Pertussis vaccination strategies for neonates: an exploratory cost-effectiveness analysis

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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
Three pertussis vaccination strategies for neonates were examined. These were a parental (both mother and father) vaccination strategy, a birth vaccination strategy and a 1-month vaccination strategy.

Type of intervention
Primary prevention.

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

Study population
The study sample comprised a hypothetical cohort of neonates.

Setting
The setting was a hospital and primary care (depending on the vaccination schedule). The economic study was carried out in Australia.

Dates to which data relate
The effectiveness data and some resource use estimates were derived from studies published between 1992 and 2003. No dates for resource use were explicitly reported. The price year was 2000.

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

Modelling
A Markov model was constructed to estimate the costs and health consequences of three strategies to reduce pertussis over the first 6 months of an infant's life. Seven health states were considered. These were susceptible, infected, disease immune, vaccinated x 1, vaccinated x 2, vaccinated =/> 3, and dead. A susceptible infant could be infected by a parent, infected by another person, remain susceptible, or die due to other causes. Infected cases that were admitted to hospital could have complications (e.g. pneumonia), and could require intensive respiratory support with an increased risk of death. For infected cases that were not admitted to a hospital, deaths occurred at a rate equal to the age specific all-cause infant mortality rates. Any deaths of infected infants were considered as pertussis-related. All notified cases were treated with the recommended antibiotic, erythromycin, which might result in idiopathic hypertrophic pyloric stenosis (IHPS). Infants who recovered from infection moved to the disease immune health state, where they were vaccinated according to the infant immunisation schedule. Immune infants were assumed to remain immune over the short time horizon of the analysis (26 weeks). The cycle length was one week. Although the model had a short time horizon, health benefits (disability-adjusted life-years, DALYs) were estimated for the individuals' lifetime.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the number of notified cases per 100,000 infants;
- the probability of infection from the parents;
- case duration;
- the hospitalisation rates for notified cases (age =/< 9 weeks and age >10 weeks);
- the probability of complication in hospitalised cases;
- the probability of death from complications;
- the all-cause mortality rates per 1,000 infants (age =/< 4 weeks and age 5 - 52 weeks);
- the probability of IHPS from erythromycin (age <1 year);
- the efficacies of the first scheduled vaccine (age 2 months), second scheduled vaccine (age 4 months) and third scheduled vaccine (age 6 months);
- the infant coverage rate for the scheduled vaccine;
- the pertussis case DALY weight;
- the IHPS DALY weight; and
- life expectancy at birth.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken. The primary studies appear to have been identified selectively. No information on the design and characteristics of the primary sources was provided. Some data came from Australian statistics.

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 appear to have been used to derive clinical estimates.

Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates.
Investigation of differences between primary studies
Not stated.

Results of the review
The number of notified cases per 100,000 infants per week was 5.171 (standard deviation, SD=3.13).

The probability of infection from the parents was 0.51 (SD=0.25).

The case duration was 6.0 (SD=2.0) weeks.

The hospitalisation rates for notified cases were 0.529 (SD=0.13) (age <= 9 weeks) and 0.386 (SD=0.10) (age >10 weeks).

The probability of complication in hospitalised cases was 0.17 (SD=0.06).

The probability of death from complications was 0.125 (SD=0.04).

The all-cause mortality rates per 1,000 infants were 3.91 (age <= 4 weeks) and 1.95 (age 5 - 52 weeks).

The probability of IHPS from erythromycin (age <1 year) was 0.05 (SD=0.02).

The efficacy of the first scheduled vaccine (age 2 months) was 0.680 (SD=0.09).

The efficacy of the second scheduled vaccine (age 4 months) was 0.918 (SD=0.03).

The efficacy of the third scheduled vaccine (age 6 months) was 0.998 (SD=0.003).

The infant coverage rate for the scheduled vaccine was 0.95 (SD= 0.17).

The pertussis case DALY weight was 0.178 (SD=0.06).

The IHPS DALY weight was 0.463 (SD=0.157).

The life expectancy at birth was 79.4 (SD=15.8) years.

Methods used to derive estimates of effectiveness
The authors made some assumptions to derive effectiveness estimates used in the decision model. Assumptions were also made to assess some SDs of estimates obtained from the literature.

Estimates of effectiveness and key assumptions
The number of general practitioner (GP) consultations per case was 2.0 (SD=0.7).

The IHPS duration was 6.0 (SD=2.0) weeks.

The effectiveness of vaccination in adults (parental vaccination strategy) was 0.750 (SD=0.250).

The reduction in first vaccine efficacy if given at birth was 0.67 (SD=0.23).

The reduction in second vaccine efficacy if first vaccine given at birth was 0.85 (SD=0.29).

The reduction in first vaccine efficacy if given at one month was 0.75 (SD=0.25).

The reduction in second vaccine efficacy if first vaccine given at one month was 0.90 (SD=0.30).
The DALY associated with a hospitalised case and no complications was 0.010 (SD=0.003).

The DALY associated with a hospitalised case with complications was 0.021 (SD=0.007).

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

The summary benefit measure used in the cost-utility analysis was the number of DALYs averted. These were estimated by combining disability weights and expected survival in the decision model. Disability weights were obtained from the literature and the person time trade-off method was used to elicit patients' preferences. An annual discount rate of 3% was applied. The summary benefit measures in the cost-effectiveness analysis were the cases averted and deaths averted. The reduction in notified cases and deaths was also reported as a model output.

**Direct costs**

The cost analysis was carried out from the perspective of the Australian public health system. The health services included in the economic evaluation were vaccination, administration of the childhood immunisation programme, GP visits and hospital admissions (with or without complications, and for IHPS). The unit costs were reported for most items, while some costs were presented as macro-categories. The source of the resource use data was unclear, although some information came from the literature. The costs were estimated from national sources, such as hospital records of all infants admitted in 1998/1999 to 1999/2000 with a diagnosis of pertussis recorded in the Health Outcomes Information Statistical Toolkit, containing a field for diagnostic-related groups. Discounting was not relevant since the costs were incurred during 6 months. The price year was 2000.

**Statistical analysis of costs**

The costs were presented as mean values and SDs.

**Indirect Costs**

The indirect costs were not considered in the economic evaluation.

**Currency**

Australian dollars (Aus$). The exchange rate in 2000 from Australian dollars into US dollars ($) and UK pounds sterling () was Aus$1.00 = $0.60 = 0.40.

**Sensitivity analysis**

The model inputs with the greatest impact on the cost-utility and cost-effectiveness estimates were identified through a multivariate sensitivity analysis using ordinary least-squares. The key factors tested in the one-way sensitivity analysis were infection data, vaccine efficacy, time horizon (extended from 6 to 18 months), cost of the vaccine and its administration, disability weights, and discount rate for health benefits. Further, given the known underestimation of pertussis by disease notifications, the rates of notified cases, hospitalisations and deaths were varied. A probabilistic sensitivity analysis was also carried out using 25,000 Monte-Carlo simulations for each vaccination strategy. Probabilistic distributions were assigned to costs, outcomes and cost-effectiveness. The probability that a strategy was cost-effective (i.e. the cost-effectiveness acceptability for given levels of society's willingness to pay) was also estimated. The authors set stochastic distributions.

**Estimated benefits used in the economic analysis**

The estimated DALYS were 0.000243 (SD=0.000203) with current practice, 0.000133 (SD=0.000122) with birth vaccination, 0.000184 (SD=0.000164) with 1-month vaccination and 0.000150 (SD=0.000141) with parental vaccination.

In comparison with current practice, vaccination at birth reduced notified cases, deaths and increased DALYS by 44.3,
44.7 and 45.3%, respectively. Vaccination at one month reduced cases, deaths and increased DALYs by 25.7, 24.1 and 24.3%, respectively. Parental vaccination reduced pertussis cases, deaths and increased DALYs by 38.6, 38.2 and 38.3%, respectively.

Cost results
The estimated costs per patient were Aus$101.50 (SD=20.29) with current practice, Aus$134.71 (SD=20.57) with birth vaccination, Aus$144.74 (SD=29.39) with 1-month vaccination and Aus$174.88 (SD=21.10) with parental vaccination.

Synthesis of costs and benefits
The incremental cost-utility ratios and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative vaccination strategies in comparison with current practice.

The incremental cost per DALY averted versus the current strategy was Aus$330,175 (SD=15,461) with birth vaccination, Aus$735,994 (SD=147,679) with 1-month vaccination and Aus$787,504 (SD=48,075) with parental vaccination.

Thus, the birth vaccination strategy was the most cost-effective strategy. Both the 1-month and parental vaccination strategies cost approximately 2.5 times more per DALY averted than the birth vaccination strategy.

The incremental cost per case averted versus the current strategy was Aus$107,161 with birth vaccination, Aus$235,994 with 1-month vaccination and Aus$271,593 with parental vaccination.

The incremental cost per death averted versus the current strategy was Aus$10.1 million with birth vaccination, Aus$23.8 million with 1-month vaccination and Aus$26.0 million with parental vaccination.

The cost-effectiveness acceptability curves showed that the birth vaccination strategy had the highest probability of being acceptable for given willingness-to-pay thresholds. For example, the probability of being below a threshold of Aus$380,000 for the median incremental cost-utility ratio was 50% for the birth vaccination strategy, while only 16.6% for the 1-month strategy and 13.4% for the parental strategy.

The multivariate analysis showed that the probabilities of infection, being admitted to hospital, complications of infection, probability of death, scheduled vaccination coverage rates, duration of pertussis symptoms, the DALY weights for pertussis and IHPS, life expectancy and the costs of hospitalisation with complications were statistically significant factors in all three models. In particular, parental vaccination at birth was most cost-effective where protection persisted for subsequent children. Changes in other model inputs affected the cost-utility ratios but did not alter the ranking of the alternative vaccination strategies.

Authors’ conclusions
The high cost per disability-adjusted life-year (DALY) achieved with all strategies was due to the very small changes in the denominator (i.e. number of DALYs) rather than changes in the costs. The least expensive strategy was the programme where neonates were vaccinated at birth. However, all three strategies were high in cost compared with the Australian guideline cost-effectiveness acceptability threshold of Aus$100,000 per life-year gained.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate and was widely discussed. The reference strategy reflected the current practice in Australia. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from the literature. However, the methods and conduct of the review were not reported. No information on the search and inclusion or exclusion criteria was provided. The number of studies included in the review was reported but, with the exception of a few studies, the primary studies were not described.
Thus, it was not possible to assess the validity of the primary studies. Some assumptions were also made to derive clinical data that were not available from the literature. The issue of uncertainty was extensively addressed in the sensitivity analysis, and all clinical parameters were varied.

**Validity of estimate of measure of benefit**

The authors justified their use of DALYs. They pointed out that pertussis could result in death or various levels and durations of morbidity, thus the choice of DALYs was appropriate. Discounting was relevant and was performed, as suggested by Australian guidelines. The use of different discount rates was investigated in the sensitivity analysis. DALYs also have the advantage of being quite comparable with the benefits of other health care interventions. However, the authors noted that the disability weights were derived using clinician panels. Other benefit measures used in the cost-effectiveness analysis were more specific to the disease considered in the study. The authors stated that the benefits of vaccination for parents were not considered in the model because the focus of the analysis was on infants.

**Validity of estimate of costs**

The costs included were consistent with the perspective adopted in the study, although they were restricted to direct medical costs. A detailed breakdown of the cost items was provided, but there was limited information on the quantities of resources used. The unit costs were reported for most items. The source of the costs was given, with national sources used whenever possible. The cost estimates were treated stochastically and were extensively varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods.

**Other issues**

The authors stated that comparisons with other studies were difficult because of the methodological characteristics of their analysis. The results of a study carried out in the UK were reported, although some rates used in the decision model were different from those used in the current study. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were performed. These enhance the external validity of the analysis. The authors noted that assumptions about key factors, such as the effectiveness of early vaccination, represent a limitation of the analysis. Moreover, other components of pertussis modelling, such as any age-shifts, herd immunity, or waning of immunity, were ignored due to the short time horizon of the analysis; this was justified. The authors noted the uncertainties around the efficacy of a pertussis vaccine given at birth. It was also stated that a strategy of vaccination at one month of age was relatively less cost-effective and could disrupt current vaccination regimens, resulting in more infants missing scheduled vaccinations.

**Implications of the study**

The study results suggested that alternative pertussis vaccination strategies in neonates might not be cost-effective within the Australian health care system. The authors noted that future research should assess birth and parental vaccination strategies, elucidating areas of uncertainty in these strategies.

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