Crucial factors that influence cost-effectiveness of universal hepatitis B immunization in India

Prakash C

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 strategies of universal hepatitis B immunisation (as part of the World Health Organization Expanded Programme on Immunisation, EPI) and a do-nothing approach (i.e. no immunisation against hepatitis B) were investigated.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population was a hypothetical cohort of 100,000 infants born in India in year 0 of the model.

Setting
The setting was the community. The economic study was carried out at Harvard University, USA.

Dates to which data relate
The model used in this study had been reported elsewhere (Prakash, see Other Publications of Related Interest). Hence, the dates to which the data related were not fully reported in this paper. However, it appears that the effectiveness data have been collected from studies published between 1990 and 1995. The resource use data were collected from studies published between 1995 and 2003. The price year was 1993.

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

Modelling
The expected costs and expected effectiveness were estimated using a Markov model. The model was constructed in two parts, (a) transmission of hepatitis B, and (b) transition of the infected population through various disease states of hepatitis B. The point of entry into the model was the mother of a member of the study population. The infants, who contracted hepatitis B at birth by vertical transmission from the mother, entered the infection tree, where they were exposed to the risk of various outcomes and manifestations of hepatitis B. The lifetime horizon was used in the model.

Outcomes assessed in the review
The outcomes assessed were:
the probability that the mother would be HBsAg (hepatitis B surface antigen) positive;
the probability that the mother would be HBeAg (hepatitis B early antigen) positive;
the probability of infection to the child if the mother was HBeAg positive;
the probability of infection to the child if the mother was HBeAg negative;
the probability that the infected child would be free of symptoms;
the probability that the infected child would develop acute hepatitis;
the probability that the acute hepatitis would be fulminant;
the probability of resolution of acute hepatitis;
the probability that the infected child would be a chronic carrier;
the probability of resolution of being a chronic carrier;
the probability that the chronic carrier would develop chronic hepatitis;
the probability that chronic hepatitis would develop into persistent hepatitis;
the probability that the chronic hepatitis would be active; and
the probability that the active chronic hepatitis would develop into cirrhosis or primary hepatocellular carcinoma (PHC).

The other outcomes assessed were the efficacy of the vaccine, the coverage for hepatitis B vaccination, and the vaccine wastage for hepatitis B vaccination as part of the EPI.

**Study designs and other criteria for inclusion in the review**
The designs of the primary studies were not reported in this paper (refer to Prakash, see Other Publications of Related Interest).

**Sources searched to identify primary studies**
Not reported (refer to Prakash, see Other Publications of Related Interest).

**Criteria used to ensure the validity of primary studies**
Not reported (refer to Prakash, see Other Publications of Related Interest).

**Methods used to judge relevance and validity, and for extracting data**
Not reported (refer to Prakash, see Other Publications of Related Interest).

**Number of primary studies included**
Not reported (refer to Prakash, see Other Publications of Related Interest).

**Methods of combining primary studies**
Not reported (refer to Prakash, see Other Publications of Related Interest).
Investigation of differences between primary studies
Not investigated (refer to Prakash, see Other Publications of Related Interest).

Results of the review
The probability that the mother would be HBsAg positive was 9.5%.

The probability that the mother would be HBeAg positive was 12.0%.

The probability of infection to the child if the mother was HBeAg positive was 90%.

The probability of infection to the child if the mother was HBeAg negative was 15%.

The probability that the infected child would be free of symptoms was 7% if the mother was HBeAg positive, and 81.1% if the mother was HBeAg negative.

The probability that the infected child would be a chronic carrier was 90.2% if the mother was HBeAg positive, and 15.7% if the mother was HBeAg negative.

The probability that the infected child would develop acute hepatitis was 2.8% if the mother was HBeAg positive, and 3.2% if the mother was HBeAg negative.

The probability that the acute hepatitis would be fulminant was 25%.

The probability of resolution of acute hepatitis was 75%.

The probability of resolution of being a chronic carrier was 10%.

The probability that a chronic carrier would develop chronic hepatitis was 90%.

The probability that chronic hepatitis would develop into persistent hepatitis was 80%.

The probability that the chronic hepatitis would be active was 20%.

The probability that the active chronic hepatitis would develop into cirrhosis or PHC was 12.5%.

The efficacy of the vaccine was 95%.

The coverage for the hepatitis B vaccination was 52%.

The vaccine wastage for hepatitis B vaccination as part of the EPI was 10%.

Measure of benefits used in the economic analysis
The measure of effectiveness used was the disability-adjusted life-years (DALYs) gained. The DALY was the sum of years of life lost and years lived with disability, adjusted for the severity of disability. The number of DALYs gained was discounted at an annual rate of 3% (as well as 0%).

Direct costs
The costs and the quantities were not reported separately. The direct costs covered paediatric vaccines, administration and treatment. The treatment costs in India were derived from a household survey conducted by the National Council of Applied Economic Research (1993-94) and a rural-urban population ratio of 73:27. The volume of services required for treating hepatitis B sequelae were obtained from a published study, owing to the paucity of Indian data. Discounting was relevant, as the costs were accrued over the lifetime of the child, and was appropriately performed at a rate of 3%.
per annum. The price year was 1993.

**Statistical analysis of costs**
No statistical analysis of the costs was performed.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($). The costs were calculated in 1993 rupees, which were then converted into 1993 US dollars using the international exchange rate for the rupee for 1993.

**Sensitivity analysis**
The author performed exhaustive sensitivity analyses (i.e. sensitivity, uncertainty and scenario analyses).

In the sensitivity analysis, the discount rate was varied from 3 to 0% for effects. The uncertainty around some of the parameters was examined using Latin hypercube sampling to determine the stability of the results. The input variables in the model were the cost per inpatient and outpatient episode per case, the HBsAg carrier rate in antenatal women, HBeAg positivity in HBsAg carriers, the cost of one dose vaccine, vaccination coverage, vaccine wastage, and vaccine efficacy. The stochastic variables were represented either by uniform or by triangular distributions.

An uncertainty analysis was carried out to identify input distributions that were significant in determining output variable value by two analytical techniques (i.e. multivariate stepwise regression analysis and a rank order correlation method). A single simulation was then run in which 1,700 iterations were executed.

The scenario analysis was performed on output variable targets based on a conditional mean analysis. If the sub-set median for the input variable was close to the overall median, the input variable was marked as insignificant. If the sub-set median for the input variable deviated significantly from the overall median, the input variable was significant.

**Estimated benefits used in the economic analysis**
The estimated benefits used in the economic analysis were not reported in this paper (refer to Prakash, see Other Publications of Related Interest).

**Cost results**
The total costs of each strategy were not reported in this paper (refer to Prakash, see Other Publications of Related Interest).

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per DALY gained using a universal hepatitis B immunisation strategy as opposed to a do-nothing approach). The cost-utility ratio was $27.36 per DALY gained.

The results from the uncertainty analyses showed that the cost-utility ratio was affected by, in the order of decreasing influence, HBsAg positivity, vaccination coverage, the cost of one dose of vaccine and vaccine efficacy.

The results from the scenario analyses showed that the cost per DALY gained could decrease to 40% with changes in the HBsAg carrier rate. A subsequent decrease to 3% was achievable by improving the vaccination coverage to approximately 92%, and by decreasing the cost of the vaccine to about $0.60. All other input variables were not very
significant in improving the cost per DALY gained.

**Authors’ conclusions**
The strategy of universal immunisation against hepatitis B was so highly cost-effective that, even if the endemicity were much lower, it would still be the preferred strategy. The most crucial factor influencing the cost-effectiveness of universal hepatitis B immunisation in India was the HBsAg positivity in carrier mothers (i.e. hepatitis B endemicity). The other important variables, as revealed by an uncertainty analysis, were vaccination coverage, vaccine cost and vaccine efficacy.

**CRD COMMENTARY - Selection of comparators**
The use of the do-nothing approach as the comparator was justified on the grounds that India had not yet incorporated hepatitis B into the EPI. You should decide if this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**
The model used to determine the effects and costs of the immunisation programme were derived from another study by the author. Consequently, the methods undertaken in the review of the literature and the synthesis of the effectiveness data were not reported in this paper. As such, it is not possible to determine whether the review and synthesis of the evidence were undertaken satisfactorily. Since the main aim of the paper was to examine the parameters crucial to the cost-effectiveness of universal hepatitis B immunisation, exhaustive sensitivity analyses were undertaken on input parameters to the model. However, the author did not justify most of the ranges used in the sensitivity analysis (+/- 10% around the value).

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The instrument used to derive a measure of health benefit, a Markov Model, was appropriate. However, the author reported that the DALY was a function of preference of the analyst, rather than a function of preference of the patients or population. Future benefits were discounted at a rate of 3% per annum.

**Validity of estimate of costs**
Although the author reported that the costs were estimated from a societal perspective, indirect costs due to mortality and morbidity (i.e. productivity losses arising from foregone work due to death or illness) were not included. Also omitted were direct non-medical costs such as the cost of time and travel. The costs and the quantities were not reported separately, which will hamper the generalisability of the author’s results to other settings. Resource use and the unit costs were derived from published sources. The author undertook an exhaustive sensitivity analysis of the cost parameters and performed appropriate currency conversions from the Indian rupee to the US dollar. Discounting was relevant, as the costs were incurred during the lifetime of the patient, and the future costs were discounted appropriately. The price year was reported, which will aid any possible inflation exercises.

**Other issues**
The author made appropriate comparisons of his findings with those from other studies that also found HBsAg positivity in antenatal women to be a very important parameter influencing the cost-effectiveness of hepatitis B vaccination. The issue of generalisability to other settings was addressed in the sensitivity analysis. The author does not appear to have presented his results selectively and the conclusions reflected the scope of the analysis. The author reported that a limitation of his study was that the model was based on available best estimates of imperfect data and on a wide range of assumptions. Hence, an uncertainty analysis was carried out to test the robustness of the results to changes in variables that are stochastic and whose values were imprecisely known. Three weaknesses of the uncertainty analysis method were also reported. First, the choice of which variables to vary and which to treat as known or fixed. Second, the amount of variation around the base value. Third, how much of a change in base result is acceptable or constitutes a robust finding.
Implications of the study
The author reported that the scenario analysis from his study showed that an increase in hepatitis B endemicity would bring the cost per DALY gained to less than 40% if India did not go for universal immunisation immediately. Therefore, if India did not institute universal hepatitis B immunisation immediately, it would have to do so in the future when endemicity rises and makes this option even more cost-effective.

Source of funding
Supported by the Takemi Program in International Health, Harvard School of Public Health.

Bibliographic details

PubMedID
12701937

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Cohort Studies; Cost-Benefit Analysis; Decision Trees; Endemic Diseases /economics; Health Care Costs; Health Services Research; Hepatitis B /epidemiology /prevention & control /transmission; Hepatitis B Vaccines /administration & dosage /economics; Humans; India; Infant, Newborn; Infectious Disease Transmission, Vertical /economics; Markov Chains; Mass Vaccination /economics; Quality-Adjusted Life Years; Uncertainty

AccessionNumber
22003008065

Date bibliographic record published
31/05/2005

Date abstract record published
31/05/2005