The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C viral infection in the United States

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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
Strategies of no vaccination, targeted vaccination and universal hepatitis A vaccination were compared for patients with chronic hepatitis C viral (HCV) infection. Targeted vaccination was given to individuals who were found to be negative for anti-hepatitis A virus (HAV) antibody after the initial screening. The vaccination consisted of a primary dose followed by a booster dose of “commercially available” HAV vaccines at 6 months. Further details of the vaccines were not reported.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The hypothetical study population consisted of patients with HCV, and in particular, those patients with HCV-related chronic liver disease.

Setting
The practice setting was primary care. The model data may have been derived from American studies, although it is unclear from the paper.

Dates to which data relate
Most of the model input data were taken from studies published between 1988 and 1999. The price year for the cost estimates ranged from 1997 to 2000.

Source of effectiveness data
The effectiveness data were obtained from a review and synthesis of completed studies.

Modelling
A Markov model was used to estimate the life expectancy, quality-adjusted life expectancy, and lifetime health care costs. The model used cycle lengths of 6 months from the age of 45 until death.

Outcomes assessed in the review
The following model parameters were estimated in the review.
For the category of HCV disease (health state at presentation), the parameters were chronic hepatitis C (CAH), compensated cirrhosis and decompensated cirrhosis.

For HCV genotype, the parameters were genotype 1 and genotype other (2,3).

The probability of receiving interferon (IFN)/ribavirin (RBV) treatment.

The probability of responding to IFN/RBV treatment for genotype 1 and genotype other (2,3).

The annual transition probabilities for CAH to compensated cirrhosis, compensated cirrhosis to decompensated cirrhosis, compensated cirrhosis to hepatocellular carcinoma (HCC), decompensated cirrhosis to HCC, decompensated cirrhosis to orthotopic liver transplantation (OLT), HCC to death, OLT to death (first year), and OLT to death (subsequent years).

The annual problem of acute complications for patients with compensated cirrhosis variceal bleeding, decompensated cirrhosis variceal bleeding, and ascites/spontaneous bacterial peritonitis.

The problem of death after variceal bleeding.

The problem of death after other acute complications.

For the category of HAV vaccination and superinfection, the prevalence of HAV anti-body (age 45), and the sensitivity and specificity of the HAV antibody test.

Response to HAV vaccination for patients with CAH or compensated cirrhosis, and patients with decompensated cirrhosis.

The annual incidence rate of HAV.

The problem of fulminant hepatic failure after HAV infection.

The problem of death after HAV-induced fulminant hepatic failure.

**Study designs and other criteria for inclusion in the review**
The authors did not state that a systematic review was carried out. The inclusion and exclusion criteria, and study designs of the literature used 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**
Eighteen primary studies were used in the review.

**Methods of combining primary studies**
The authors combined the results of the primary studies for some parameter estimates. For instance, the estimate of the annual transition probability from CAH to compensated cirrhosis was derived from two sources. The authors did not report the methods used to combine the results.

**Investigation of differences between primary studies**
The fact that the authors combined some results from the primary studies suggests that there were some differences between these studies. The authors did not discuss these potential differences.

**Results of the review**
For HCV disease (health state at presentation), the parameter estimates were 0.80 for CAH, 0.16 for compensated cirrhosis and 0.04 for decompensated cirrhosis.

For HCV genotype, the parameter estimates were 0.72 for genotype 1 and 0.28 for genotype other (2,3).

The probability of receiving IFN/RBV treatment was 0.50.

The probability of responding to IFN/RBV treatment was 0.30 for genotype 1 and 0.65 for genotype other (2,3).

The annual transition probabilities were:

- 0.073 for CAH to compensated cirrhosis;
- 0.04 for compensated cirrhosis to decompensated cirrhosis;
- 0.015 for compensated cirrhosis to HCC;
- 0.04 for decompensated cirrhosis to HCC;
- 0.03 for decompensated cirrhosis to OLT;
- 0.90 for HCC to death;
- 0.10 for OLT to death (first year); and
- 0.069 for OLT to death (subsequent years).

The annual problem of acute complications was:

- 0.15 for patients with compensated cirrhosis variceal bleeding;
- 0.35 for patients with decompensated cirrhosis variceal bleeding; and
- 0.15 for ascites/spontaneous bacterial peritonitis.

The problem of death after variceal bleeding was 0.35.

The problem of death after other acute complications was 0.30.

For HAV vaccination and superinfection, the prevalence of HAV antibody (age 45) was 0.34, the sensitivity of the HAV antibody test was 0.997, and the specificity was 0.998.

The response to HAV vaccination was 0.94 for patients with CAH or compensated cirrhosis, and 0.5 for patients with decompensated cirrhosis.

The annual incidence rate of HAV was 0.0001.
The problem of fulminant hepatic failure after HAV infection was 0.41.

The problem of death after HAV-induced fulminant hepatic failure was 0.85.

**Methods used to derive estimates of effectiveness**
The effectiveness estimates from the literature were supplemented with some authors’ assumptions.

**Estimates of effectiveness and key assumptions**
The authors assumed the following:

- full compliance with the vaccination schedule in all patients;
- the persistence of protective antibodies over the time horizon; and
- in susceptible patients, HAV infection occurred according to the reported incidence of disease in the United States (1/10,000 per year).

**Measure of benefits used in the economic analysis**
The quality-adjusted life-years (QALYs) were used to measure benefit in the economic analysis. The QALYs were calculated by multiplying each year lived in a given state by a health-related quality of life (HRQL) score for that state. The HRQL weights were based on a review of published literature and the "modified" Delphi approach. The Delphi panel consisted of hepatologists, gastroenterologists, and general internists at the authors' institution. The authors reported that the HRQL weights measured in their study were elicited using the standard gamble method. The benefits were discounted at 3% in the base-case, which was appropriate since the benefits were measured from the age of 45 until death.

**Direct costs**
The direct costs comprised a variety of health service costs. The cost analysis focused on the cost of HCV disease (long-term health states), the cost of HCC diagnosis, the cost of CAH treatment, the cost of acute complications, and the cost of HAV vaccination and superinfection.

The costs were discounted at a rate of 3%. The life expectancy of the model population was a function of the model parameters. The states that incurred costs occurred at different stages of the population's lives, so the authors anticipated that life expectancy would exceed two years and discounting was appropriate. The costs and the quantities were not reported separately. The inpatient and outpatient costs were obtained from diagnosis-related group or Current Procedural Terminology Medicare reimbursement rates from the authors' institution, in other words, actual data. The price year for the cost estimates from these sources was 1999. The estimates were supplemented with data from published material dating between 1997 and 2000. The cost of medication was taken from the Drug Topics Red Book, 2000, also actual data. The authors reported that these costs were altered to account for the additional costs related to supplies, clinical and biochemical monitoring, and the treatment of drug-related side effects.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The authors reported that they adopted a societal perspective, but the indirect costs do not appear to have been accounted for. The patients were assumed to be aged 45 years on entering the model.
Currency
US dollars ($).

Sensitivity analysis
The authors carried out sensitivity analyses to explore the impact of uncertainty in the parameter values. A one-way sensitivity analysis was used to explore the annual incidence of HAV, the prevalence of HAV antibody, the problem of fulminant hepatitis after HAV superinfection, the problem of death after HAV-induced fulminant hepatic failure, the cost of vaccination, the cost of screening, and the discount rate. In addition, a two-way sensitivity analysis was used to analyse the impact of pairs of variables found to be influential during the one-way sensitivity analysis.

Estimated benefits used in the economic analysis
The benefits were discounted at an annual rate of 3%.

The do nothing strategy gave 12.641336 QALYs, the targeted strategy gave 12.643368 QALYs, and the universal strategy gave 12.643372 QALYs.

Relative to do nothing, the targeted strategy gave an additional 0.002032 QALYs. Relative to the targeted strategy, the universal strategy gave an additional 0.000004 QALYs.

Cost results
The costs were discounted at an annual rate of 3%.

The do nothing strategy cost $22,693, the targeted vaccination strategy cost $22,796, and the universal strategy cost $22,812.

Relative to do nothing, the targeted strategy cost an additional $103. Relative to the targeted strategy, the universal strategy cost an additional $16.

Synthesis of costs and benefits
The benefits and the costs were combined to estimate an incremental cost-effectiveness ratio.

The incremental cost-effectiveness ratio of targeted vaccination relative to do nothing was $51,000. The incremental cost-effectiveness ratio of universal vaccination relative to targeted vaccination was $3,900,000.

The authors reported that "in most sensitivity analyses, the incremental cost-effectiveness ratio remained in a range that would generally be considered cost-ineffective, whereas the results of targeted vaccination were more sensitive to some of the model's assumptions". Targeted vaccination was said to be cost-effective (given a threshold of $100,000 per QALY gained) as long as the annual incidence of HAV infection was greater than 6 per 100,000, and as long as the probability of fulminant hepatic failure after HAV superinfection was greater than 0.21. The authors also reported that the results were sensitive to the costs of HAV antibody screening and vaccination. A two-way sensitivity analysis was then used to explore the joint impact of the cost of screening and the cost of vaccination. At the $50,000 per QALY threshold, when the costs of screening and vaccination were both low, targeting was optimal. When the costs were both high, do nothing was optimal. The authors used this analysis to discuss the potential impact of under- and over-estimations of costs in their analysis.

Authors' conclusions
The authors cautiously advocate the cost-effectiveness of a targeted vaccination strategy. They rightly point out that the results of the cost-effectiveness analysis depend heavily on society's willingness to pay for gains in health. They suggest that their analysis questions the cost-effectiveness of universal screening.
CRD COMMENTARY - Selection of comparators

The authors compared strategies of no vaccination, targeted vaccination and universal vaccination among patients with chronic HCV disease. None of the alternatives was explicitly stated as current practice, although the authors informed the reader that the Advisory Committee on Immunization Practices recommends vaccination for patients with chronic liver disease. The comparators were appropriate for the objective of the study. You should decide if they are appropriate for your setting.

Validity of estimate of measure of effectiveness

The authors did not state that they carried out a systematic review of the literature. They appear to have used the primary studies selectively. Data from the primary studies were combined in some cases, but the methods used to derive a final estimate were not discussed. There was no discussion of potential differences between the studies. The authors did, however, carry out sensitivity analyses on a number of parameters to explore the impact of uncertainty in parameter values. The authors made some assumptions that were well explained and backed up with relevant literature.

Validity of estimate of measure of benefit

The economic benefit was measured by QALYs, which were estimated using a Markov state-transition model. The model took account of the various health states that the patients could enter, and the probability of moving between those states. The HRQL weights were estimated from the literature and from a modified Delphi panel. It was reported that the weights estimated directly for this study were derived using the standard gamble method.

Validity of estimate of costs

The authors reported that the costs were estimated from the societal perspective. However, the reference to the societal perspective was made in the abstract, whereas the paper did not include costs that might be incurred from the wider societal perspective, such as indirect costs to the patient.

The authors were thorough in their inclusion of cost categories and costs within each category. The costs were taken from the literature and from the University of Alabama at Birmingham Hospital Business School. The results were sensitive to changes in the cost estimates, particularly the cost of screening and vaccination, given the small differences in cost between the vaccination strategies. The authors explored the impacts of changes to these costs in a thorough, and well presented and discussed, two-way sensitivity analysis. The costs and the quantities were not reported separately. The price dates were specified, which helps the generalisability of the results.

Other issues

The authors made appropriate comparisons of their study with other relevant studies (one study concluded that HAV vaccination was not a cost-effective strategy in HCV-infected patients), and clearly explained possible reasons for differences between the results. Some prior studies were described as reporting the cost per HCV avoided. The authors could have reported this measure of effectiveness to facilitate comparisons. The issue of generalisability of the study to alternative settings was considered through the sensitivity analyses performed.

The authors did not appear to have presented their results fully. The results given in the analysis were presented clearly, were well explained, and followed intuition. Where the results were not as expected, the authors provided a thorough discussion.

The authors’ conclusions accurately represent the results presented in the study and closely reflect the scope and objective of the study. Limitations were presented in the form of uncertainty in parameter values and the need for improved clinical estimates.

Implications of the study

The authors do not make any recommendations for policy or practice. Further clinical research is suggested to improve measurements of the consequences of HCV superinfection in patients with HCV disease.
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