



REVIEWS

Cost-Effectiveness of Hepatitis A Vaccination in Patients with Hepatitis C: A Systematic Review

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Keywords

Hepatitis A • Hepatitis C • vaccination • Cost-effectiveness • Economic evaluation • Systematic review

Summary

Background. In patients who have chronic Hepatitis C virus (HCV), hepatitis A virus (HAV) infection may cause such debilitating complications as fulminant hepatitis and liver failure. This population is considered a priority group for HAV vaccination against HAV although its cost-effectiveness is still questioned. This is a systematic review to assess the cost-effectiveness of HAV vaccination against chronic HCV to guide clinical practice and the policy of the general population.

Methods. A comprehensive literature search was performed in the databases of PubMed, Scopus, Web of Science, and Embase between January 1990 and August 2024. The studies that were taken were those that determined the cost-effectiveness, cost-utility, or cost-benefit of HAV vaccination in HCV patients and reported economic consequences including incremental cost-effectiveness ratios (ICERs), quality-adjusted life years (QALYs) or life-years saved. After surveying through the records to narrow down the potential studies to 216, the number of potential research papers had to be filtered out to the four studies which satisfied the inclusion criteria, but which did not contain any duplicates, irrelevant studies or lacked any economic assessment. Data were extracted and synthesized narratively.

Results. The included studies were conducted in the USA and Canada and used decision-analysis or Markov models to compare no vaccination, selective/screen-and-vaccinate strategies, and universal vaccination. Selective vaccination was consistently the most cost-effective strategy, with an ICER of approximately \$51,000 per QALY gained in one study and cost per life-year saved ranging from \$22,256 to \$102,064 depending on age in another. Selective vaccination also prevented 128 symptomatic HAV cases per million population over 5 years. Universal vaccination was cost-effective only when HAV infection rates were high (>0.56% per year) or under specific cost structures, such as those of the Department of Veterans Affairs. These findings remained robust in sensitivity analyses.

Conclusion. This is because selective HAV vaccination is the most cost-effective solution in patients with chronic HCV, which happens to be more affordable in areas with low HAV prevalence. Universal immunization can be reasonably justified when the rates are high enough but care should be taken to maximize resource use. The evidence-based vaccination strategies can help to decrease the burden of HAV in this vulnerable population with the help of these findings.

Introduction

Hepatitis A and Hepatitis C are important health issues in the world with their own epidemiological and clinical peculiarities [1, 2]. Hepatitis A virus (HAV) is most commonly transmitted fecal-orally whereby acute self-limiting liver disease is commonly experienced. On the contrary, Hepatitis C virus (HCV) is a blood pathogen, which results in chronic liver disease, and millions of individuals worldwide are infected, and the virus causes serious patients as liver cirrhosis and hepatocellular carcinoma [3, 4]. There is an increased risk of adverse events in patients with chronic liver diseases (especially those with HCV infection) in case of co-infection with HAV; fulminant hepatitis and liver failure, which is why preventive interventions need to be taken into account [5].

HAV vaccination has proven both a safe and efficient method of preventing Hepatitis A and strong immune responses have been observed even in patients with underlying liver conditions [6]. The world health organizations such as the World Health Organization (WHO) and Centers of Disease Control and Prevention (CDC) recommend HAV vaccination in people with chronic liver disease including those who are infected with the HCV [7].

Vaccination, by preventing cases of HAV infection superimposition, can play an important role in reducing the clinical and economic burden of dealing with co-infections in this at-risk group. In spite of these suggestions the cost-effectiveness of routine HAV vaccination in HCV patients is a matter of ongoing debate [8].

Cost-effectiveness studies are important in informing healthcare policies, especially in health care environments where healthcare services are scarce [9]. The economic analysis of the state of vaccination programs is based on the costs of their implementation compared against healthcare savings due to prevented complications and enhanced health results. The case of HAV vaccination against HCV-infected people might have the advantage of informing the public health policy, allocating resources more effectively and eventually enhance a patient outcome. Nevertheless, the research is not covered with thorough reviews synthesizing the evidence on the same topic, which forms the gap in the literature [10].

This systematic review has a chance to fill this gap because it will evaluate the available evidence on the cost-effectiveness of HAV vaccination in the HCV patients. The objective of this review is to offer a detailed insight into the economic and clinical consequences of HAV vaccination among this high-risk group by synthesizing the research results of the various healthcare settings and groups of people. It is hoped that the results can be used by policymakers, healthcare providers and researchers to influence the adoption of evidence-based interventions to vaccinate people with chronic HCV infection.

Methods

SEARCH STRATEGY

A comprehensive literature search was conducted to locate the studies that measure the cost-effectiveness of the Hepatitis A vaccination among Hepatitis C patients. The search of electronic databases including PubMed, Scopus, Web of Science, and Embase was conducted between January 1, 1990, and August 30, 2024. The search strategy included Medical Subject Headings (MeSH) and free-text terms (*e.g.* Hepatitis A, Hepatitis C, vaccination, cost-effectiveness, economic evaluation and so forth) and additional synonyms. Further search of the reference lists of the relevant articles and gray literature such as reports by health organizations was conducted. No language limitations were imposed so as to make the search as extensive as possible.

INCLUSION CRITERIA

Studies that satisfied the following requirements were included:

1. Concentrated on the Hepatitis A vaccination's cost-effectiveness, cost-utility, or cost-benefit.
2. Patients with persistent Hepatitis C infection were the target.
3. Economic results that are reported, such as cost savings, quality-adjusted life years (QALYs) or life-years saved, or incremental cost-effectiveness ratios (ICERs).
4. Made use of well-known frameworks for economic evaluation, such as decision tree analysis and Markov models.

5. Published in reputable health economic evaluation sources or peer-reviewed journals.

EXCLUSION CRITERIA

Research was disqualified if it

1. Ignored economic analysis and concentrated only on the clinical effectiveness or safety of the Hepatitis A vaccine.
2. Targeted groups or general populations that weren't Hepatitis C patients.
3. Were case reports, editorials, commentary, or narrative reviews.
4. Insufficient information to extract important economic indicators.

RISK OF BIAS ASSESSMENT

At the individual study level, the risk of bias was assessed with a modified Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. The tool is used to measure the quality of methodology of economic assessment, results reporting, modelling practices, and input transparency. The two independent reviewers assessed each study and possibly agreed or came to a consensus with a third reviewer to overcome the differences [11]. Based on predetermined criteria, studies were categorized as having a low, moderate, or high risk of bias.

DATA EXTRACTION AND ANALYSIS

Two reviewers analyzed the data using a standardized form and independently extracted it. Data extracted were characteristics of the study (*e.g.*, author, year, and country), population (*e.g.*, age, level of disease, *etc.*), strategy of vaccination, methods of economic evaluation, and outcomes (*e.g.*, ICERs, QALYs). The major result was that Hepatitis A immunization was cost effective in comparison to none, or other interventions.

Results

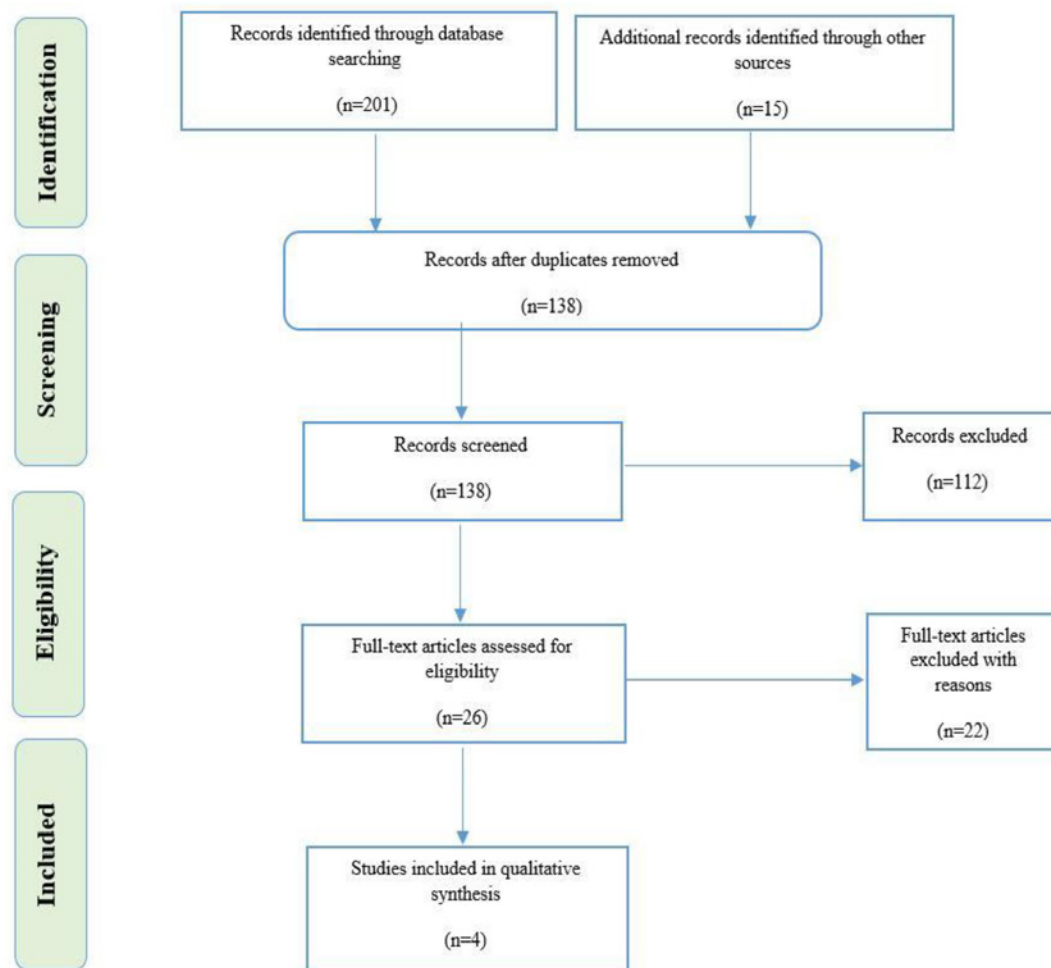
The initial literature search located a number of 216 studies. Having eliminated 78 duplicates, 138 unique studies were left to screen. Screening of these studies was done using their titles and abstracts to determine how relevant they are to the research question. In this step, 112 studies were eliminated as they failed to meet the inclusion criteria such as they either did not deal with general populations, or lacked economic appraisals and dealt with unrelated issues.

The remaining 26 studies underwent full-text eligibility assessments. Following such stringent screening process there were 4 studies, which had all the inclusion criteria and were chosen to undergo the final analysis. Figure 1 presents a flowchart that gives an overview of the selection procedure of the study.

In this study, Table I provides an overview of the characteristics, methodologies, and key findings of the included studies. The quality and transparency of the included studies were assessed with the help

Tab. I. Characteristics and Key Findings of Included Studies.

Study	First Author	Country	Year	Number of Patients	Follow-Up Duration	Hepatitis A Vaccine Dose	Study Methodology	Key Findings
Cost-Effectiveness of Hepatitis A Vaccination for Individuals with Chronic Hepatitis C	Michael K. Chapko	USA	2010	Not specified	Not specified	Not specified	Decision analysis model using Markov models to simulate different vaccination strategies (no vaccination, targeted, and universal) with costs evaluated from VA and private sector perspectives.	Vaccination is cost-effective only for individuals who cleared HCV when using VA costs; otherwise, it is not cost-effective.
Cost-Effectiveness of Hepatitis A Vaccination in Patients with Chronic Hepatitis C Viral Infection in the United States	Miguel R. Arguedas	USA	2002	Hypothetical population	Until death (long-term)	Primary + booster doses (assumed)	Markov state-transition model comparing no vaccination, targeted vaccination, and universal vaccination. Probabilities of HCV progression and quality-of-life weights were used, with societal costs (Medicare) factored in.	Targeted vaccination is cost-effective at \$51,000 per QALY gained; universal vaccination is not cost-effective due to extremely high incremental cost per QALY.
The Cost-Effectiveness of Hepatitis A Vaccination in Patients with Chronic Hepatitis C	Robert P. Myers	Canada	2000	Hypothetical cohort	5 years	Havrix, primary + booster	Decision analysis with three strategies: compared no vaccination, selective vaccination, and universal vaccination. Hospital data and literature were used for cost and outcome estimates. Sensitivity and threshold analyses were conducted for optimal strategies under different scenarios.	Selective vaccination prevents 128 HAV cases per 1 million patients. Universal vaccination is cost-effective only if HAV infection rate exceeds 0.56%.
Study The Cost-Effectiveness of Vaccinating Chronic Hepatitis C Patients Against Hepatitis A	R. Jake Jacobs	USA	2002	Hypothetical cohorts of 100,000 chronic HCV patients	Lifetime (Markov model; life-years saved)	+ booster (two-dose series; 45,000 initiate, 35,550 receive second dose)	Markov model comparing screen-and-vaccinate strategy (anti-HAV screening followed by vaccination of susceptible patients) with no vaccination; health system and societal perspectives; sensitivity analyses.	Vaccination reduced symptomatic HAV cases by 63-72% depending on age. Screening and vaccination costs \$5.2 million per cohort, partially offset by \$1.5-\$2.8 million reductions in HAV treatment costs and \$0.2-\$1.0 million reductions in work-loss costs. Health system cost per life-year saved: \$22,256 (age 30), \$50,391 (age 45), \$102,064 (age 60); societal ratios: \$13,222, \$41,656, \$97,651. Cost-effectiveness most favorable for younger patients; most sensitive to HAV infection and hospitalization rates and discount rate.

Fig. 1. PRISMA Flowchart of Study Selection Process.

of the CHEERS checklist. This evaluation covered several important areas of the respective studies, such as their report clarity, methodological rigor, and study results transparency. The results of this analysis are presented in Table II that gives an in-depth description of the compliance of each study with the CHEERS criteria [11].

Decision analysis models were used to assess the cost-effectiveness of hepatitis A vaccination in hepatitis C patients with chronic hepatitis. These studies used decision-analysis or Markov models to compare no vaccination with selective and vaccinate strategies and in some cases, universal vaccination [10, 12-14]. The key findings are as follows:

- **Chapko et al. (2010)** concluded that vaccination was cost-effective only to patients who had overcome hepatitis C when the healthcare costs of the Department of Veterans Affairs (VA) were considered. Quite to the contrary, it was not cost-effective in private sector or low HAV infection rates [13].
- **Arguedas et al. (2002)** established a numerically significant incremental cost-effectiveness ratio (ICER) of targeted vaccination with no vaccination of 51,000 per quality-adjusted life year (QALY). Targeted vaccination was better than universal vaccination by a wide margin, as the ICER of universal vaccination was 3.9 million dollars per QALY [12].
- **Myers et al. (2000)** demonstrated the preventive cases of 128 symptomatic HAV per 1 million patients in five years with selective vaccination. Nevertheless, the cost-effectiveness of universal vaccination became effective in the case when HAV infection rate annually was more than 0.56 per year. The cost effective type below this threshold was selective vaccination and the cost of universal vaccination was huge [14].
- **Jacobs et al. (2002)** evaluated a screen-and-vaccinate strategy in hypothetical cohorts of 100,000 chronic HCV patients at ages 30, 45, and

Tab. II. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) for Evaluating Included Studies.

CHEERS Item	Chapko et al. (2010)	Arguedas et al. (2002)	Myers et al. (2000)	Jacobs et al. (2002)
1. Title	Yes	Yes	Yes	Yes
2. Abstract	Yes	Yes	Yes	Yes
3. Introduction: Background and objectives	Yes	Yes	Yes	Yes
4. Methods: Target population and subgroups	Partially	Yes	Yes	Yes
5. Methods: Setting and location	Yes	Yes	Yes	Yes
6. Methods: Study perspective	Yes	Yes	Yes	Yes
7. Methods: Comparators	Yes	Yes	Yes	Yes
8. Methods: Time horizon	Yes	Yes	Yes	Yes
9. Methods: Discount rate	Yes	Yes	Yes	Yes
10. Methods: Choice of health outcomes	Yes	Yes	Yes	Yes
11. Methods: Measurement of effectiveness	Yes	Yes	Yes	Yes
12. Methods: Measurement and valuation of preference-based outcomes	Yes	Yes	Yes	No
13. Methods: Estimating resources and costs	Yes	Yes	Yes	Yes
14. Methods: Currency, price date, and conversion	Yes	Yes	Yes	Yes
15. Methods: Model assumptions	Yes	Yes	Yes	Yes
16. Methods: Analytic methods	Yes	Yes	Yes	Yes
17. Methods: Study parameters	Yes	Yes	Yes	Yes
18. Methods: Incremental costs and outcomes	Yes	Yes	Yes	Yes
19. Methods: Characterizing uncertainty	Yes	Yes	Yes	Yes
20. Methods: Characterizing heterogeneity	Partially	Partially	Partially	Partially
21. Results: Study findings	Yes	Yes	Yes	Yes
22. Results: Summary of main results	Yes	Yes	Yes	Yes
23. Results: Subgroup analyses	No	No	No	Yes
24. Results: Sensitivity analyses	Yes	Yes	Yes	Yes
25. Results: Limitations	Yes	Yes	Yes	Yes
26. Discussion: Generalizability	Partially	Partially	Partially	Partially
27. Discussion: Current knowledge	Yes	Yes	Yes	Yes
28. Other: Funding source	Unclear	Unclear	Unclear	Yes
29. Other: Conflicts of interest	No	No	No	No

60 years. Vaccination reduced symptomatic HAV cases by 63-72% depending on age. Screening and vaccination costs (\$5.2 million per cohort) were partially offset by reductions in HAV treatment costs (\$1.5-\$2.8 million) and work-loss costs (\$0.2-\$1.0 million). From the health system perspective, the cost per life-year saved was \$22,256 at age 30, \$50,391 at age 45, and \$102,064 at age 60; societal ratios were \$13,222, \$41,656, and \$97,651, respectively. Cost-effectiveness was most favorable for younger patients and was most sensitive to HAV infection and hospitalization rates and the discount rate [10].

These findings imply that selective vaccination of HAV in patients with chronic hepatitis C is cost-effective, particularly in younger patients and in areas with low HAV infection rates [10]. Universal vaccination can only be justified in those populations, which have a higher rate of infection, and the incremental ratio of cost-effectiveness is better [12, 14].

Discussion

This systematic review suggests that Hepatitis A vaccination is cost effective on chronic Hepatitis C patients particularly when they are subjected to particular or selective vaccination procedures. The research articles involved in the study continually established that selective vaccination, i.e. vaccinating individuals who have never received a HAV vaccination previously, is economically the most efficient means to apply especially in regions with low incidences of HAV infection [12]. On the other hand, the price of the universal vaccination became cost-effective only in a setting with higher infection rates of HAV (>0.56%) or on specific cost-structure, such as in the Department of Veterans Affairs (VA) setting [14]. The implications of these results to clinical practice, the policy of health care of the people and future research are important.

The reviewed studies have also presented consistent results in that target vaccination measures are more

cost-effective compared to universal vaccination [12-15]. For example, Arguedas et al. (2002) reported an ICER of approximately \$51,000 per QALY gained for targeted vaccination, whereas universal vaccination had an ICER of about \$3.9 million per QALY and was not economically viable in most situations [13]. Similarly, Jacobs et al. (2002) found that screen-and-vaccinate strategies cost \$22,256-\$102,064 per life-year saved depending on age, with the most favorable ratios in younger patients [10]. Equally, Chapko et al. (2010) reported that in the VA cost analysis, vaccination only proved to be cost-effective among patients who had passed the Hepatitis C infection, but not in the market [13]. Such results highlight the necessity of micro-adapting the approaches to vaccination in relation to special types of patients and healthcare facilities.

Myers et al. (2000) emphasized that selective vaccination could prevent 128 symptomatic HAV cases per million patients and remained cost-effective unless annual HAV infection rates exceeded 0.56% [16]. Jacobs et al. (2002) further demonstrated that cost-effectiveness improves substantially when vaccination is provided at younger ages [10].

These findings are consistent with the broader literature regarding cost-effectiveness of vaccination among high-risk groups [16-19]. As an example, the research of influenza and pneumococcal vaccines has also shown that directed vaccination has low costs compared to general ones on certain subsets of people, like the elderly, or people with weakened immunity [16]. Nevertheless, HAV vaccination is cost-effective among Hepatitis C patients and these factors which include the prevalence of the HAV immunity, the cost of vaccination and the progression of Hepatitis C are unique determinants of the cost-effectiveness of the vaccination [12, 14]. All these draw our attention to the fact that the analysis of the strategies of vaccination requires specific backgrounds when considered.

IMPLICATIONS FOR PRACTICE AND POLICY

These findings of this review have a number of significant implications on the clinical practice and the policy of public health. To begin with, selective vaccination must be fundamental among patients with chronic Hepatitis C, especially those that lack previous immunity against HAV. This is a solution that will maximize health benefits and minimize costs. Second, vaccination programs should be made according to the regional HAV infection rates, which should be considered by policy-makers. Universal vaccination might not be necessary in a region with a low prevalence of HAV but one where the HAV is prevalent, it may be an affordable solution. Lastly, the issue of low access and affordability of vaccines should be considered by healthcare systems as they have a profound impact on the cost-effectiveness of the procedure. In addition, vaccination strategies should prioritize younger patients with chronic HCV, in whom cost-effectiveness is most favorable.

STRENGTHS AND LIMITATIONS

The strengths of this review are that it has a good search strategy, has study selection, and has used good economic evaluation frameworks to synthesize the findings. Nevertheless, there exist some restrictions as well. First, the studies obtained included those which were carried out in high-income states (USA and Canada), thus restricting the extrapolation of the results to the low- and middle-income countries where the prevalence of Hepatitis C and HAV might vary. Second, other studies utilized hypothetical cohorts or presumptions regarding the query of HAV infection rates that would not reflect the reality. Lastly, only the studies published in English were reviewed which may exclude some of the relevant data in the non-English speaking regions. One included study (Jacobs et al., 2002) reported outcomes as life-years saved rather than QALYs, which limits direct comparability with other economic evaluations.

Conclusion

To sum up, this systematic review has shown that selective Hepatitis A immunization is the most cost-effective strategy for patients with chronic Hepatitis C, especially in younger patients and in areas with low levels of HAV infection. Universal vaccination can be based on high-prevalence regions or following certain cost design, but the targeted interventions should be in the first place to maximize resources expenditure. These results can inform clinicians, policymakers, and researchers, as it is possible to use evidence-based vaccination strategies to enhance the results in this group of high risk.

Key Point

This systematic review suggests that selective vaccination against Hepatitis A is usually the most cost-efficient strategy to use with chronic Hepatitis C patients and has benefits over universal vaccination or no vaccination in the majority of epidemiological settings. Universal vaccination seems to be cost-effective in the environment with high incidence of HAV or in healthcare systems with particular cost models, including the U.S. Veterans Affairs. The results indicate the significance of integrating the vaccination plans with epidemiological characteristics of the region and the resources available to maximize the health outcomes. Specific vaccination activities can have a significant impact on the clinical and economic cost of HAV-HCV coinfection and the distribution of resources in a more effective way. However, the relevance of the existing evidence is limited due to the prevalence of model-based studies in high-income nations, which highlights the necessity of real-life research in various healthcare settings.

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Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Center for Health Management and Economics Research, Health Management Research Institute, Iran University of Medical Sciences (Project Code. 28260).

Consent for publication

Not applicable.

Availability of data and materials

This review is based entirely on previously published studies. No new datasets were generated or analysed. All data supporting the findings of this review are included in the published article, and are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

BDT, MB, and SA contributed to the conception and design of the study. BDT, SA conducted the search, and MGh was co-moderator. BDT, SA, MB, MM, PH, and MGh conducted screening and selecting the final studies, which AR discussed regularly. BDT, AR, SA, MM, MB, MGh, and PH wrote the initial draft and contributed to manuscript revisions. BDT, PH, MB: performed a search of the literature. BDT, MB: editing All authors read and confirmed the final manuscript.

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