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Hepatitis D double reflex testing of all hepatitis B carriers in low HBV and high HBV/  
high HDV prevalence countries

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**Hepatitis D double reflex testing of all hepatitis B carriers in low HBV and high HBV/high HDV prevalence countries**

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**Abstract**

Hepatitis D virus (HDV) infection occurs as a coinfection with hepatitis B and increases the risk of hepatocellular carcinoma, decompensated cirrhosis, and mortality compared to hepatitis B virus (HBV) mono-infection. Reliable estimates of HDV infection prevalence and disease burden are essential to formulate strategies to find coinfecting individuals more effectively and efficiently.

The global prevalence of the HBV+ population is estimated at 262,240,000 in 2021. Only 1,994,000 of the HBV infections were newly diagnosed in 2021, with more than half of them in China. Initial estimates of HDV prevalence found a much lower prevalence of HDV antibody (anti-HDV) and HDV RNA-positive (RNA+) cases compared to published studies.

There is need for accurate estimates of HDV prevalence. The most effective method to develop the estimates of anti-HDV+ and HDV RNA+ prevalence and find undiagnosed individuals at the national level is to implement double reflex testing. This requires anti-HDV testing of all hepatitis B surface antigen (HBsAg)-positive individuals and HDV RNA testing of all anti-HDV+ individuals. This strategy is bearable for healthcare systems since the number of newly diagnosed HBV patients is small. At the global level, a comprehensive HDV screening strategy would require only 1,994,000 HDV antibody tests and less than 89,000 HDV PCR tests. Double reflex testing is the preferred strategy in low HBV prevalence or high HBV and high HDV prevalence settings. For example, in the European Union and North America only 35,000 and 22,000 will need anti-HDV testing annually.

**Key Points:** 3-5 bullet points, maximum 120 characters including spaces per bullet

- Accurate estimates of anti-HDV and HDV RNA+ prevalence is needed to assess national, regional and global burden.
- We recommend double reflex testing of all HBV infected individuals for anti HDV and HDV RNA.
- Double reflex testing (anti-HDV and PCR) burden will be small as only newly diagnosed HBV cases will require testing.
- Globally, less than 2 million people will require anti-HDV testing and less than 90,000 will require PCR testing.
- This recommendation makes the most sense for low HBV prevalence or high HBV/high HDV prevalence settings (most countries).

**Background** – Hepatitis D virus (HDV) infection, which occurs as a coinfection with hepatitis B, increases the risk of hepatocellular carcinoma (HCC), decompensated cirrhosis, and mortality 3.2 (95% confidence interval, 1.0–10.0), 2.2 (0.8–5.7), and 2.0 (0.7–5.7) fold, respectively, compared to hepatitis B virus (HBV) mono-infections (1-5). Therefore, reliable estimates of HDV infection prevalence and disease burden are essential to formulate strategies to find coinfecting individuals more effectively and efficiently. Early diagnosis of HDV will also allow for more appropriate counseling (e.g., reduce alcohol consumption, lose weight) to reduce the risk of disease progression and prevent HDV transmission, interventions including antiviral treatment, and follow-up (ultrasound and HCC surveillance). In addition, early detection of complications will save lives by proper interventions (e.g., liver transplantation or HCC treatment). Knowledge of HDV infection will raise awareness of the infection among healthcare professionals with potential access to therapy and may empower patients to take action.

**Methods** – The Polaris Observatory started the task of quantifying the global prevalence of HDV infection. A comprehensive literature review was conducted for anti-HDV & HDV-RNA-positive prevalence for individual countries/territories. Virtual meetings were held with experts from each setting to discuss the literature search findings and collect unpublished data/ reports. The crude reported prevalence was adjusted for patient segments & regional heterogeneity to estimate the adjusted HDV prevalence in the HBV-infected population. The findings were then combined with the Polaris Observatory HBV data (6) to estimate the overall anti-HDV & HDV-RNA prevalence in each country/territory at the population level.

The number of newly diagnosed HBV infections in each country was updated annually using the following methodologies: In countries where HBsAg was a notifiable infection, the annual reported data was collected. In countries where the number of newly diagnosed cases was not available, expert panel input was used. Lastly, secant method was used to solve for the proportion of diagnosed HBsAg-infected population to match the reported number of diagnosed cases to modeled in a given year (7). This method assumed that at base, those in later stages of the disease are more likely to be diagnosed than those in earlier stages. Details of the data sources for each country were described previously in table 6 of the Appendix (6).

For countries where no data was available, the weighted average of countries within the same region as defined by the Global Burden of Diseases (GBD) was applied. The regional estimates (income group, continent, and the European Union) were calculated by summing data from countries in each region. The World Bank data list of all countries in each income group was used (8).

**Results** – We found a much lower prevalence of HDV antibody (anti-HDV) and HDV RNA-positive (RNA+) cases compared to published studies (9-12). Key drivers of this discrepancy were the lack of nationally representative studies and the use of crude or pooled prevalence in meta-analyses, rather than adjusted prevalence (i.e., HDV prevalence of a study adjusted for age, gender, population, or geography of the country). Most data on prevalence estimates relied on studies within smaller regions and subpopulations, which can lead to overestimation of the actual disease prevalence in the general population. As an example, most studies in Brazil report a high anti-HDV+ prevalence in the Amazon region. However, the Amazon region also has a small population. After adjusting for the population, HBV prevalence, and HDV infection prevalence in different regions of Brazil, the anti-HDV+ prevalence dropped by half, from 3.2% to 1.6%, among HBV+ individuals in the same study (13). Previous studies have also shown a 5- to 10-fold difference in anti-HDV+ prevalence among blood donors and patients with cirrhosis in Italy, Turkey, and Uzbekistan (14, 15).

The total HBsAg positive infections and the number of newly diagnosed HBsAg infections from the Polaris Observatory is shown below.

Table 1. Total HBsAg infections and newly diagnosed HBsAg infections

Regions/Countries	Total HBsAg-Positive Infections, 2021	Newly Diagnosed HBsAg infections, 2021
<b>Global</b>	<b>262,240,000</b>	<b>1,994,000</b>
<b>Regions by Income Groups</b>		
High income	11,375,000	114,000
Upper middle income	98,193,000	1,128,000
Lower middle income	116,585,000	631,000
Low income	35,636,000	119,000
<b>Regions by Continent</b>		
Africa	69,512,000	187,000
Asia	178,978,000	1,694,000
Australia	316,000	6,000
Europe	7,502,000	66,000
North America	2,710,000	22,000
Oceania	788,000	1,000
South America	2,433,000	19,000
<b>European Union</b>	<b>2,828,000</b>	<b>35,000</b>
<b>China, Mainland</b>	<b>80,952,000</b>	<b>1,000,000</b>

**Discussion** – The most effective method to develop accurate estimates of anti-HDV+ and HDV RNA+ prevalence and find undiagnosed individuals at the national level is to implement double reflex testing. This requires anti-HDV testing of all hepatitis B surface antigen (HBsAg)-positive individuals and HDV RNA testing of all anti-HDV+ individuals.

A study in Spain showed that implementation of reflex anti-HDV testing resulted in an increased diagnosis of anti-HDV+ individuals (16). Without reflex testing, national registries will report a greater HDV prevalence because of selection bias; patients suspected of having hepatitis D, most of them with advanced liver disease, are referred for testing and recorded in the national registry (17).

The current European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver guidelines already recommend HDV screening of all HBsAg-positive individuals, whereas the American Association for the Study of Liver Diseases guidelines only recommend screening populations at greater risk for this infection (18-20). There is already HDV reflex testing at specific hospitals or regions within a limited set of countries (e.g., Spain, France, Brazil, Sweden, Canada), but not at the national level (21-23). In most cases, only individuals suspected of HDV infection (elevated alanine transaminase level, early-age cirrhosis, or HCC) are screened, leading to high prevalence estimates as a result of selection bias. This strategy also has the limitation that screening individuals suspected of having advanced liver disease is often too late to implement any preventive measures.

On the surface, double reflex testing may appear to put an undue burden on healthcare systems, but analysis of the hepatitis B cascade of care provides a different story, because only individuals diagnosed with HBsAg will have to be tested for anti-HDV (24).

As shown in Table 1, an estimated 2 million HBsAg-positive people worldwide are diagnosed annually, with half of them residing in mainland China. In all of Europe, an estimated 65,800 patients with HBV would require reflex anti-HDV testing, and only 34,500 in the European Union. Therefore, at the national level, the numbers that require anti-HDV testing will be even fewer. The estimated number of patients requiring testing would be less in North America, South America, and Australia. The total annual number that should be tested for anti-HDV in all of Africa is also less than 180,000. The overall cost could be managed further by not testing for HDV if patients have the same diagnosis already noted in their medical record.

HDV prevalence among HBsAg-positive individuals was estimated to be between 4.5% and 14.6% (10-12). This is likely an overestimate; but, if we use it as a placeholder, only an estimated 89,000 people will need annual HDV polymerase chain reaction (PCR) tests globally. Table 1 suggests that double reflex testing for

HDV will not overburden healthcare systems and may result in cost savings by reducing costly end-stage disease (25).

The only exception for this recommendation is for countries and regions with a high HBV and low HDV infection prevalence (e.g., mainland China, Taiwan, Korea, Japan), for which a cost-effectiveness study is needed to assess the benefit of reflex testing, or serum pooling techniques could be used (26). Nonetheless, in regions and at-risk groups with a high HDV prevalence, such as persons who inject drugs and prisoners (26), reflex testing remains beneficial. In addition, individuals diagnosed previously with HBV and who engage in high-risk behavior may need reflex testing as well. Our recommendation still applies to countries with a low prevalence of HBV infection (Europe and North America), where fewer HBV+ individuals will be diagnosed, and thus fewer reflex tests will be needed. The recommendation does not apply to quantitative HBsAg testing, which is used repeatedly for reasons other than diagnosis.

Today, there is limited availability and standardization of HDV RNA PCR tests in anti-HDV tests used in different countries and there are no WHO prequalified tests. However, this limitation is mainly a result of the low demand for these tests, given current practices. With the implementation of double reflex testing, there will be an incentive for diagnostics companies to register their tests and compete based on quality and price, as well as to commercialize rapid anti-HDV diagnostic tests with high sensitivity and specificity that can be used in resource-limited settings as well as other countries (27).

The double reflex test is bearable for healthcare systems. In addition, it will provide more accurate estimates of the prevalence of HDV infection as well as help develop more reasonable strategies to identify HDV-infected individuals early in the disease course and offer appropriate linkage to care, counseling, follow-up, and interventions, with the ultimate goals of reducing morbidity and mortality.

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