Cost-effectiveness of routine childhood vaccination for hepatitis A in the United States


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 study examined three strategies for the prevention of hepatitis A. The strategies were:

- routine nationwide vaccination at age 1 year;
- no vaccination; and
- vaccination limited to children living in areas with disease rates higher than the national average or periodic outbreaks.

Type of intervention
Primary prevention (vaccination).

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

Study population
The study population comprised children aged 1 year.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2005. The costs and some resource use data came from studies published between 1996 and 2006. The price year was 2005.

Source of effectiveness data
The clinical and epidemiological data used in the decision model were:

- infection incidence,
- annual decline in incidence without vaccination,
- vaccination coverage,
- antibody titre parameters,
- the probabilities of symptomatic disease,
- the rates of transplant,
the death rates, and
the probabilities of hospitalisation given an icteric infection.

Modelling
A Markov model was constructed to simulate the natural history of disease in a single US birth cohort from birth in 2005 through age 95 years. All of the cohort members were born susceptible to hepatitis A. In each subsequent time period without vaccination, cohort members could be uninfected and susceptible to future infection, actively infected with hepatitis A, recovered and thereby immune to infection, or dead from hepatitis A or other causes. The model incorporated all potential hepatitis A symptomatic states from asymptomatic infection to fulminant liver failure (FLF). Vaccinated patients would immediately develop immunity that would wane slowly over time. Herd immunisation was not considered in the model. Cycle length, transition probabilities and other model details were extensively reported in a technical appendix. A diagram of the model structure was also provided.

Sources searched to identify primary studies
Much of the clinical data came from the National Notifiable Disease Surveillance System and the National Hospital Discharge Survey. Vaccine efficacy and duration of vaccine-acquired immunity were obtained both from published and unpublished data (written communications). Some estimates were based on expert opinion. Most of the details of the sources used were presented in the technical appendix.

Methods used to judge relevance and validity, and for extracting data
The clinical estimates were derived from published studies, notifiable disease data, unpublished vaccine efficacy data, proprietary adult vaccine sales data, expert opinion and assumptions. It was unclear whether a systematic review of the literature was undertaken. Generally, each model parameter was derived from a single source, thus there was no need to combine the estimates.

Measure of benefits used in the economic analysis
The summary benefit measures used were the life-years (LYs) and quality-adjusted life-years (QALYs). These were estimated using the decision model. Other model outputs, such as the number of infections and deaths, were also reported. The utility weights used to calculate the QALYs were derived directly from a published time trade-off estimation of utility losses associated with hepatitis A. The benefits were discounted to present values at an annual rate of 3%.

Direct costs
The analysis of the costs was carried out from a societal perspective. It included the direct medical costs associated with the treatment of hepatitis A (outpatient care, inpatient care, FLF and liver transplantation), vaccination (acquisition, administration and treatment of adverse events) and public health impact of the vaccine campaign (surveillance, contact tracing and outbreak response). The unit costs were not presented separately from the resource quantities. The costs and quantities were derived from published studies and surveys as well as public contract prices (Centers for Disease Control and Prevention). Some assumptions were also made. Discounting was relevant, as the long-term costs were evaluated and an annual rate of 3% was used. The price year was 2005.

Statistical analysis of costs
Probabilistic distributions were assigned to the economic inputs in the sensitivity analysis.

Indirect Costs
Productivity costs, based on the expected duration of the episode of illness and the expected wage of the patient or carer, were included in the analysis. However, only work losses incurred by caregivers were incorporated in the
numerator used to calculate the cost per QALY saved ratio, whereas all of the productivity losses were incorporated in the numerator used to calculate the cost per LYs saved. This was done because, in the survey used to determine QALY values, patients were asked to consider work losses that they would experience as adults. The unit costs and the quantities of resources used were not presented separately. As in the analysis of the direct costs, an annual discount rate of 3% was applied and the price year was 2005.

Currency
US dollars ($).

Sensitivity analysis
A univariate sensitivity analysis was performed to assess the robustness of the cost-effectiveness results to variations in the following:

the discount rate,
the baseline and annual rates of decline of hepatitis A incidence,
the long-term decline in antibody to hepatitis A virus after immunisation,
the rate of adult vaccination,
the value of QALY decrements associated with illness,
public health costs, and
symptomatic adverse events.

A multiway, probabilistic sensitivity analysis was also carried out by assigning stochastic distributions to the model inputs. Details of these distributions were provided in the technical appendix. Given the uncertainty in the calculation of the QALYs, different approaches to derive QALYs were also considered.

Estimated benefits used in the economic analysis
Compared with no childhood vaccination, routine vaccination at age 1 year would result in 172,334 fewer infections (135,486 in regions 1 and 2, and 36,848 in region 3) and 32 fewer deaths nationwide (22 in regions 1 and 2, and 10 in region 3). This reduction would produce a gain of 247 discounted LYs (178 in regions 1 and 2, and 70 in region 3) or 2,154 discounted QALYs (1,640 in regions 1 and 2, and 514 in region 3).

Compared with coverage levels in 2003, routine nationwide vaccination at age 1 year would result in 112,411 fewer infections. The LYs and QALYs gained were not reported for this comparison. Most of the advantages of the vaccination strategies were related to a reduction in morbidity rather than to any reduction in mortality.

Cost results
Routine vaccination at age 1 year would cost $49.3 million more than no vaccination (or $60.9 million when productivity losses of patients were not included).

Specifically, nationwide vaccination was cost-saving in regions 1 and 2 with a reduction of $16 million, but more expensive in region 3 by $65.3 million. The extra cost was totally attributable to vaccination cost. Hepatitis A medical costs, public health costs and productivity costs were reduced with the vaccination strategy.

Routine vaccination at age 1 year would cost an additional $55.8 million in comparison with coverage levels in 2003.
Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies.

The incremental cost per LY gained with routine vaccination over no vaccination was $199,000. The incremental cost per QALY gained with routine vaccination over no vaccination was $28,000.

The incremental cost per LY gained with routine vaccination over coverage levels in 2003 was $338,000. The incremental cost per QALY gained with routine vaccination over coverage levels in 2003 was $45,000.

From the viewpoint of the health care system (excluding productivity losses), nationwide routine vaccination cost $40,000 per QALY saved compared with no vaccination and $57,000 per QALY saved when compared with coverage levels in 2003.

When the analysis was performed in the different regions, substantial differences were found. For example, when compared with no vaccination, routine vaccination at age 1 year was dominant in regions 1 and 2 while costing $933,000 per LY saved and $133,000 per QALY saved in region 3. Compared with immunisation at 2003 vaccine coverage levels, routine vaccination was again dominant in regions 1 and 2 while costing $927,000 per LY saved and $132,000 per QALY saved in region 3.

The sensitivity analysis showed that the cost-effectiveness of vaccination was sensitive to the combined cost of a vaccine dose and administration, the baseline incidence value, the discount rate, and the use of a more conservative QALY decrement associated with illness. The results of the analysis were less sensitive to the rate of decline in vaccine-induced antibody to hepatitis A virus.

The probabilistic sensitivity analysis showed that the cost per QALY ratio for nationwide vaccination versus no vaccination fell below $50,000 in 82% of the simulations, between $50,000 and $75,000 in 15% of the simulations, between $75,000 and $100,000 in less than 3% of the simulations, and above $100,000 in less than 1% of the simulations. Vaccination was cost-neutral or cost-saving in 8% of the simulations.

Authors' conclusions
The nationwide hepatitis A vaccination of all US children ages 12 to 23 months was cost-effective.

CRD COMMENTARY - Selection of comparators
The authors provided a clear justification for their choice of the comparators, which were appropriately selected. The proposed immunisation programme was compared not only with a strategy of no vaccination, but also with the previously implemented vaccination strategy in the authors' setting. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The authors provided some information on the sources used to derive the clinical data, although the majority of the details were given in the technical appendix. It was unclear whether a systematic review of the literature was undertaken, thus it is possible that the primary studies might have been identified selectively. However, a very extensive sensitivity analysis was conducted in order to take the variability and uncertainty around key model clinical and epidemiological estimates into account.

Validity of estimate of measure of benefit
The choice of the benefit measures was appropriate as they are comparable with the benefits of other health care interventions. They also capture the impact of the preventive strategies on length and quality of survival, which are two relevant dimensions of health. The sources and methods used to estimate the utility weights were described and appear to have been appropriate. Discounting was performed as recommended in international guidelines, and the impact of variations in the discount rate was investigated. Alternative values of the utility weights were used in the analysis to
capture the uncertainty in QALY calculations.

**Validity of estimate of costs**
The analysis of the costs was consistent with the perspective of the study. The results were also reported from the perspective of the health care payer. There was little information on the unit costs and resource quantities since most costs were obtained from published studies. This could limit the possibility of replicating the analysis in other settings. The sources of the data were reported and the impact of changes in the cost estimates was investigated in the sensitivity analysis. The price year was reported and appropriate discounting was performed.

**Other issues**
The authors stated that their findings were similar to those from a previous analysis. The issue of the generalisability of the study results to other settings was investigated in the sensitivity analysis. This analysis was performed credibly and the results of it reported extensively. The authors noted some limitations to their analysis, such as the fact that the model did not consider the cyclic nature of hepatitis A incidence or the fact that it might take time to reach high coverage levels (as assumed in the base-case analysis).

**Implications of the study**
The study results support the recommendation made by the ACIP to implement a nationwide immunisation programme to prevent hepatitis A.

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None stated.

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**Other publications of related interest**
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