vaccination and Aus$127.3 million (undiscounted Aus$139.5 million) with vaccination. The difference was Aus$16.9 million (undiscounted Aus$31 million). Thus, the net vaccination costs over no vaccination were Aus$61.6 million (undiscounted Aus$47.6 million).

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

The incremental cost per death averted with vaccination over no vaccination was Aus$5 million (undiscounted Aus$3.5 million).

The incremental cost per life-year saved with vaccination over no vaccination was Aus$230,130 (undiscounted Aus$44,740).

The incremental cost per DALY averted with vaccination over no vaccination was Aus$121,100 (undiscounted Aus$28,140).

The sensitivity analysis revealed that the base-case results were sensitive to variations in the discount rate and vaccine price.

The break-even price of the vaccine (i.e. the price at which the net cost of vaccination was zero) was Aus$15.40 per dose. Also, when vaccine efficacy was set at the lower limit of the 95% CI, the cost per life-year saved increased to Aus$291,300; when it was set at the higher limit it fell to Aus$143,700 per life-year saved.

The two-way sensitivity analysis showed that when either vaccine efficacy against pneumonia or pneumonia incidence were relatively low, the cost per DALY averted remained in the range Aus$142,000 - Aus$147,000. However, when efficacy was set at 16.3% and incidence was 36 cases per 1,000 population, the cost per DALY averted fell to Aus$89,600.

Authors’ conclusions
A programme of vaccinating children not at high risk with the heptavalent pneumococcal conjugate vaccine (PCV7) was at the upper limit of the cost per disability-adjusted life-year (DALY) previously approved under Australian pharmaceutical funding guidelines.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (no vaccination) was appropriate as it reflected standard care in Australia. The authors stated that a comparative analysis of universal versus targeted vaccination would have been interesting. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The clinical data that were used in the decision model came from published studies and local sources. However, it was not stated explicitly whether a systematic review of the literature had been undertaken to identify the primary studies, which appear to have been identified selectively. A description of the primary studies was not provided and detailed information was given only for the clinical trial used to derive vaccine efficacy data. This limits the possibility of assessing the validity of the primary sources. Similarly, the issue of potential differences among the primary studies was not addressed. Some assumptions were also made. Only key model inputs were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
Several summary benefit measures were used in the economic analysis. The use of life-years lost and DALYs was appropriate because they are commonly comparable with the benefits of other health care interventions. Published disability weights were used to calculate DALYs using a common methodology. However, no information on the sources used was provided. Discounting was carried out.

Validity of estimate of costs
The economic evaluation was carried out following Australian guidelines. Thus, only direct costs were considered, although the authors stated that a societal perspective had been adopted. Limited information on the unit costs and...
quantities of resources used was given, which limits the possibility of replicating the cost analysis in other settings. Much of the resource use data were based on authors’ assumptions and were not tested in the sensitivity analysis. The price year was reported, which aids reflation exercises in other settings. The cost data were mainly derived from published studies and were treated deterministically. Only the vaccine price was varied in the sensitivity analysis.

Other issues
The authors stated that their findings were consisted with other published studies. The issue of the generalisability of the study results to other settings was not explicitly addressed and limited sensitivity analyses were carried out. This reduces the external validity of the analysis. The authors noted some limitations of their study. For example, the use of uncertain model inputs such as duration of vaccine protection or number of vaccine doses required. Also, the authors underlined that some assumptions might have biased the results against the vaccine (e.g. the exclusion of herd immunity and the exclusion of impact of vaccination on antibiotic resistance).

Implications of the study
The study results did not support the implementation of a programme of universal pneumococcal conjugate vaccination in Australia.

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None stated.

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Other publications of related interest


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MeSH
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