The economic value of diagnostic strategies in hepatitis D: a methodological review of cost-effectiveness models

Tushar Srivastava[1] , Devian Parra[2] , R Lakshmi[3] , Saeed Anwar[3] , Raju Gautam[1], James Karichu[4], Thaison Tong[5]

[1]ConnectHEOR, United Kingdom, [2]ConnectHEOR, The Netherlands, [3]ConnectHEOR, India, [4]Roche Molecular Systems Inc, USA, [5]ConnectHEOR, Vietnam

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BACKGROUND AND OBJECTIVES

- Hepatitis D virus (HDV) infection affects individuals already infected with hepatitis B virus (HBV) and is associated with a substantially higher risk of adverse liver-related outcomes compared with HBV mono-infection. [1, 2, 3]
- Inconsistent screening and diagnostic guidelines, insufficient awareness of HDV epidemiology, and limited diagnostic resources frequently result in delayed diagnosis, often only after the onset of advanced liver disease.[2]
- As testing strategies for HDV evolve, understanding their economic value and clinical impact is essential to guide health policy and resource allocation.
- This study aimed to assess the current evidence on the cost-effectiveness of screening and diagnostic strategies for HDV infection and summarize key methodological considerations.

METHODS

- A targeted literature review (TLR) of cost-effectiveness analyses was conducted in PubMed, covering publications from inception to April 21, 2025. The eligibility and inclusion criteria are summarized in Figure 1.
- No restrictions on timeframe or geography were considered. Only studies published in English were included. Partial economic evaluations and studies that did not address the relevant populations or outcomes of interest were excluded
- Data were extracted on study population, perspective, time horizon, model structure, diagnostic algorithms, outcomes, and key limitations.

Figure 1: PICOS criteria for the review

Population	Individuals susceptible to hepatitis D virus infection (i.e., hepatitis B surface antigen-positive subjects)
Intervention	Testing strategies for hepatitis D virus infection detection
Comparator	No testing or alternative testing strategies for the diagnosis of hepatitis D virus infection
Outcomes	Economic costs, life-years (LYs), quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER), and net monetary benefit (NMB). Intermediate outcomes were also considered relevant.
Study design	Full economic evaluations (i.e., cost-effectiveness or cost-utility analyses).

RESULTS

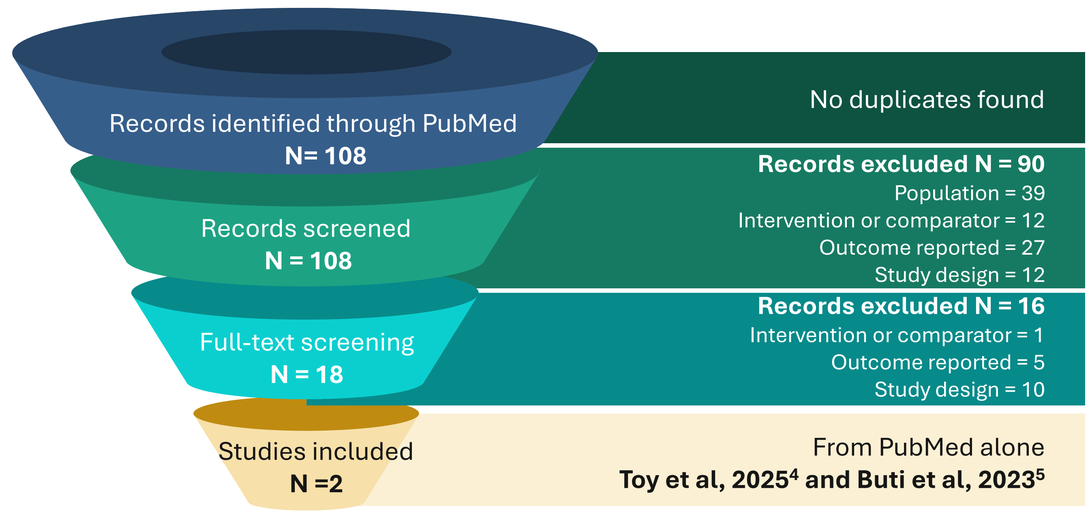
- The identification and selection process is shown in Figure 2.
- All studies included (n = 4) evaluated testing strategies on individuals with current HBV infection without considering any risk stratification. Two studies compared distinct screening scenarios: universal (100%) vs. status quo (12.9% and 7.6%).
- The decision tree models typically represented the initial diagnostic process of HDV in individuals with HBV, while the Markov models simulated the subsequent liver disease process and treatment pathway. The studies using Markov models employed lifetime horizons (Figure 3).
- The Markov models differed in their representation of health states describing liver disease progression before compensated or decompensated cirrhosis.[4,6]
- Only one study explicitly modeled changes in HBV infection status, while only one study included alanine aminotransferase testing (ALT) in the decision tree structure.[4,6]
- Results across studies were sensitive to assumptions regarding HDV prevalence, test performance, treatment eligibility, and cost parameters. Several limitations were identified (Figure 4).

CONCLUSIONS

- Existing modeling studies provide insights, but methodological variability hinders comparisons.
- Future studies should standardize methods while allowing flexible evaluation of HDV screening across settings to support policy decisions.

This review evaluated cost-effectiveness analyses of diagnostic strategies for hepatitis D virus (HDV) infection. Considerable heterogeneity in model structures and assumptions revealed key methodological limitations. Standardized yet adaptable frameworks are needed to improve comparability across studies, support evidence-based decision-making, and enhance outcomes for individuals at risk of HDV infection

Figure 2: Flow chart of the identification and selection process



Two **additional** records were retrieved through desk search (grey literature and manual search) **von Hein et al, 2024[6] and Fuentes et al, 2025[7]**

Figure 3: Frequency of model structures across included studies

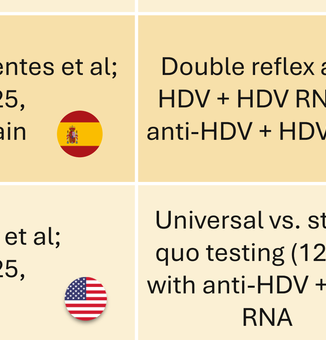


Figure 4: Identified limitations of studies included

- Assumptions on long-term disease course and HDV-related mortality
- Simplifying assumptions on the clinical effect of treatments after testing
- Uncertainty in test performance statistics used to estimate positive and true positive cases after initial resting
- Uncertainty in treatment rate estimates among confirmed cases

Table 1: Overview of study design and results of the studies included

Author, Year & Country	Intervention & comparators	Perspective & Time Horizon	Results
Buti et al; 2023, Spain	Universal anti-HDV + HDV RNA vs. status quo testing with anti-HDV testing (7,6%)	Healthcare system, 8 years	Anti-HDV reflex testing could increase CHD diagnoses, reduce the number of liver complications, liver mortality, and total economic costs (36 million Euros in savings estimated) vs anti-HDV testing alone.
Von Hein et al; 2024, UK	No testing vs anti-HDV + HDV RNA testing	Not reported, Lifetime	Testing was considered cost-effective and resulting in positive incremental QALYs, LYs, and lower events of decompensated cirrhosis, hepatocellular carcinoma, and liver transplants while generating higher total costs
Fuentes et al; 2025, Spain	Double reflex anti-HDV + HDV RNA vs anti-HDV + HDV RNA	Healthcare system, Not reported	Double reflex testing led to higher cases detected and testing costs. The improved clinical outcomes would generate lower specialist visits costs (79%), leading to overall lower total costs.
Toy et al; 2025, US	Universal vs. status quo testing (12,9%) with anti-HDV + HDV RNA	Healthcare system, Lifetime	Universal testing would avert HDV-related deaths, cases of cirrhosis, and hepatocellular carcinoma, resulting in potential QALY gains and value for money.

Abbreviations: anti-HDV = antibody to hepatitis D virus; CHD = chronic hepatitis D; HDV = hepatitis D virus; ICER =incremental cost-effectiveness ratio; LYs = life years;; QALY = quality-adjusted life years; RNA = ribonucleic acid

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CONFLICT OF INTEREST

- The authors declare no conflicts of interest related to this work, and no external funding was received for its development.