Benefits and costs of immunization of children with pneumococcal conjugate vaccine in Canada
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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 a seven-valent pneumococcal conjugate vaccine (PCV-7), administered in four doses, for the routine vaccination of young infants aged from 2 to 6 months. Also investigated was the use of one (children aged 2 - 4 years), two (children aged 12 - 23 months), or three (children aged 7 - 11 months) doses for catch-up programmes in older children.

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 340,000 Canadian newborns followed up to the age of 106 years, the maximum life expectancy.

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

Dates to which data relate
The studies used mainly dated from 1986 to 2000. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and expert opinion.

Modelling
A simulation model representing mutually exclusive clinical outcomes and policy options was constructed. The no vaccination policy portrayed the present epidemiological situation. Under the vaccination policy, the probability of each outcome at each age was reduced, in proportion to the expected population effectiveness of the immunisation programme.

Outcomes assessed in the review
The outcomes assessed in the review were:
the incidence rate, according to age, of pneumococcal-related outcomes such as pneumococcal meningitis and
bacteraemia, hospitalisation for pneumonia, hospitalisation for all other causes, acute otitis media (AOM), and cases of otitis media requiring myringotomy with ventilation tube insertion (MVT);

the proportion of pneumonia attributable to S. pneumoniae;

the proportion of otitis media attributable to S. pneumoniae;

the short-term efficacy for invasive pneumococcal infection, all-cause pneumonia, all-causes AOM and MVT.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

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

**Number of primary studies included**
Eleven studies were included in the review. In addition, Canadian health databases were used to estimate the age-specific incidence rates of pneumococcal-related outcomes.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The incidence rate of pneumococcal-related outcomes fell with age.

The proportion of pneumonia attributable to S. pneumoniae was set at 22%.

The proportion of otitis media attributable to S. pneumoniae was set at 19%.

Short-term efficacy was 97% for invasive pneumococcal infection, 10.7% for all-cause pneumonia, 8.2% for all-cause AOM, and 24.9% for MVT.

**Methods used to derive estimates of effectiveness**
To estimate the protection from routine and catch-up immunisation up to age 9 years, eight Canadian experts were consulted through a Delphi panel.

**Estimates of effectiveness and key assumptions**
The experts reached consensus and estimated the decline in efficacy rate to be less than 1% per year.

For invasive pneumococcal disease, the population effectiveness of the programme was calculated by multiplying together the age-specific vaccine efficacy for serotypes included in the PCV-7, the proportion of infections caused by the serotypes included in the vaccine, the vaccination coverage in the target population (80%), and the expected proportion of children who would develop immunity (95%).

For non-invasive disease, population effectiveness was estimated by multiplying the vaccine efficacy rates observed in a US trial for all-cause pneumonia, all-cause AOM and MVT by the vaccination coverage in the target population.

Vaccine protection was assumed to begin after the third dose of PCV-7 at 6 months and to continue up to 9 years of age.

Measure of benefits used in the economic analysis
The measures of benefits used were the pneumococcal infections averted, deaths avoided, life-years gained and quality-adjusted life-years gained (QALYs). The health states were valued using the utilities used in Torrance (1982).

Direct costs
The resource quantities were determined using the model. The direct costs included were those to the health system and to the families. The health care system costs were for hospitalisation, vaccination including administration, and additional visits needed in the catch-up programme. It is unclear which costs were included in the family perspective. The average unit costs of pneumococcal-related outcomes were estimated from administrative health databases and the results from a survey in a sample of patients in Quebec and Manitoba. The unit costs were multiplied by the frequency of episodes to estimate the economic burden of pneumococcal disease. The price for the vaccine was based on expert opinion. Discounting was relevant, as the time perspective could be as long as 106 years, and was undertaken using a rate of 3% per annum. All the financial costs were expressed in year 2000 prices. To handle inflation, all prices were adjusted using the Canadian Price Index for health and personal care. Future costs were not inflated. The total costs were reported.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were included in the analysis. These were for productivity losses and gains due to vaccination. Productivity losses and gains were calculated using gender-specific earnings of Canadians in 1998, and age- and gender-specific employment rates in 1999. Discounting was relevant and was undertaken using a rate of 3% per annum. All financial costs were expressed in year 2000 prices. The total costs were reported.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A sensitivity analysis of the costs and benefits was carried out. Threshold analyses of the vaccine purchase price were conducted for the base model, to determine the breakeven point for Net Present Costs (i.e. NPC to society including productivity gains = 0). The effects of different immunisation coverage and discount rates were also explored. Extreme values and theoretical distributions for 36 input variables were investigated in a multivariate sensitivity analysis. For epidemiological parameters, lower and upper values were assumed to be 0.5 to 1.5 times the base model values, and the distributions were triangular. For vaccine efficacy rates and administration costs, the lower and upper values were assumed to be 0.75 to 1.25 times the base model values. Lower 10% and upper 90% bounds of distribution of outcome
variables were computed using 10,000 Monte Carlo simulations.

Estimated benefits used in the economic analysis
The number of life-years lost due to pneumococcal infection without vaccination was 1,536. The percentage reduction following vaccination was 57% with routine four-dose vaccination, 38% with three-dose catch-up, 20% with two-dose catch-up, and 13% with one-dose catch-up.

The number of QALYs lost due to pneumococcal infection without vaccination was 1,453. The percentage reduction following vaccination was 58% with routine four-dose vaccination, 36% with three-dose catch-up, 19% with two-dose catch-up, and 12% with one-dose catch-up.

Cost results
The total undiscounted costs, excluding productivity losses, without vaccination were $126,899,000.

The total discounted costs to society were $71,490,000 for the routine four-dose vaccination programme, $72,904,000 for the three-dose catch-up programme, $37,898,000 for the two-dose catch-up programme, and $23,452,000 for the one-dose catch-up programme.

The total discounted costs averted to society due to the routine four-dose vaccination programme were $41,094,000. The corresponding costs due to the catch-up programmes were $32,285,000 (three-dose programme), $21,082,000 (two-dose programme), and $12,721,000 (one-dose programme).

Hence, the total discounted net costs to society for the routine four-dose vaccination programme were $30,396,000. The corresponding costs for the catch-up programmes were $32,285,000 (three-dose programme), $16,817,000 (two-dose programme), and $10,731,000 (one-dose programme).

Synthesis of costs and benefits
The costs and benefits were combined as the net present cost (i.e. the discounted costs of the vaccine programme minus the discounted benefits (i.e. savings) of the vaccine programme) per case of pneumococcal infection averted, per death averted, per life-year gained, and per QALY gained. In order to avoid double-counting, productivity gains were excluded when calculating the cost-effectiveness and utility ratios.

The net cost per avoided death was $3,766,000 for routine vaccination, $7,071,000 for three-dose catch-up, $5,655,000 for two-dose catch-up, and $5,622,000 for the one-dose catch-up.

The net cost per avoided case of pneumococcal disease was $389 for routine vaccination, $619 for three-dose catch-up, $390 for two-dose catch-up, and $414 for the one-dose catch-up.

The net cost per life-year gained was $125,000 for routine vaccination, $240,000 for three-dose catch-up, $201,000 for two-dose catch-up, and $206,000 for the one-dose catch-up.

The net cost per QALY gained was $116,000 for routine vaccination, $238,000 for three-dose catch-up, $202,000 for two-dose catch-up, and $202,000 for the one-dose catch-up.

The results of the threshold analysis from a societal perspective under the base scenario indicated that the breakeven cost for purchasing the vaccine was $30 per dose. From the perspective of the health system, the breakeven vaccine purchase cost was $6.

The cost-effectiveness ratios and breakeven costs were not influenced by the vaccination coverage rate. Variation in the discount rate affected the results significantly.

The results of the multivariate Monte Carlo sensitivity analyses showed that the lower limit of the 90% bounds of net health system and societal costs did not cross the breakeven mark. This indicated that the costs will be greater than
economic benefits in most likely scenarios. Vaccine purchase price was by far the most important input variable in the model. It accounted for 83% of the variability in the net societal programme costs and 98% of the variability in the net health system programme costs.

Authors' conclusions
The introduction of the seven-valent pneumococcal conjugate vaccine (PCV-7) in Canada has the potential to significantly reduce morbidity and societal costs associated with pneumococcal disease in children. The authors concluded that at a unitary vaccine purchase cost of $30 or lower, the programme could save money for society.

CRD COMMENTARY - Selection of comparators
A justification was given for using the no vaccination programme as the comparator. It represented the current epidemiological situation in Canada. You should decide if this is a widely health technology in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature was undertaken to identify relevant research and minimise bias. The authors did not report any information on how they conducted their literature review, or how the primary studies used to derive the same measure of effectiveness were combined. To supplement the results from the literature review, a Delphi panel of eight Canadian experts was consulted, and estimates of efficacy were reached by consensus. The authors did not report how consensus was reached, or how the experts were selected. The estimates derived from the literature and from experts were appropriately investigated in a sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. Even though the benefits would appear to have been discounted in the synthesis of the costs and benefits, the authors did not report the actual discounted benefits.

Validity of estimate of costs
All the categories relevant to the perspectives adopted were included in the analysis. It would also appear that for each category of cost, all the relevant costs were included, for example, the unit costs of treating meningitis and hospitalised bacteraemia. No cost was added in the base-case for the treatment of vaccine-related side effects, as a US trial did not reveal any severe adverse events due to the vaccine. However, an additional "side effect" cost of $5 per dose was included in the sensitivity analysis. A sensitivity analysis of the prices was conducted, using ranges that appear to have been appropriate. The authors performed appropriate inflation exercises and, as the costs were incurred during a long time period, the costs were discounted at 3% per annum. The price year was reported, which will aid any inflation exercises.

Other issues
The authors made comparisons with other studies that looked at other vaccine programmes in Canada. However, they did not compare their results with any study investigating the use of pneumococcal vaccination. The issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors did not present their results selectively. The authors reported that their base model was likely to be conservative, as it did not consider possible protection against approximately 3 to 6% of cases of invasive pneumococcal disease in children caused by serotype 6A and 19A.

The study had several further limitations. First, the authors do not appear to have performed a proper incremental analysis, as the net costs of the no vaccination programme were not subtracted from the net costs of the vaccination programme. Without this, it is not possible to determine the incremental cost-effectiveness or cost-utility of the vaccination programme over no vaccination. Hence, we cannot determine whether vaccination is indeed cost-effective. Second, the authors did not include the costs of society in their synthesis of the costs and benefits. Hence, these results will not reflect a societal point of view.
Implications of the study
The authors appear to recommend the use of pneumococcal vaccination in Canadian children, especially if the unitary purchase cost is $30 or lower.

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Other publications of related interest


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