An economic evaluation of universal infant vaccination against hepatitis B virus using a combination vaccine (Hib-HepB): a decision analytic approach to cost effectiveness

Harris A, Yong K, Kermode M

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 universal vaccination of infants using the combination Haemophilus influenzae-hepatitis B (Hib-HepB) vaccine COMVAX (Merck & Co. Inc and CSL Ltd.), in order to prevent hepatitis B virus (HBV) infection, was studied. This combination vaccine strategy consisted of first administering a monovalent hepatitis B vaccine when the babies were just born. This was followed by a diphtheria, tetanus, acellular pertussis (DTaP) vaccine plus a Hib-HepB vaccine when they were 2 and 4 months old, then a DTaP vaccine when they were 6 months, and a Hib-HepB vaccine when they were 12 months.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The hypothetical study population depended on the vaccine strategy considered. For the combination vaccine it was all children (newborns until 12 months old), including both high- and low-risk children. For selective vaccine it was only children at high-risk of being infected with HBV. In other words, those born either to hepatitis B surface antigen positive mothers (identified through antenatal screening) or those born into families with at least one member from a country with intermediate to high prevalence of hepatitis B.

Setting
The hypothetical practice setting was primary care. The model parameters were derived using data from Australia.

Dates to which data relate
The effectiveness data were obtained from studies published between 1989 and 1999. The costs were generally reported in the year 2000. The exceptions were visits (others than the GP visits) related to the vaccine administration, which were taken from a study published in 1994). Also, the annual cost of asymptomatic cirrhosis, average cost per episode of liver failure, and hepatoma, which were collected from a study published in 1997. There did not appear to be a price year, but different dates for different costs were reported.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and experts' opinions.

Modelling
A Markov model was used to model the health outcomes and costs resulting from vaccine administration and infection
with HBV. These were modelled for a hypothetical Australian birth cohort of 260,000 infants using each of the two vaccination strategies. The health outcomes and costs were modelled separately for infants at high and low risk of HBV infection. The transitions between the health states were modelled over 80 cycles of one year each.

Outcomes assessed in the review
The authors derived parameter estimates from published studies and from expert clinical opinion. It was not clear from the paper which estimates were derived using which method. The following model parameters were derived.

The proportion of high-and low-risk infants fully vaccinated for the combination vaccine, the proportion of high-risk infants fully vaccinated under the selective vaccination strategy, and the annual risk of HBV infection.

The annual probabilities of experiencing acute HBV infection (either non-fulminant or fulminant infection), or either recovering from infection or having chronic infection for the case of non-fulminant acute hepatitis.

The annual probabilities of either dying from HBV infection, recovering and/or becoming immunised, or having a chronic infection for the case of fulminant acute hepatitis.

The annual probabilities of recovering and/or becoming immunised, having persistent infection with active disease, or having hepatoma for the case of immunotolerant phase under chronic HBV.

The annual probabilities of experiencing cirrhosis, hepatoma or death for the case of immune clearance phase under chronic HBV, and the annual probability of experiencing hepatoma for the case of quiescent phase of chronic HBV.

The annual probabilities of recovering and/or becoming immunised, having persistent infection with active disease, or having hepatoma for the case of immunotolerant phase under chronic HBV.

These annual probabilities were reported for three different age groups. The age groups were 0 to 19-year-olds, 20 to 39-year-olds, and 40 years or older. The authors also assessed the percentage of infants that would be immunised by receiving the complete set of vaccines corresponding to either combination or selective vaccine, and the relative risk of HBV infection for high-risk infants compared with low-risk infants.

Study designs and other criteria for inclusion in the review
One randomised clinical trial was included in the review. Two studies were based on surveys. The designs of the other studies included in the review were 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
At least 7 published studies were included in the review as sources of the effectiveness data.

Methods of combining primary studies
Not reported.
Investigation of differences between primary studies
Not reported.

Results of the review
The proportion of high- and low-risk infants fully vaccinated under the combination vaccine was 87.4% of 12 to 15-month-old children.

The proportion of high-risk infants fully vaccinated under the selective vaccination strategy was 65%.

Due to space constraints, only the probabilities for the 0 to 19 age group are reported here.

The annual risk of HBV infection was between 0.0002 and 0.001.

The annual probability of experiencing non-fulminant acute HBV infection was between 0.998 and 0.999.

The annual probability of experiencing fulminant acute HBV infection was between 0.001 and 0.002.

The annual probability of recovering from infection after a non-fulminant acute hepatitis was between 0.07 and 0.9.

The annual probability of experiencing chronic infection after a non-fulminant acute HBV infection was between 0.1 and 0.93.

The annual probability of dying from HBV infection after a fulminant acute hepatitis was 0.7. This was independent of the age group.

The annual probability of recovering and/or becoming immunised after a fulminant acute hepatitis was 0.06. This was independent of the age group.

The annual probability of experiencing a chronic infection after a fulminant acute hepatitis was 0.24. This was independent of the age group.

The annual probability of recovering and/or becoming immunised during the immunotolerant phase of chronic HBV infection was 0.02. This was independent of the age group.

The annual probability of experiencing persistent infection with active disease during the immunotolerant phase of chronic HBV infection was 0.0012.

The annual probability of experiencing hepatoma during the immunotolerant phase under chronic HBV infection was 0.0005.

During the immune clearance phase under chronic HBV infection, the annual probabilities of experiencing either cirrhosis, hepatoma or death (independent of age) were 0.02 (cirrhosis), 0.005 (hepatoma) and 0.0028 (death), respectively.

The annual probability of experiencing hepatoma during the quiescent phase of chronic HBV infection was 0.005, independently on the age.

The annual probabilities of experiencing either hepatoma or death because of a cirrhosis state were 0.0465 (hepatoma) and 0.0771 (death), respectively.

The annual probability of dying because of a hepatoma state was 0.95.

The proportion of infants that would be immunised by receiving the complete set of vaccines under either combination or selective vaccine was 98%.
The relative risk of HBV infection for high-risk infants compared with low-risk infants was 24.9.

Methods used to derive estimates of effectiveness
See the 'Outcomes Assessed in the Review' section.

Estimates of effectiveness and key assumptions
The authors made assumptions, including the following.

The introduction of universal hepatitis B vaccination of infants using a combination vaccine would increase the proportion of high-risk infants fully vaccinated against hepatitis B to a level equivalent to the proportion fully vaccinated against Hib disease.

There was no account for the impact of herd immunity on susceptibility to infection.

The protection against hepatitis B following infection or vaccination is life long.

Measure of benefits used in the economic analysis
The summary measure of health benefit used in the economic analysis was the discounted life-years gained by implementing the combination strategy, compared with the selective strategy. Other related, intermediate outcomes derived by the model were the number of cases of HBV infection and chronic HBV infection for each of the vaccination strategies.

Direct costs
The direct costs considered at analysis were those of the health service. These included the costs associated with vaccine administration, acute HBV infection without hospitalisation, acute HBV infection with hospitalisation, the immunotolerant and the immune clearance phases, cirrhosis (both asymptomatic cirrhosis and liver failure), and hepatoma. The costs related to vaccine administration were for doses of vaccine, the notification fee per vaccine administered, GP consultation and other visits. The costs of acute HBV infection without hospitalisation included diagnostic serology, other pathology tests and medical consultations. The costs of the immunotolerant and the immune clearance phases included pathology tests, medical consultations and medications, in case of receiving treatment. The costs of Hib vaccination were not included because they were considered to be the same with both strategies. Moreover, the costs of a birth dose of monovalent HBV vaccine for low-risk infants were not included.

Most of the costs were obtained from CSL Limited, the Department of Health and Aged Care, the Australian Childhood Immunisation Register, the Medical Benefits Schedule, the Pharmaceutical Benefits schedule, the Victorian Department of Human Services, and two published economic evaluations. A panel of five experts was assembled to derive the resource utilisation of patients with acute and chronic HBV infection not requiring hospitalisation. These costs were included in the Markov model. Some, but not all of the resource quantities were reported separately from the costs.

Discounting was performed using a 5% discount rate, which was relevant since the economic analysis had a lifetime time horizon. Most of the costs related to the year 2000, with the exception of the costs obtained from the economic evaluations (i.e. other visits associated with vaccine administration and costs related to cirrhosis and hepatoma), which related to 1997 and 1994. It was not reported if these were reflated.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The authors stated that they considered the social health care costs of the vaccination strategies, but they did not consider the productivity lost due to the infection. Therefore, they did not report the indirect costs.

**Currency**

Australian dollars (Aus$).

**Sensitivity analysis**

One-way sensitivity analyses were performed to investigate variability in the data. The parameters varied were the risk of HBV infection (4.1%), compliance with the vaccination strategy (82.5%), vaccine effectiveness (90%), the discount rate (0 and 3%), and the incremental cost-effectiveness ratio (ICER) when the dose of monovalent HBV vaccine at birth for low-risk infants was included in the combination strategy costs.

**Estimated benefits used in the economic analysis**

A discount rate of 5% was used to discount the health benefits. The numbers of discounted life-years obtained were 4,973,855 with the selective strategy and 4,973,069 with the combination strategy. A gain of 217 discounted life-years per 260,000 infants would be obtained with the combination vaccine strategy, when compared with the selective vaccine strategy.

A related outcome was the number of cases of HBV infection. This was 19,189 under the selective vaccination strategy and 4,323 under the combination strategy. A 77% reduction (-14,866 cases) in the number of cases of HBV infection was obtained when the combination strategy was implemented, compared with the selective vaccination strategy.

**Cost results**

The total discounted direct costs (including the costs of both vaccination and HBV disease) were Aus$13,080,842 under the selective strategy and Aus$15,616,048 under the combination strategy. When compared with the selective strategy, the combination strategy resulted in an incremental cost of Aus$2,535,206.

**Synthesis of costs and benefits**

The ICER of the combination strategy, compared with the selective strategy, was calculated as a weighted average of the changes in the costs and outcomes for the high and low-risk groups. This considered the number of life-years saved under the combination strategy as the summary measure of benefit. In the base-case analysis, the ICER was Aus$11,862 per life-year saved.

The ICER was sensitive to variations in the discount rate. Reducing the discount rate from 5% to 3% or below would make the combination strategy dominant, because it generated more life-years at a lower cost when compared with the selective strategy. The ICER was also sensitive to variations in the incidence of HBV infection. At half the initial incidence rate, the ICER became Aus$34,103. When the cost of the monovalent HBV vaccine at birth for low-risk infants was included in the combination strategy costs, the ICER rose to Aus$17,411 per life-year gained with the combination strategy, compared with the selective strategy.

**Authors’ conclusions**

The results suggest that universal hepatitis B vaccination of Australian infants using a combination strategy represents a worthwhile investment of public funds when both the health benefits and costs are considered.

**CRD COMMENTARY - Selection of comparators**

The comparator chosen, a selective strategy, was justified on the grounds that it was the current practice in the authors' setting. The authors also stated that there is another combination vaccine (DTPa-HepB; Infanrix-HepB, SmithKline Beecham) that was not considered, because the effectiveness and costs were expected to be similar to those of the
combination vaccine considered at analysis. You should consider if these are widely used health technologies in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not report that a systematic review of the literature had been undertaken. It was unclear how the authors derived their parameter estimates from the available studies. Although experts’ opinions were used to derive estimates of effectiveness, it was not clear from the paper which estimates were determined in this way or how they were determined. It is therefore difficult to assess the reliability of the results. In addition, only some of the effectiveness estimators were varied in the sensitivity analysis.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled using a Markov model, which seems to have been appropriate. The health benefits were discounted at a 5% discount rate. The authors reported that the health benefits of the combination strategy may have been underestimated, because the benefits derived from the convenience of a combination vaccine and those derived from herd immunity due to increased compliance with hepatitis B immunisation were not considered in the economic study.

**Validity of estimate of costs**
No perspective was stated. The cost categories relating to the health service appear to have been included in the analysis. Most of the resource quantities were reported separately from the costs, but not all. Some resource utilisation was derived from an expert panel. However, there were no sensitivity analyses on this, which introduces uncertainty into the reliability of the conclusions. No unique price year was stated, which makes the interpretation of the results difficult. It also, hinders relfation exercises to other settings.

**Other issues**
The authors compared their findings with those from other studies, and they found consistency among these results. The issue of generalisability of the results to other settings was not addressed, but some sensitivity analysis was performed. The results were reported in full and the authors’ conclusions reflected the scope of the analysis.

**Implications of the study**
The results of the study appear to show that the universal combination strategy against HBV infection was preferred to a selective vaccination strategy. However, the lack of detailed reporting on the derivation of the model parameter estimates makes it hard to judge its validity.

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**Other publications of related interest**


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