Regional variation in the cost effectiveness of childhood hepatitis A immunization

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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
The use of hepatitis A vaccination in children aged 2 years, without catch-up immunisation of older children, in regions of the USA with varying incidence of hepatitis A. Hepatitis A immunisation was compared with no immunisation programme.

Type of intervention
Primary prevention.

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

Study population
The study population comprised a hypothetical cohort of US children aged 2 years in 2002 (i.e. born in 2000). Those with asymptomatic or symptomatic infections were excluded from the follow-up because of presumed lifelong immunity.

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

Dates to which data relate
The effectiveness data were derived from studies relating, approximately, to 1973 to 2002. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, supplemented by the authors' assumptions.

Modelling
The authors developed a Markov model to predict the lifetime hepatitis A outcomes. The model considered birth cohorts from four US regions defined by their hepatitis A incidence rates. More specifically, regions with incidence rates of over 200% (region 1), 100 to 199% (region 2), 50 to 99% (region 3), and less than 50% (region 4) of the US average. Each regional model used identical assumptions about the costs and outcomes of hepatitis A. Between age 2 and 3 years, and in each subsequent year, the cohort members were allocated to one of four health states. The health states were uninfected but susceptible to hepatitis A, infected with hepatitis A, uninfected and immune to hepatitis A, and deceased. When infection was predicted to occur, the authors modelled the risk of disease transmission to other members.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the incidence rates of hepatitis A in each of the US states;
- the proportion of children being immune to hepatitis A;
- the average annual rate of decline in hepatitis A rates;
- the age-specific rates of symptomatic infection;
- the proportion of cases due to sexual, household or other contact with a hepatitis A-infected person;
- the coverage rates at 2 years of age for measles-mumps-rubella and varicella vaccines;
- the proportion of children producing protective concentrations of hepatitis A antibodies after the first and second vaccine doses;
- the probability of overt disease at age less than 4 years, 5 to 9 years, and 10 to 17 years;
- hospitalisation, liver transplant and case fatality rates for those with disease symptoms; and
- days missed from paid employment.

**Study designs and other criteria for inclusion in the review**
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**
An expert panel estimated the hepatitis A outcomes on the basis of the review of published literature.

**Number of primary studies included**
At least 27 studies were included in the review.

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

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

**Results of the review**
Eleven US states were found to have rates of greater than 200% of the national average, while six had rates of 100 to 199% of the national average. The states with the highest incidence rates were west of the Mississippi River. The incidence rates were lowest in Eastern USA, particularly in the south and New England.
The data from 1988 to 1994 documented 9% seropositivity among US children aged 6 to 11 years.

The average annual rate of decline in hepatitis A was 2.1%.

The age-specific probabilities of icteric infections being captured by current surveillance systems were 22 to 25%.

Twenty-two per cent of all cases of hepatitis A were due to sexual, household or other contact with hepatitis A-infected people, with 49% of cases being attributed to personal contact due to sexual contact.

The vaccination coverage rates at 2 years of age were 89% for measles-mumps-rubella and 69% for varicella vaccines.

After the first vaccine dose, 98% of children would produce protective concentrations of hepatitis A antibody. This rose to 99% after the second vaccine dose.

The probability of overt disease was 7% for children infected at age less than 4 years, 37% for those aged 5 to 9 years, and 71% for those aged 10 to 17 years.

Among those with disease symptoms, the hospitalisation rates were 5 to 43%, the liver transplant rates were 0 to 0.008%, and case fatality rates were 0.14 to 3.85%.

The number of days missed from paid employment, computed by applying age-specific workforce participation rates, was 15 for non-hospitalised patients and 33 for hospitalised patients.

Methods used to derive estimates of effectiveness
It would appear that authors’ assumptions, based on the available literature, were used to derive estimates of effectiveness and outcomes.

Estimates of effectiveness and key assumptions
Based on 1988 to 1994 data documenting seropositivity among 6 to 11 year olds, the authors assumed that 3% of children would be immune to hepatitis A at age 2.

The authors assumed that the average annual rate of decline in hepatitis A rates of 2.1% seen from 1976 to 1998 would continue indefinitely. Thus, they predicted 48, 70 and 82% declines by the time the cohort reached ages 25, 50 and 75 years, respectively.

When using a model that considered the number and age distribution of household contacts, the age-specific rates of seropositivity, and the probabilities of disease transmission and development of overt disease, the authors estimated that 55 to 231 intra-household hepatitis A cases per 1,000 primary infections would occur, depending on the index case age.

As the proportion of cases attributable to personal contact was found to be stable across age groups, the authors assumed that one case of inter-household transmission would occur for each case of intra-household transmission, and that the age distribution of these secondary cases would be identical.

The authors assumed that the immunisation policy would continue in subsequent years. Hence, they assumed that those born after 2000 would also be immunised.

On the basis of coverage rates for other vaccines, the authors assumed that 69% of children would receive 2 hepatitis A vaccine doses, 20% would receive 1, and 11% would receive 0.

Based on the proportion of children producing protective antibodies after vaccination, and the loss of immunity in subsequent years, the authors assumed that one-half of fully vaccinated children would lose protection within 30 years and that the loss of protection would be linear (i.e. 2.7% per annum). The authors also assumed that the loss of immunity would occur twice as quickly among children receiving only one vaccine dose.
Measure of benefits used in the economic analysis
The measures of benefits used in the economic analysis were the life-years and quality-adjusted life-years (QALYs) gained. To estimate the QALYs lost to nonfatal hepatitis A, a written description of hepatitis A was presented to 181 adults, who judged the amount of life span they would forego to avoid its symptoms using the time trade-off approach. Based on the responses reflecting a willingness to forego 23 days of life expectancy to avoid 40 days of illness, a utility score of 0.43 was applied to an expected 39 days of hepatitis A symptoms. This represented 0.06 lost QALYs per nonfatal infection. Each life-year lost to fatal hepatitis A represented one lost QALY.

Direct costs
The resource quantities and the costs were not reported separately. The direct costs in the analysis were those of the health service. These included the costs of the vaccine, vaccine administration, hospitalisation and liver transplant. The vaccine and administration costs were derived from prices and reimbursements in the public and private sectors. The public sector price of the vaccine was based on the current federal contract, while the private sector prices were derived from a survey of paediatricians. The vaccine administration cost was based on the weighted average reimbursement in the USA. The medical costs were based on amounts reimbursed to providers. The authors reviewed medical utilisation data from a case series study, and applied Medicare national fees to outpatient procedures. The hospital costs were based on reimbursements for diagnosis-related groups 205 and 206 (diseases of the liver, except malignancy, cirrhosis and alcoholic hepatitis). The liver transplant costs were derived from a descriptive study that documented charges for the procedure and first year of follow-up.

As all the costs were incurred over a lifetime, discounting was necessary. It was appropriately performed at an annual rate of 3%, following recommendations of the panel on cost-effectiveness in health and medicine. The study reported the incremental (or reduction in) costs of vaccination compared with no vaccination. All the costs were adjusted to 2002 prices.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs included were those arising from lost working days. These were derived on the basis of median US age-specific wages adjusted to reflect employer paid benefits, and assuming that real wages would increase by 1.4% annually. As with the direct costs, all the indirect costs were discounted at an annual rate of 3% and all the work loss costs were adjusted to 2002 levels.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses to examine the effect of selected assumptions on the primary end points were performed. The discount rate was varied between 0 and 5% to account for differing time preferences. To consider a plausible range of hepatitis A risks with no vaccination, the predicted annual decline in incidence was varied from 1.1% to 3.2% per annum, and the predicted risk of transmission from a member of the cohort was varied by +/- 50%. The vaccination costs were also varied. The degree of quality of life impairment caused by hepatitis A was varied by simultaneously substituting the inter-quartile range for symptom duration and the 95% confidence interval (CI) for time trade-off responses. Hospitalisation, liver transplant and case fatality rates were also simultaneously varied between the 95% CIs around expert panel estimates.

Estimated benefits used in the economic analysis
Four US regions were considered. Those with hepatitis A incidence rates of over 200% (region 1), 100 to 199% (region
2), 50 to 99% (region 3), and less than 50% (region 4) of the US national average.

Over the lifetimes of the year 2000 birth cohort, the number of discounted life-years saved due to hepatitis A immunisation was 2,299 in region 1, 1,348 in region 2, 1,211 in region 3, and 329 in region 4. Thus, immunisation on a national basis would have prevented the loss of 5,187 life-years.

The number of discounted QALYs saved due to hepatitis A immunisation was 4,915 in region 1, 2,193 in region 2, 1,968 in region 3, and 535 in region 4. Thus, immunisation on a national basis would have prevented the loss of 9,611 QALYs.

**Cost results**

From the health system perspective, the net costs were defined as the vaccination costs minus future reductions in medical costs. The net discounted costs ($000s) to the health system were $2,448 for region 1, $3,975 for region 2, $42,744 for region 3, and $38,256 for region 4. Hence, from this perspective, nationally vaccinating the year 2000 birth cohort would incur a cost of $87,423 million.

From the societal perspective, the net costs were defined as the vaccination costs minus future reductions in medical and work loss costs. The net discounted costs ($000s) to society were -$35,002 (i.e. savings of $35 million) for region 1, -$12,183 (i.e. savings of over $12 million) for region 2, $27,141 for region 3, and $33,673 for region 4. Hence, from this perspective, nationally vaccinating the year 2000 birth cohort would incur a cost of $13.629 million.

**Synthesis of costs and benefits**

The costs and benefits were combined by calculating a cost-utility ratio (additional cost required per QALY gained) and by calculating a cost-effectiveness ratio (additional cost required per life-year gained, LYG).

From the health system perspective, when compared with no vaccination, vaccination would cost an extra $800 per LYG in region 1, $3,000 per LYG in region 2, $35,300 per LYG in region 3, and $116,000 per LYG in region 3. Hence, from this perspective, vaccination would cost an extra $800 per LYG in all states of the USA when compared with no vaccination.

From the societal perspective, vaccination would be dominant (i.e. less costly and more effective) in regions with incidences of over 100% the national average, and would cost an extra $22,400 per LYG and $102,100 per LYG when compared with no vaccination in regions 3 and 4, respectively. Hence, from this perspective, vaccination would cost an extra $22,400 per LYG in all states of the USA when compared with no vaccination.

From the health system perspective, when compared with no vaccination, vaccination would cost an extra $500 per QALY gained in region 1, $1,800 in region 2, $23,700 in region 3, and $71,500 in region 4. Hence, from the this perspective, vaccination would cost an extra $500 per QALY gained in all states of the USA when compared with no vaccination.

From the societal perspective, vaccination would be dominant (i.e. less costly and more effective) in regions with incidences of over 100% the national average, and would cost an extra $13,800 pre QALY gained and $63,000 per QALY gained when compared with no vaccination in regions 3 and 4, respectively. Hence, from this perspective, vaccination would cost an extra $13,800 per QALY gained in all states of the USA when compared with no vaccination.

The sensitivity analysis showed that the results were most sensitive to the vaccination costs and rates of disease transmission through personal contact. When the higher costs of vaccination were used, the cost of an extra QALY from the societal perspective and for all states in the USA was $7,500. When the lower costs were used, vaccination was the dominant strategy. When disease transmission was 50% more likely, the cost of an extra QALY was $45,200. This cost increased to $94,500 per QALY gained when disease transmission was 50% less likely.

**Authors' conclusions**

The authors concluded that their study demonstrated the strong relationship between infection risks and vaccination cost-
effectiveness, with childhood hepatitis A vaccination being most cost-effective in areas with the highest incidence rates. However, they also concluded that vaccination would also meet accepted standards of economic efficiency in most of the USA.

**CRD COMMENTARY - Selection of comparators**

A justification was given for choosing no childhood hepatitis A vaccination as the comparator. Current recommendations in the USA only recommended vaccination in regions with hepatitis A incidence rates of over 100% the national average. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature was conducted to identify relevant research and minimise biases. However, the review appears to have been exhaustive, with both published and unpublished data being included. Further, an expert panel undertook the review and the authors reported the number of experts in the panel. When the results from different studies were used to derive an estimate of effectiveness, the authors failed to report how these results were combined. Further, there was little detail on the characteristics of the included studies and how differences between the studies were investigated. However, this seems warranted due to the large number of studies included in the review and the different areas they covered. Estimates of effectiveness derived from the review were supplemented by the authors’ assumptions, many of which were based on evidence from the literature. The authors appropriately carried out sensitivity analyses to investigate all estimates, whether derived from the literature or based on their assumptions. The ranges used appear to have been appropriate.

**Validity of estimate of measure of benefit**

The estimation of benefits was modelled. Both life-years and QALYs gained were used as measures of health benefit. The utility values were appropriately derived from 181 American adults through the time trade-off approach. All benefits were discounted at a rate of 3% per annum.

**Validity of estimate of costs**

The authors reported that the costs were estimated from a societal perspective. However, the costs due to transportation to and from health care providers and caregiver burden were not included in the analysis. Therefore, as the authors acknowledged, this cost accounting cannot be considered fully societal. It would appear that these omissions would bias the results in favour of no vaccination. Contrary to the authors’ statement, it does not matter that lost wages due to mortality were not considered, as the effectiveness measure adequately took account of this. From the health system perspective, the authors did not consider the costs to the state and local health departments of managing hepatitis A outbreaks.

The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The unit costs were derived from published sources and Medicare reimbursements. A sensitivity analysis of the prices was conducted, using ranges that appear to have been appropriate. As all the costs were accrued over a lifetime, they were appropriately discounted. The discount rate was justified. Medicare reimbursements were used to proxy prices, which, as the authors pointed out, will be lower than those of other third-party payers. All the costs were adjusted to 2002 prices.

**Other issues**

The authors made appropriate comparisons of their findings with those from other studies that had also found that greater health benefits were provided to personal contacts than to vaccinees themselves. The issue of generalisability to other settings was addressed through the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. One of these was the assumption that symptomatic and asymptomatic children were equally likely to spread hepatitis A, although studies were based solely on index cases with overt disease.
Implications of the study
The authors reported that if hepatitis A vaccines were to be combined with other vaccines given to infants, this would vastly improve the cost-effectiveness because vaccine administration represents nearly one half of the cost of hepatitis A immunisation. The authors recommended extending the recommendations on hepatitis A immunisation to the whole of the USA, thus providing twice the health benefits and preventing substantial morbidity and mortality.

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