A pharmacoeconomic evaluation of 7-valent pneumococcal conjugate vaccine in Canada

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 7-valent pneumococcal conjugate vaccine (PCV-7) for the prevention of Streptococcus pneumoniae in children. The following dosing and administration schedules were considered:

3 doses (8 weeks apart) for the primary series and 1 dose at 12 - 15 months as a booster dose for the age class 6 weeks to 6 months (primary vaccination);

2 doses (8 weeks apart) for the primary series and 1 dose at 12 - 15 months as a booster dose for the age class 7 to 11 months (infant catch-up);

2 doses (8 weeks apart) for the primary series and no booster dose for the age class 12 to 23 months (toddler catch-up); and

1 dose for the primary series and no booster dose for children older than 24 months (child catch-up).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of healthy children aged less than 5 years.

Setting
The setting was primary care. The economic study was conducted in Canada.

Dates to which data relate
The effectiveness evidence and resource use data came partly from studies published between 1982 and 2002. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies.

Modelling
A state transition model was used to assess the long-term impact of vaccination over no vaccination in a birth cohort of 340,000 children for a 10-year time period. The health states considered were well, meningitis, bacteraemia, pneumonia, otitis media, myringotomy and ventilation tube (MVT), and death. Children entered the model in the 'well'
health state. They could remain in the same state or move to other states over time. The cycle length was 6 months. The structure of the model was illustrated.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the incidence rates for pneumococcal meningitis, bacteraemia, pneumonia, otitis media, and MVT;
- mortality rates; and
- vaccine efficacy rates.

**Study designs and other criteria for inclusion in the review**
A systematic review of the literature does not appear to have been conducted. The design of the primary studies was not reported in detail. Some of the data were derived from a clinical trial, the Northern California Kaiser Permanente Study.

**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**
Nine primary studies provided the effectiveness evidence.

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

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

**Results of the review**
All the incidence rates were in children aged less than 10 years.

The mean annual incidence rate was 3 cases per 100,000 children for pneumococcal meningitis and 25 cases per 100,000 children for pneumococcal bacteraemia.

The incidence of pneumonia was 2,561.7 cases per year per 100,000 children.

The incidence of otitis media was 49,000 cases per year per 100,000 children.

The incidence of MVT was 1,585 cases per 100,000 children.
The mortality rate per 100 children was 6.6 for pneumococcal meningitis and 1.26 for bacteraemia.

Vaccine efficacy was 90%.

In particular, the use of the vaccine reduced the incidence of all-cause pneumonia by 11.4% and all-cause otitis media by 5.8%.

There was also a 10.6% reduction in recurrent acute otitis media, a 24.9% reduction in MVT procedures, and a 33% reduction in episodes of radiographically confirmed pneumonia.

Efficacy decreased by 3% per year for years 6 to 10 after initial vaccination.

Vaccine efficacy for infants aged less than 6 months was 33%.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the number of life-years saved with vaccination over no vaccination. This was derived from the decision model. An annual discount rate of 3% was applied as the long-term benefits were estimated. Other relevant outputs of the model were the total number of cases of disease and deaths associated with the two strategies.

**Direct costs**
An annual discount rate of 3% was applied as the costs were incurred over a long timeframe. The unit costs were presented, while the quantities of resources used were derived from probabilities of events used in the model. The health services included in the economic evaluation were medical costs (physician visits, hospital stay, vaccine, diagnostic tests, antibiotic therapy) and non-medical costs (transportation). The cost/resource boundary of the health care system was adopted for the analysis of the direct costs. Resource use was estimated on the basis of patterns of care defined by a panel of experts and published evidence. The costs were derived from several sources, such as Ontario payment rates, a published study, and experts' opinions. All the costs were presented in 2000 values.

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

**Indirect Costs**
The indirect costs (i.e. those associated with productivity losses) were included in the analysis since a societal perspective was adopted. The unit costs were presented separately from the quantities of resources used. The costs were estimated using the mean hourly wage for Ontario, as given by Statistics of Canada. Resource use was based on experts’ assumptions. An annual discount rate of 3% was applied and the costs were presented in 2000 values.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
Multivariate sensitivity analyses were conducted to assess the robustness of the estimated cost-effectiveness ratios to variations in the model inputs. It was reported that the results were tabulated for 10,000 different combinations of possible values. The efficacy rates for each of the four diseases were varied simultaneously across their 95% confidence intervals. Incidence estimates were varied simultaneously within a range of +/- 50% of the baseline values. Univariate sensitivity analyses were carried out on the incidence of meningitis using an alternative source of estimate. Finally, an analysis of the three catch-up populations was also conducted.
Estimated benefits used in the economic analysis
In a birth cohort of 340,000 children for a 10-year time period, the total number of cases of disease would be:

1,713,564 (241 bacteraemia, 29 meningitis, 78,908 pneumonia, 1,591,114 otitis media, and 43,272 MVT) with vaccination; and

1,813,451 (850 bacteraemia, 103 meningitis, 87,095 pneumonia, 1,671,532 otitis media, and 53,871 MVT) without vaccination.

Therefore, the vaccination strategy led to a reduction of 99,887 cases of disease (609 bacteraemia, 74 meningitis, 8,187 pneumonia, 80,418 otitis media, and 10,599 MVT).

The number of deaths was 5 with vaccination and 17 without vaccination. Therefore, 12 cases were avoided with vaccination.

Assuming a life-expectancy of 78 years, there would be 938 undiscounted life-years gained (or 349 discounted life-years gained) with vaccination over no vaccination.

Cost results
The direct medical costs accounted for the highest proportion of the total costs.

The total disease costs (in millions) without vaccination were Can$898.5 (i.e. Can$483.8 for direct medical costs, Can$414.7 for indirect and direct non-medical costs, and Can$5.1 for future productivity costs).

The total disease costs (in millions) with vaccination were Can$835.5 (i.e. Can$447.2 for direct medical costs, Can$388.3 for indirect and direct non-medical costs, and Can$1.4 for future productivity costs).

Thus vaccination led to cost-savings of Can$63 (Can$36.6 for direct medical costs, Can$26.4 for indirect and direct non-medical costs, and Can$3.7 for future productivity costs).

The break-even cost of vaccination (including an administration fee and discounted fourth dose) was Can$50 from the societal perspective and Can$27 when only the direct costs relevant to the health care system were considered.

At the baseline vaccine cost of Can$67.50, the expected total costs (in million) from the societal perspective would be Can$903.5 without vaccination and Can$927.4 with vaccination. This resulted in an extra cost of Can$23.8 for the whole cohort with vaccination.

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

From a societal perspective, the incremental cost per life-year gained with vaccination over no vaccination (after excluding future productivity costs in order to avoid double-counting) was Can$29,287 when the health benefits were not discounted and Can$78,778 when the benefits were discounted.

From the health care payer perspective, the incremental cost per life-year gained was Can$154,591 after discounting the health benefits.

From the societal perspective, the incremental cost per illness avoided was Can$275 at a vaccine cost of Can$67.50.

The analysis of the three catch-up populations showed that the break-even cost of vaccination was:

Can$64 (societal) and Can$35 (payer) for children who received initial vaccination during the age of 7 to 11 months (catch-up 1: 3-dose schedule);
Can$87 (societal) and Can$47 (payer) for children who received initial vaccination during the age of 12 to 23 months (catch-up 2: 2-dose schedule);

Can$94 (societal) and Can$54 (payer) for children who received initial vaccination during the age of 2 to 5 years (catch-up 3: 1-dose schedule).

The multivariate sensitivity analysis showed that the undiscounted cost per life-year gained ranged from Can$16,415 to Can$39,633 when vaccine efficacy was varied. In addition, it ranged from Can$1,568 to Can$71,106 when disease incidence changed, and it was Can$26,475 when an alternative estimate of meningitis incidence was used.

Authors’ conclusions
Universal vaccination with the 7-valent pneumococcal conjugate vaccine (PCV-7) for children was a potentially cost-effective strategy. It compared favourably with the cost-effectiveness of other health care interventions currently used in Canada.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. No vaccination was selected not only to reflect standard care in some settings, but also to assess the active value of vaccination. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies. It was unclear whether a review of the literature was conducted, or whether the primary estimates were identified selectively. The design of only one primary study was reported and information on other sources was not provided. Therefore, the validity of the primary studies was unknown. The methods used to extract and then combine the primary estimates were not reported. All model inputs were varied in the sensitivity analysis to address the issue of uncertainty in the probability values.

Validity of estimate of measure of benefit
The summary benefit measure was the life-years gained, which was appropriate as the impact of the intervention on the patients’ health was assessed. Since the strategy of vaccination affected not only mortality but also morbidity, the use of quality-adjusted survival would have been more interesting. Discounted and undiscounted results were presented.

Validity of estimate of costs
The authors adopted a societal perspective in the cost analysis and, accordingly, all the relevant costs were included. The estimated costs were grouped as direct medical costs, direct non-medical costs, and indirect costs, which permitted the calculation of costs relevant to the health care payer. Discounting was relevant and was conducted. The unit costs were provided. However, information on the quantities of resources used was not totally clear for some items, such as the direct costs. The source of the data was reported. The price year was given, which makes reflation exercises in other settings easy. The cost estimates were specific to the study setting and the economic estimates were not varied in the sensitivity analysis. Most of the evidence on resource use was derived from experts’ opinions.

Other issues
The authors did not compare their findings with those from other published studies. In terms of the generalisability of the study results to other settings, the authors stated that their analysis referred to the Canadian setting and caution is therefore required when extrapolating the results to other settings. The authors also noted that due to the lack of data, the analysis did not consider some relevant benefits of universal vaccination, such as the reduced antibiotic resistance, herd immunity, and impact of vaccination on other Streptococcus pneumoniae-associated diseases. The authors noted also some limitations of their analysis. For example, variations in the patients’ characteristics were not evaluated since an "average patient" was considered.
Implications of the study
The study results suggested that the decision to implement universal vaccination with PCV-7 should be based not only on economic issues, but also on qualitative health improvements.

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