

Title:

Hepatitis D prevalence: problems with extrapolation to global population estimates

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We read the recent meta-analysis of global hepatitis D prevalence by Chen et al and have some serious concerns relating to the proposed epidemiological estimates.¹

The primary outcome, HDV seroprevalence, was not adequately defined. In the methods section hepatitis delta antibody (anti-HDV), HDV RNA detection, and HDV antigen (HDAg) were described as markers of HDV infection. In Supplementary Table S8, it is evident that total, IgG, IgM anti-HDV and HDAg were variably used to define HDV infection. HDAg is a transient marker of HDV infection, whereas IgM expression is inconsistently associated with both acute and chronic infection² and neither are suitable epidemiological markers of chronic HDV infection.

A total of 50 cohorts were used to inform the primary outcome, global HDV seroprevalence in the general population; of these 30 were conducted in the last 20 years. The authors estimated that nearly 11% of HBV carriers and nearly 1% of the global population are infected with HDV. Their figures imply global HBsAg prevalence of 9.3%. Yet recent estimates are between 3.2% and 3.9%.^{3,4}

Several problematic aspects of the analysis, and how selected datasets were extrapolated to wider prevalence estimates, may have contributed to this discordance. The authors weighted samples relative to survey size without consideration of the population represented by the sample, such that samples from China (population 1.4 billion), were given equal weight to similarly sized samples from Nauru (population 13,000) although the population represented is 100,000 times larger. The authors used survey data from isolated high-prevalence populations, as in the case of Venezuelan Amazonian Amerindians⁵ to estimate national prevalence. Further, the authors included laboratory-based samples that reported results of clinician-initiated testing⁶. Clinically-driven, targeted HDV testing is likely to introduce bias, for example in favour of patients with severe liver disease. The authors stated that the analysis of HDV prevalence in the general population was based on 40 million samples. This statement is somewhat misleading since a single study from France- a nationwide study of blood donors over a 15-year period- contributed 39,911,011 of 40,026,625 (99.7%) samples and only 4492 of 6214 (72%) HBsAg positive individuals were tested for HDV in that study.⁷

In the general population analysis, the authors included individuals recruited from hospital settings.⁸ Convenience samples from hospital populations are more likely to comprise individuals with chronic liver disease relative to community studies and therefore to overestimate HDV prevalence. Testing for anti-HDV in patients with established liver disease has an important role in HDV epidemiology, since HDV infection accelerates progression to cirrhosis and death.⁹ However, inpatient populations and community screening data should not be combined in a single prevalence analysis. Conversely, the authors excluded HIV-positive patients, which particularly in populations with generalised HIV epidemics in Southern and Eastern Africa, provide valuable data.¹⁰

Finally the authors did not undertake a quality assessment to look at selection bias, representativeness of the samples, significant exclusions, bias from retrospective data or loss to follow up. While the authors have performed a sensitivity analysis (Table S7), it is unclear from the main paper or supplementary text what exactly was done as part of this. By example, exclusion of small Amerindian or Island populations, samples from inpatients and laboratory-based samples, would reduce the estimate of global prevalence from 0.98% to 0.82% (from 72 to 61 million individuals) (Figure).

Due to these shortcomings, we do not believe that this analysis provides a reliable estimation of global hepatitis D seroprevalence. The authors' point estimates of HDV seroprevalence and interpretation that hepatitis D is twice as prevalent as previous estimations should be treated with caution.

Competing Interests:

The authors are presently working on estimates of global hepatitis D prevalence for the World Health Organisation.

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Figure: Meta-analysis of HDV seroprevalence from general populations in Chen et al¹ following exclusion of inpatients, samples from isolated Amazonian Amerindian or small island populations and laboratory-based studies