**Title:**

Hepatitis D prevalence: problems with extrapolation to global population estimates

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

Seroprevalence of hepatitis delta virus (HDV) was not adequately defined. In the methods, hepatitis delta antibody (anti-HDV), HDV RNA, and HDV antigen (HDAg) were described as markers of HDV infection. In Supplementary Table S8, it is evident that total, IgG, and 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 infection; neither are suitable epidemiological markers of chronic HDV infection.2

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 hepatitis B virus (HBV) carriers and nearly 1% of the global population are infected with HDV. Their figures imply a global hepatitis B surface antigen (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). Survey data from isolated high-prevalence populations, as in the case of Venezuelan Amazonian Amerindians,5 were used to estimate national prevalence. Further, 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 survey of blood donors over a 15-year period – contributed 99.7% of the samples (39,911,011 of 40,026,625); only 4492 of 6214 (72%) HBsAg positive individuals were tested for HDV in that study.6

The authors included laboratory-based samples that reported results of clinician-initiated testing.7 Clinically-driven HDV testing is likely to introduce bias, for example in favour of patients with severe liver disease resulting in overestimation of HDV prevalence. Individuals recruited from hospital settings were included in the general population analysis.8 Convenience samples from hospital populations are more likely to comprise individuals with severe liver disease relative to community studies. Inclusion of these samples is therefore also prone to overestimating HDV prevalence. Testing for anti-HDV in patients with established liver disease has an important role in HDV epidemiology, since HDV accelerates progression to cirrhosis and death.9 However, the data should not be combined with those of community screening to produce a single prevalence estimate. Conversely, the authors excluded HIV-positive patients, which provide valuable data, particularly in populations with generalised HIV epidemics in Southern and Eastern Africa.10 By example, exclusion of small Amerindian or Island populations, laboratory-based samples, and samples from hospital populations would reduce the global prevalence estimate from 0.98% to 0.82% (from 72 to 61 million individuals) (Figure).

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. Whereas the authors indicate that they performed a sensitivity analysis in Table S7, it is unclear from the main paper and supplementary text what exactly was done as part of this.

Due to these shortcomings, we do not believe that the analysis, as presented, provides a reliable estimation of global hepatitis D seroprevalence. The proposed estimates, 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 in collaboration with 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

