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MAJOR ARTICLE

Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection

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(See the Editorial Commentary by Yurdaydin and Toy, on pages 1573–5.)

Background. Hepatitis delta virus (HDV) coinfects with hepatitis B virus (HBV) causing the most severe form of viral hepatitis. However, its exact global disease burden remains largely obscure. We aim to establish the global epidemiology, infection mode-stratified disease progression, and clinical outcome of HDV infection.

Methods. We conducted a meta-analysis with a random-effects model and performed data synthesis.

Results. The pooled prevalence of HDV is 0.80% (95% confidence interval [CI], 0.63–1.00) among the general population and 13.02% (95% CI, 11.96–14.11) among HBV carriers, corresponding to 48–60 million infections globally. Among HBV patients with fulminant hepatitis, cirrhosis, or hepatocellular carcinoma, HDV prevalence is 26.75% (95% CI, 19.84–34.29), 25.77% (95% CI, 20.62–31.27), and 19.80% (95% CI, 10.97–30.45), respectively. The odds ratio (OR) of HDV infection among HBV patients with chronic liver disease compared with asymptomatic controls is 4.55 (95% CI, 3.65–5.67). Hepatitis delta virus-coinfected patients are more likely to develop cirrhosis than HBV-monoinfected patients with OR of 3.84 (95% CI, 1.79–8.24). Overall, HDV infection progresses to cirrhosis within 5 years and to hepatocellular carcinoma within 10 years, on average.

Conclusions. Findings suggest that HDV poses a heavy global burden with rapid progression to severe liver diseases, urging effective strategies for screening, prevention, and treatment.

Keywords. cirrhosis; disease progression; epidemiology; hepatitis delta virus; hepatocellular carcinoma.

Hepatitis delta virus (also known as hepatitis D virus [HDV]) is a defective subvirus that requires hepatitis B virus (HBV) surface antigens (HBsAgs) to propagate. After its discovery in the 1970s, HDV has been largely neglected over the past decades, and establishing HDV status has been relatively uncommon in routine clinical practice. Early reported global prevalence of HDV was estimated at 15–20 million infections, corresponding to approximately 5% of HBV carriers [1]. This relatively complacent view on the HDV public health problem was challenged in 2017, when a study targeting sub-Saharan Africa estimated the presence of 7 million infections in this specific region alone [2]. Indeed, a subsequent study in 2018 estimated the worldwide number of HDV infections at approximately 62–72 million [3], and this number was recently upwardly revised to 74 million [4]. Thus, the public health problem posed by HDV infection appears much bigger than initially assumed. However, there is ongoing debate regarding the exact global prevalence of HDV [5, 6], and regional estimates remain largely lacking.

Globally, viral hepatitis causes approximately 1.34 million deaths annually, with 66% of the deaths attributed to HBV infection [7]. However, which fraction of the HBV-associated mortality involves disease complicated by HDV infection remains uncertain. Despite being a defective virus, HDV is generally associated with the most severe forms of acute and chronic viral hepatitis in humans. Patients infected with both HDV and HBV display apparently dramatically accelerated progression to cirrhosis and development of hepatocellular carcinoma compared with those patients displaying HBV infection alone [8–10]. Thus, it is likely that HBV complicated by HDV infection is associated with alternative disease progression, treatment response, and patient outcome compared with non-HDV-complicated HBV infection, but quantitative data on the contribution of HDV infection on outcome of HBV infection are largely lacking [11–13]. It is interesting to note that HDV infection can occur either via simultaneous coinfection with HBV of a susceptible individual or through superinfection of an HBV carrier [14]. These 2 transmission modes may also lead to distinct clinical outcome, but, again, systematic analysis of such an effect has not been performed [14]. By performing a systematic review, meta-analysis, and additional data synthesis, we aimed to generate a high-confidence estimate of the global prevalence of HDV infection and its relation to outcome

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HBV infection in the context of both HBV/HDV coinfection as well as of HDV superinfection in an existing HBV infection.

MATERIALS AND METHODS

Literature Search and Selection Criteria

For this systematic review and meta-analysis, we searched EMBASE, Medline Ovid, Cochrane Database, and China Knowledge Resource Integrated database for cross-sectional and longitudinal observational studies measuring the prevalence and outcome of HDV infection, published in English and Chinese languages from database inception to February 2019. The prevalence of HDV was defined by the detection of HDV antibodies (anti-HDV immunoglobulin [Ig]G and/or anti-HDV IgM) using immunoassay, supplemented by the additional detection of delta antigen and HDV ribonucleic acid (RNA). Study subjects were classified either as general population or HBsAg-positive carriers, and for further subanalysis groups were divided into blood donors, population at large (general group), intravenous drug users (IDUs), people with high-risk sexual activity, human immunodeficiency virus (HIV) patients, hepatitis C virus (HCV) patients, blood transfusion recipients, mixed patients, patients with liver disease, and asymptomatic HBV carriers, as per cohort information. Hepatitis B virus patients with liver disease were divided into different categories: acute hepatitis (AH), fulminant hepatitis (FH), chronic hepatitis (CH), liver cirrhosis, and hepatocellular carcinoma (HCC).

Data Collection and Processing

Nonredundant records were initially screened by title and abstract according to the selection criteria independently performed by Z.Mi. and S.L. The selected results were cross-checked to resolve discrepancies, and the remaining disagreements were discussed with J.L. and Q.P. and resolved by consensus. Subsequently, the selected records were subjected full-text assessment, and data were extracted from the primary literature independently by Z.Mi. and S.L. Discrepancies were identified and resolved by discussing or arbitrage by J.L. and Q.P. For exclusion of potential duplicate data from the same geographical location, consensus by the investigational team was achieved. Authors from primary studies were contacted for clarification if required.

The quality of the studies included was assessed by a scoring system [15, 16], which was independently performed by 2 investigators (Z.Mi. and S.L.) and reviewed by the other investigators (J.L. and Q.P.). Then, sensitivity analyses were performed to assess the effects of study quality and data source. Our study was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statements [17, 18].

Statistical Analysis

The Metaprop module in the R-3.4.2 statistical software package was used for meta-analysis. The pooled prevalence was calculated by the DerSimonian-Laird random-effects model with Freeman-Tukey double arcsine transformation [19, 20]. The 95% confidence interval (CI) was estimated using Wilson score method. Odds ratios (ORs) were pooled with DerSimonian-Laird random-effects model. To avoid small sample bias in the random effects model, we excluded studies with fewer than 100 subjects for the general population and 20 for HBsAg-positive carriers. Detailed information regarding materials, methods, and related references as well as additional discussion are provided in the online Supplementary Data File.

RESULTS

Estimates of Hepatitis D Virus Prevalence at National, Regional, and Global Levels

Our search returned 3518 records, and 634 of these met the inclusion criteria (Figure 1). In total, 332 155 individuals of the general populations from 48 countries and regions and 271 629 HBsAg-positive carriers from 83 countries and regions were included (Supplementary Figure 1). For estimating the global prevalence, we calculated that the pooled prevalence of HDV is 0.80% (95% CI, 0.63–1.00) in the general population and 13.02% (95% CI, 11.96–14.11) among HBsAg-positive carriers, corresponding to 48–60 million infections worldwide (Figure 2). China, India, and Nigeria are the leading countries in this respect (Figure 2 and Supplementary Table 1). Regionally, HDV is highly prevalent in central Asia, eastern Europe, tropical and central Latin America, as well as central and west sub-Saharan Africa (Table 1). Asia (44.41%–56.55%) followed by Africa (22.30%–38.37%) are predominant with respect to global HDV burden. Hepatitis D virus infection is especially prevalent in low-income and lower-middle-income countries, but concomitantly data from these resource-limited countries are relatively limited (Table 1 and Supplementary Figure 2).

Analysis of Risk Factors for Hepatitis D Virus Transmission

Further analysis of our data showed that the prevalence of HDV is high among IDUs but low among blood donors (Supplementary Table 2). Intravenous drug use, HIV, and HCV are the remain risk factors for HDV transmission observed in HBsAg-positive carriers with respective ORs of 15.44 (95% CI, 8.68–27.49), 2.99 (95% CI, 1.84–4.88), and 3.05 (95% CI, 1.19–7.86), relative to controls (Supplementary Table 2). There is no significant difference for the prevalence of HDV in males (14.95%; 95% CI, 12.43–17.67) versus females (14.18%; 95% CI, 11.49–17.10) among HBsAg-positive carriers, with an OR of 1.05 (95% CI, 0.91–1.21) (Supplementary Figure 3–5).

Hepatitis D Virus Infection Presents a Distinct Epidemiological Profile Among Hepatitis B Virus Patients

There are hardly data that comprehensively capture how and to what extent HDV contributes to severe liver diseases. It is interesting to note that the prevalence of HDV infection in HBsAg-positive patients is very distinct between different

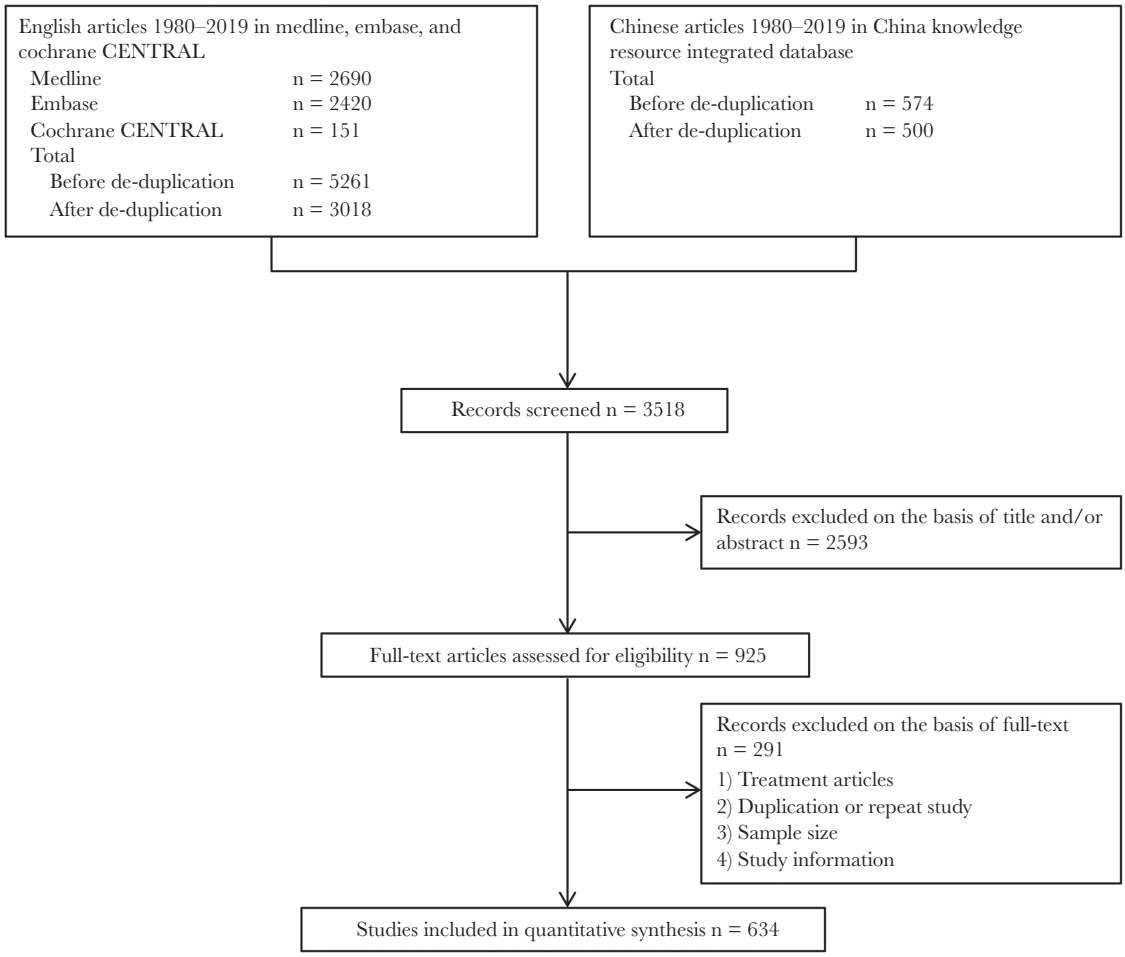

Figure 1. Flowchart of study selection.

forms of liver pathology. Among acute HBV patients, the rate of HDV infection is much higher in FH (26.75%; 95% CI, 19.84–34.29) compared with less symptomatic cases of AH (11.70%; 95% CI, 8.90–14.81) (Figure 3A). In chronic HBV patients, HDV infection rates are low in asymptomatic carrier (3.96%; 95% CI, 3.13–4.88), but they are high in CH (16.75%; 95% CI, 14.00–19.69), cirrhosis (25.77%; 95% CI, 20.62–31.27), and HCC (19.80%; 95% CI, 10.97–30.45) (Figure 3B). Comparison of symptomatic chronic HBV patients with asymptomatic controls of the same population yielded an OR for HDV infection of 3.56 (95% CI, 2.72–4.65), 6.75 (95% CI, 4.42–10.30), and 5.61 (95% CI, 2.60–12.09) for CH, cirrhosis, and HCC, respectively (Figure 3C). The pooled OR of these severe liver diseases is 4.55 (95% CI, 3.65–5.67), and thus HDV infection is significantly linked to more serious pathology in HBV patients.

Different Infection Patterns of Hepatitis D Virus Infection Result in Distinct Outcomes

Two major HDV infection patterns, coinfection and superinfection, provoke different outcomes (Figure 4A). The majority of HBV-HDV-coinfected patients spontaneously recover from HDV infection (80.96%; 95% CI, 48.71–98.91), but only a minor proportion of superinfected patients recover (30.35%; 95% CI, 12.05–52.70). In contrast, only a relatively small proportion of coinfected patients develop chronic disease (10.45%; 95% CI, 4.49–18.52), but a substantial proportion of superinfected patients progress to chronic disease (77.38%; 95% CI, 55.09–93.54). The OR to recover or become chronically infected after HDV coinfection are 5.05 (95% CI, 1.45–17.56) and 0.05 (95% CI, 0.01–0.27), respectively, relative to HDV superinfection. Stratification according to the pattern of viral infection reveals that most patients are HDV dominant (69.28%; range, 56.30–85.25) or HBV-HDV codominant (27.56%; range, 14.52–40.60), with only a small fraction of patients being HBV dominant (3.16%; range, 3.10–3.23). Thus, patients with HBV infection will clearly benefit from measures that prevent further HDV infection.

Hepatitis D Virus Infection Leads to Rapid Progression to Severe Liver Diseases

We observe that HDV infection predisposes to rapid progression into severe liver diseases (Figure 4B). Upon acute infection,

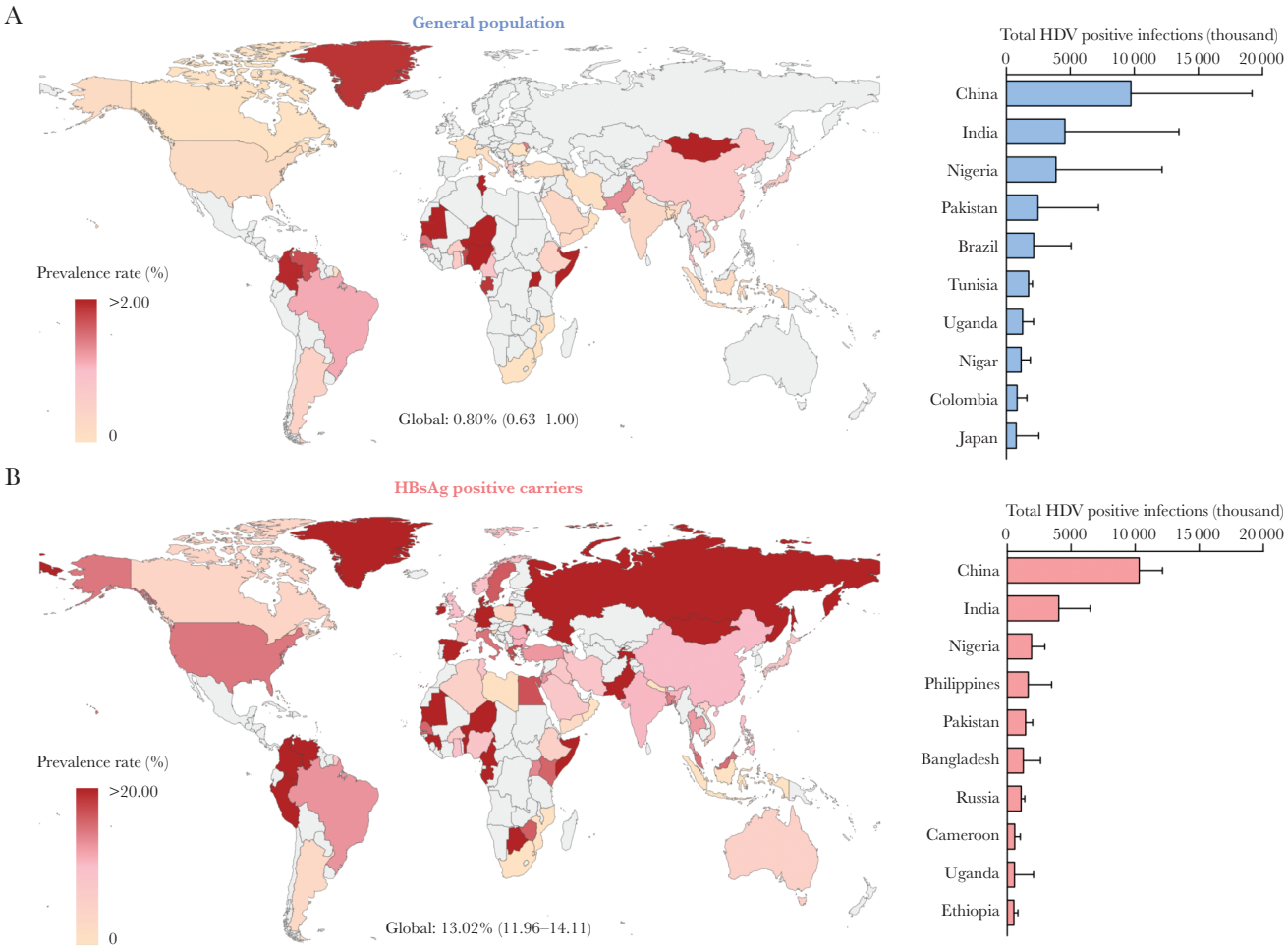

Figure 2. Global prevalence of hepatitis D virus (HDV) infection. (A) General population; (B) hepatitis B virus surface antigens-positive carriers. Blank means HDV-pooled prevalence is not applicable due to lacking HDV epidemiological data. First 10 counties for the estimates of HDV burden were listed, respectively.

39.20% (95% CI, 13.14–69.16) of HDV-infected patients develop CH within a mean of 1.5 years (range, 1.0–1.7), and 30.44% (95% CI, 13.32–50.99) will progress to cirrhosis within 3 years (mean; range, 1.5–4.0). For established chronic infection, 76.47% (95% CI, 63.98–86.98) of HDV-infected patients develop CH within a mean of 3 years, and 29.74% (95% CI, 19.43–41.22) will progress to cirrhosis within 3.1 years (mean; range, 0.5–12.0). With respect to patients with CH, 53.79% (95% CI, 35.16–71.88) of the patients with CH will progress to cirrhosis within a mean of 3.3 years (range, 0.5–8.0), and 14.04% (95% CI, 9.51–19.30) of the cirrhotic patients will progress to HCC within a mean of 3.7 years (range, 1.0–9.0). In general, HDV infection progresses to cirrhosis, on average, within 5 years and to HCC, on average, within 10 years.

Compared with HBV monoinfection, double infection with HDV results in more severe clinical outcome. Among double-infected patients, only 14.99% (95% CI, 2.87–34.22) are asymptomatic but 38.85% (95% CI, 31.57–46.39) are cirrhotic (Figure 5A). In contrast, from the HBV-monoinfected patients, 14.36% (95% CI, 10.04–19.30) are cirrhotic, whereas 57.2% (95% CI, 26.10–85.42) are asymptomatic. For double-infected patients, the ORs for being asymptomatic or having a diagnosis of cirrhosis, HCC, or mortality are 0.12 (95% CI, 0.06–0.21), 3.90 (95% CI, 2.94–5.18), 1.97 (95% CI, 1.02–3.78), and 2.05 (95% CI, 1.18–3.56), respectively, relative to HBV-monoinfected patients (Figure 5B). The observed probability for cirrhosis development is much higher among double-infected patients (40.50%; 95% CI, 22.09–60.43) than HBV-monoinfected patients (14.22%; 95% CI, 8.46–21.17), with an OR of 3.84 (95% CI, 1.79–8.24) (Figure 5C). It is interesting to note that the positive rates of either HBeAg and HBV deoxyribonucleic acid in serum of double-infected patients are lower than those observed in HBV-monoinfected patients with respective ORs of 0.74 (95% CI, 0.06–0.93) and 0.47 (95% CI, 0.30–0.74) (Figure 5D).

Quality and Sensitivity Analyses

In our quality and sensitivity analyses (Supplementary Tables 3 and 4, Supplementary Figures 6–11), the exclusion of low-scoring studies or the data from literature of Chinese language only

Table 1. Estimates of HDV Infection Prevalence by GBD, WHO, or World Bank Region

Regions	General Population			HBsAg + Carrier		
	Population, Thousand	HDV Prevalence (95% CI)[a]	HDV Population, Thousand	HBsAg Population, Thousand (Prevalence)	HDV Prevalence (95% CI)[a]	HDV Population, Thousand
GBD Region						
Asia Pacific, high income	182 909	0.65% (0.02–2.12)[1]	1189 (37–3878)	2561 (1.40%)	5.55% (2.86–9.06)	142 (73–232)
Asia, central	90 018	8.31% (4.15–13.73)[1]	7481 (3736–12 359)	5851 (6.50%)	51.27% (33.69–68.69)	3000 (1971–4019)
Asia, east	1 455 952	0.69% (0.24–1.36)[1]	10 046 (3494–19 801)	106 284 (7.30%)	10.16% (8.50–11.95)[1]	10 799 (9034–12 701)
Asia, south	1 712 556	0.36% (0.02–1.12)	6165 (343–19 181)	53 089 (3.10%)	17.53% (12.08–23.74)	9307 (6413–12 603)
Asia, southeast	660 824	0.26% (0.05–0.61)	1718 (330–4031)	56 831 (8.60%)	6.62% (2.13–13.33)	3762 (1210–7576)
Australasia	29 909			359 (1.20%)	5.13% (3.94–6.46)[1]	18 (14–23)
Europe, central	113 765	0.09% (0.00–0.38)	102 (0–432)	2275 (2.00%)	5.64% (1.82–11.38)	128 (41–259)
Europe, eastern	211 400	1.40% (0.71–2.32)[1]	2960 (1501–4904)	4439 (2.10%)	29.15% (14.70–46.19)	1294 (653–2051)
Europe, western	400 667	0.25% (0.11–0.47)	1002 (441–1883)	2404 (0.60%)	14.72% (13.11–16.40)	354 (315–394)
Latin America, Andean	56 667			227 (0.40%)	65.52% (55.26–75.09)[1]	149 (125–170)
Latin America, central	225 750	1.76% (1.06–2.62)	3973 (2393–5915)	1355 (0.60%)	40.57% (18.57–64.80)	550 (252–878)
Latin America, tropical	196 250	1.13% (0.24–2.66)[1]	2218 (471–5220)	1178 (0.60%)	12.86% (6.21–21.47)[1]	151 (73–253)
Latin America, southern	55 000	0.48% (0.00–3.95)[1]	264 (0–2173)	110 (0.20%)	2.91% (0.89–6.03)[1]	3 (1–7)
North Africa and Middle East	501 333	0.35% (0.14–0.65)	1755 (702–3259)	13 035 (2.60%)	8.58% (7.07–10.21)	1118 (922–1331)
North America, high income	368 667	0.20% (0.15–0.26)	737 (553–959)	1106 (0.30%)	13.01% (8.54–18.25)	144 (94–202)
Oceania	11 065	4.04% (3.53–4.58)	447 (391–507)	1217 (11.00%)	44.22% (13.58–77.58)	538 (165–944)
Sub-Saharan Africa, central	120 941	1.32% (0.68–2.16)	1596 (822–2612)	15 239 (12.60%)	26.18% (14.81–39.46)	3989 (2257–6013)
Sub-Saharan Africa, east	436 157	1.03% (0.34–2.09)	4492 (1483–9116)	34 456 (7.90%)	11.6% (6.78–17.51)	3997 (2336–6033)
Sub-Saharan Africa, southern	80 671	0.00% (0.00–0.02)[1]	0 (0–16)	12 423 (15.40%)	11.41% (0.00–43.96)	1417 (0–5461)
Sub-Saharan Africa, west	399 653	1.38% (0.84–2.03)	5515 (3357–8113)	47 159 (11.80%)	16.55% (11.56–22.24)	7805 (5452–10 488)
WHO Region						
AFRO	1 085 639	1.02% (0.61–1.52)	1107 (6622–16 502)	103 136 (9.50%)	15.29% (11.16–19.93)	15 769 (11 510–20 555)
EMRO	707 500	0.7% (0.34–1.20)	4953 (2406–8490)	21 225 (3.00%)	12.56% (9.56–15.91)	2666 (2029–3377)
EURO	901 625	0.23% (0.12–0.36)	2074 (1082–3246)	18 033 (2.00%)	13.81% (12.38–15.31)	2490 (2232–2761)
PAHO	990 250	0.92% (0.46–1.52)	9110 (4555–15 052)	5942 (0.60%)	14.82% (10.96–19.16)	881 (651–1138)
SEARO	1 969 943	0.17% (0.01–0.50)	3349 (197–9850)	78 798 (4.00%)	8.98% (4.95–14.07)	7076 (3900–11 087)
WPRO	1 906 526	1.47% (0.77–2.40)	28 026 (14 680–45 757)	135 363 (7.10%)	11.14% (9.59–12.78)	15 079 (12 981–17 299)
World Bank Region						
High income	1 145 222	0.30% (0.17–0.47)	3436 (1947–5383)	12 597 (1.10%)	12.38% (10.91–13.93)	1560 (1374–1755)
Upper-middle income	2 670 725	0.59% (0.38–0.85)	15 757 (10 149–22 701)	128 195 (4.80%)	11.04% (9.71–12.44)	14 153 (12 448–15 947)
Lower-middle income	2 974 795	1.73% (0.98–2.70)	51 464 (29 153–80 319)	157 664 (5.30%)	18.39% (14.67–22.42)	28 994 (23 129–35 348)
Low income	704 758	1.02% (0.54–1.64)	7189 (3806–11 558)	57 085 (8.10%)	14.46% (10.10–19.44)	8255 (5766–11 097)
Global	7 486 974	0.80% (0.63–1.00)	59 896 (47 168–74 870)	366 862 (4.90%)	13.02% (11.96–14.11)	47 765 (43 877–51 764)

Abbreviations: AFRO, Regional Office for Africa; CI, confidence interval; EMRO, Eastern Mediterranean Regional Office; EURO, Regional Office for Europe; GBD, Global Burden of Diseases; HBsAg, hepatitis B virus surface antigen; HDV, hepatitis D virus; PAHO, Pan American Health Organization; SEARO, South-East Asia Regional Office; WHO, World Health Organization; WPRO, Western Pacific Regional Office.

[a]Regional data of HDV infection available from only one country is marked (1); HDV prevalence equal to 0.00% standing for negative HDV infection among samples; blank means no HDV infection data are available among the general population.

showed minor effects on the estimates of the overall prevalence of HDV infection both among the general population and HBsAg-positive population. However, the exclusion of these Chinese studies published in the Chinese language decreased the pooled prevalence in China of the general population from 0.69% to 0.48%, probably due to the influence by an extremely large negative cohort study from Hong Kong, but it increased the rate of HBsAg-positive individuals from 10.16% to 14.37%. In addition, we noted significant heterogeneity within our meta-analysis.

DISCUSSION

In the present study, we estimate that there are 48 to 60 million cases of HDV infection in HBV-infected individuals worldwide, yielding a global prevalence of 0.80% in the general population and 13.02% in HBsAg-positive carriers. A recent study reported a global prevalence of 0.98% [3], but our study provides a more accurate estimate (Supplementary Data), and it is in line with the recently postulated global prevalence of 0.82% [6]. The discrepancy with earlier studies can largely be attributed to the stratification for different populations and the exclusion of nonrepresentative populations (eg, IDUs, HIV patients, and patients with liver diseases). This avoids overestimation as was the criticism made with regard to the previous studies [5, 6].

The substantial global burden of HDV infection is fostered by several factors. Although it was previously identified as the satellite virus of HBV, a recent experimental study has demonstrated

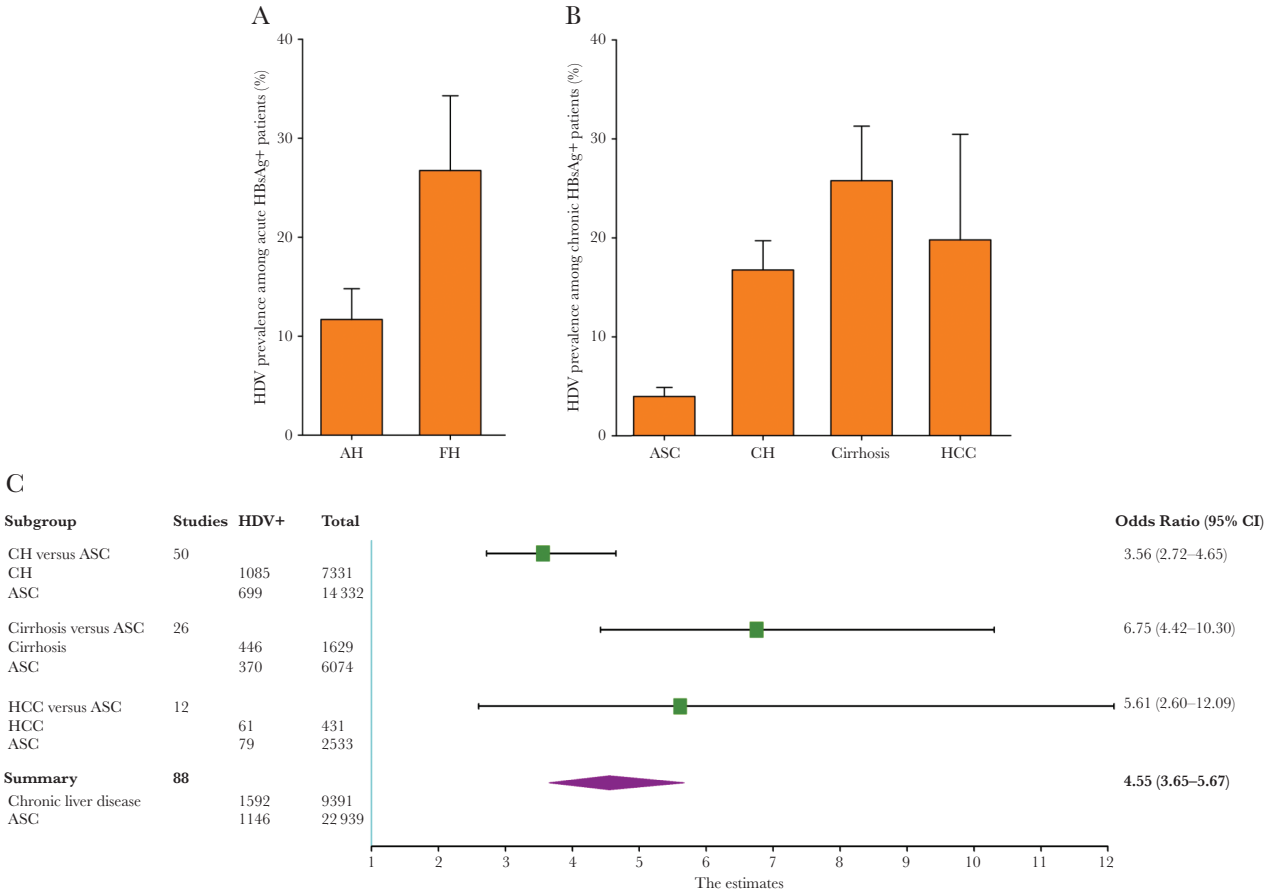

Figure 3. The epidemiological profile of hepatitis D virus (HDV) infection. (A) Prevalence of HDV among acute hepatitis B virus (HBV) patients. (B) Prevalence of HDV among chronic HBV patients. (C) Forest plot of HDV prevalence among patients with chronic liver diseases compared with asymptomatic controls. Data are pooled from a random-effects model. ASC, asymptomatic carrier; CH, chronic hepatitis; CI, confidence interval; FH, fulminant hepatitis; HBsAg, HBV surface antigen; HCC, hepatocellular carcinoma.

that HBV-unrelated viruses can also act as helper viruses for HDV transmission, such as HCV [21]. To our surprise, we observed a high prevalence rate and a 3 times increase in the odds for HDV infection among HBV-HCV double-infected patients. These results appear to support the experimental findings that HCV may assist the assembly and secretion of HDV infectious particles in patients, but it requires further confirmatory investigation [21]. Moreover, our study shows that the prevalence of HDV is extremely high among HBV-positive IDUs. Thus, our study fits well with previous work showing the importance of injection drug use in driving HDV transmission [2, 3]. Also of note, previous study reported that IDUs represent a large reservoir of HDV burden [7]. Indeed, we observe a 15 times increase in the odds for HDV infection in HBV-positive IDUs compared with HBV-positive nondrug using counterparts. However, we estimate that only approximately 1.24%–1.56% and 1.04%–1.31% of the HDV burden can be attributed to users of intravenous drugs (743 000 cases) and HIV exposure (624 000 cases), respectively [16, 22]. Thus, strategies aimed at reducing HDV transmission by IDUs are mainly effective in reducing HDV prevalence because they prevent contagion of the population at large.

The prevalence of HDV varied substantially between geographical regions. With respect to the general population, in 18 countries the prevalence is over 1%, and over half of the countries involved are from Africa, whereas Latin America also has a fair number of high- prevalence countries. In particular, HDV infection rates highly prevail in Tunisia (15.33%), Mongolia (8.31%), and Niger (5.04%). Among HBsAg-positive carriers, the prevalence of HDV in 13 countries exceeds 30%, whereas in 10 countries the prevalence is between 20% and 30%, and in 23 countries it is between 10% and 20%. Consistent with previous observations, central Asia, eastern Europe, tropical and central Latin America, as well as central and west sub-Saharan Africa are high-endemic areas of HDV infection [3]. Our findings show that Asia (44.41%–56.55%) and Africa (22.30%–38.37%) constitute the largest populations hit by HDV infections. It is interesting to note that Asia and Africa are the large reservoirs for HBV infection and accordingly are also the worst-hit areas with respect to HDV burden [23].

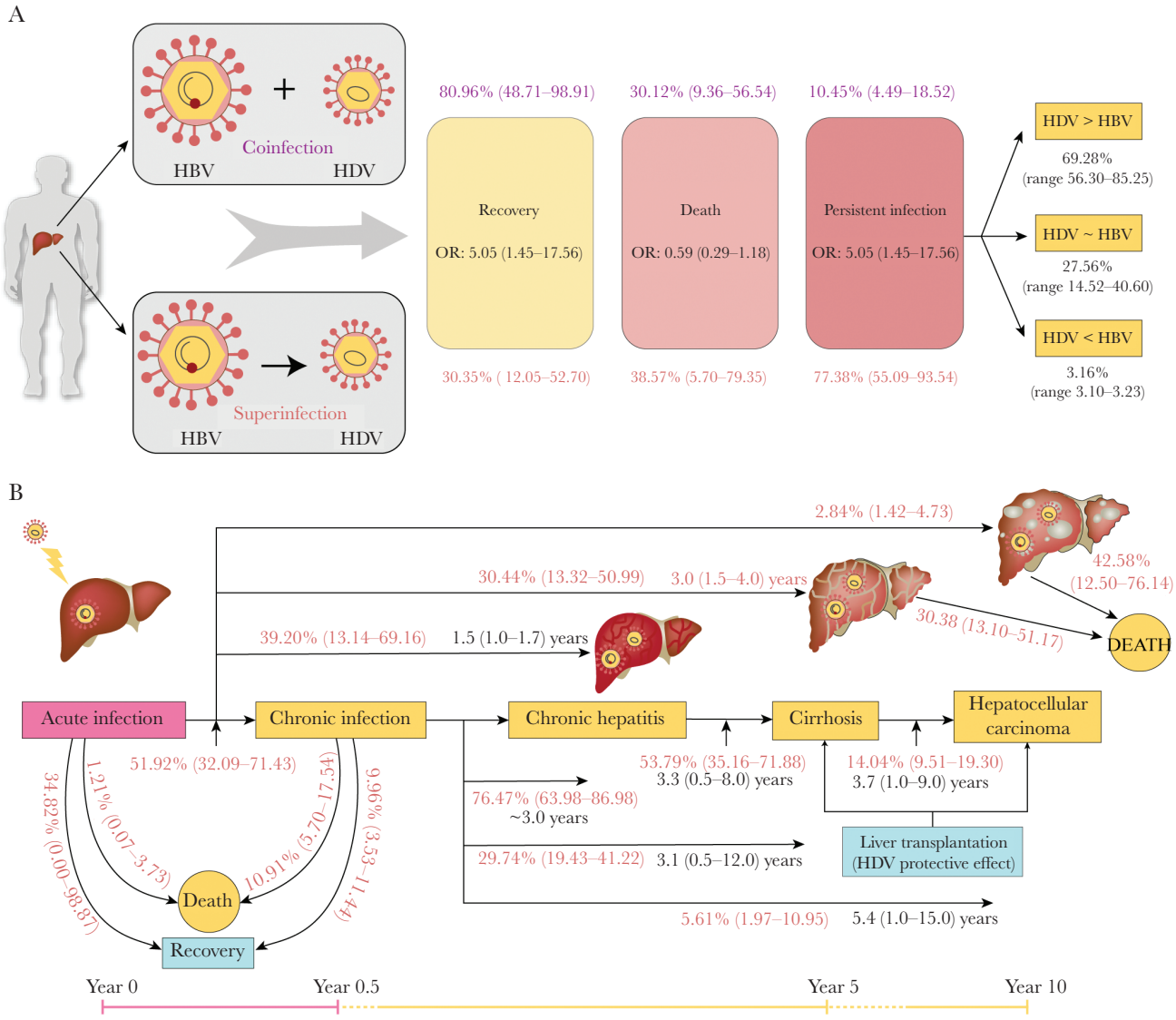

Figure 4. Schematic diagram of hepatitis D virus (HDV) infection and disease progression. (A) Hepatitis D virus infection patterns. Coinfection is that HDV and hepatitis B virus (HBV) simultaneously infect an individual or HDV infects the individual at the early stage after HBV infection. The essential diagnostic marker of this pattern is positive HBV surface antigen (HBsAg) and high titer of anti-hepatitis B core (HBc) immunoglobulin (Ig)M antibodies. Superinfection is that HDV infects the individual who has already established HBV infection or is a chronic HBV carrier (HBsAg positive). Anti-HBc IgM antibodies are absent in this pattern. HDV > HBV, HDV replication dominant; HDV ~ HBV, HDV and HBV codominant; HDV < HBV, HBV replication dominant. (B) Clinical progression of HDV infection. Pooled probability was shown with 95% confidence interval unless specifically indicated. Time was shown as mean (range). The total percentage exceed 100% after data synthesis.

Regarding the estimation at national level, potential bias may be present in particular countries. Because of the limited sample number, there could be overestimation in the general population from these countries, such as Colombia (1703), Nigeria (1419), Pakistan (2076), Tunisia (750), and Uganda (358), compared with the estimations among HBsAg-positive carriers (Supplementary Table 1). Moreover, the limited origin of the samples among general population may also lead to overestimation in country like Brazil (Supplementary Data). Finally, the national estimations of HDV prevalence are balanced by the estimations among general population and HBsAg-positive carriers (Supplementary Data). Our results show that China, India, and Nigeria are the top 3 countries with respect to the number of HDV-infected individuals.

The importance of highlighting the high global prevalence of HDV infection is illustrated by the neglect in screening for HDV. Indeed, there is a paucity of studies about HDV prevalence in low-income and lower-middle-income countries. Such countries account for 50% of the world population, 60% of HBV burden, but 70.34%–75.34% of HDV burden [23]. Also in view of the observed propensity for serious liver disease in HDV-superinfected individuals observed in the present study, a global health need emerges for effective prevention especially aimed at these countries.

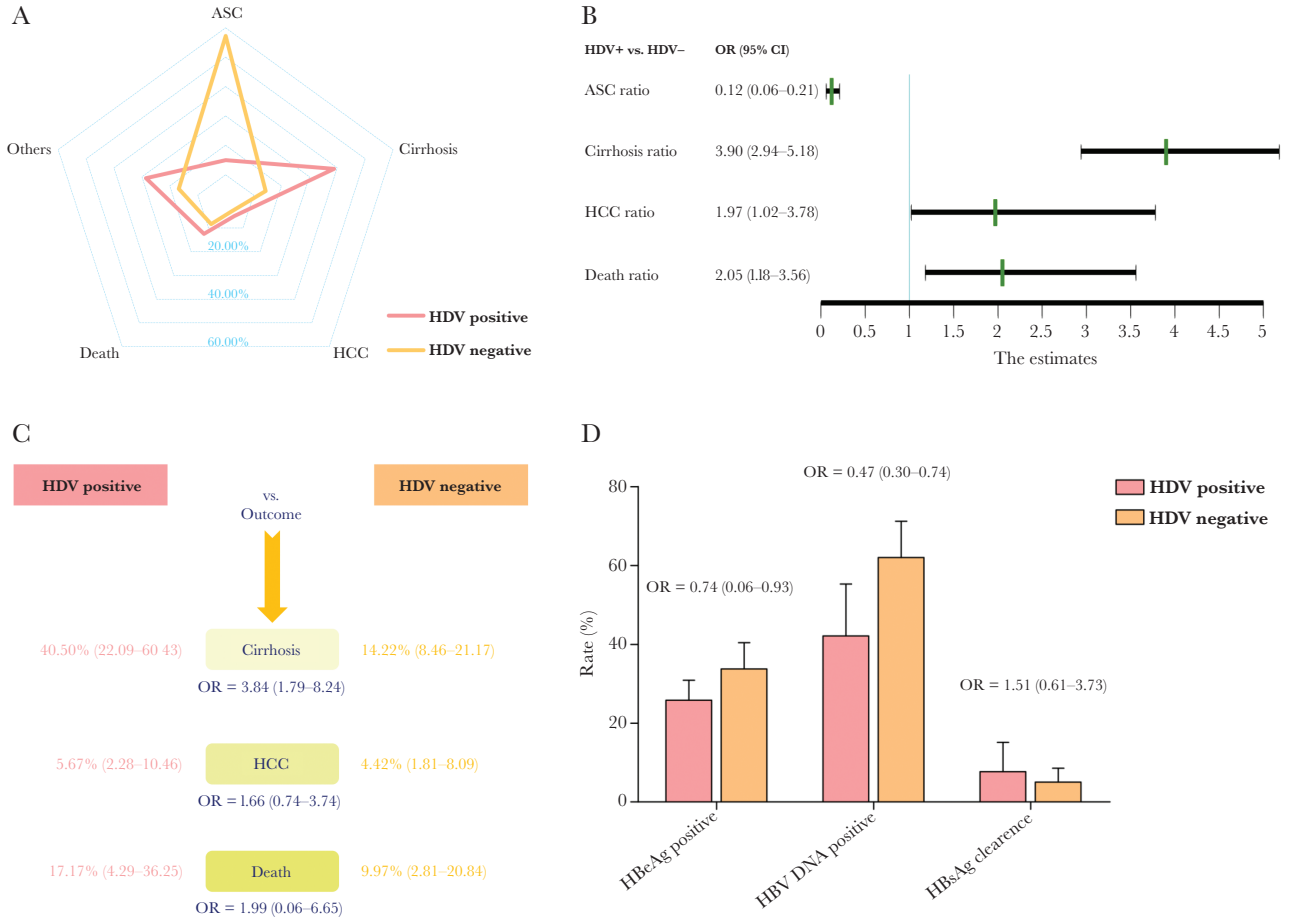

Figure 5. Clinical outcome comparison between hepatitis D virus (HDV)-positive and HDV-negative patients. (A) Radar chart represents the composition of liver diseases among patients. (B) Forest plot of liver disease ratio among HDV-positive patients compared with HDV-negative patients. Data are pooled from a random-effects model. (C) The development of liver diseases among HDV-positive patients compared with HDV-negative patients. (D) The suppressive effect of HDV on hepatitis B virus (HBV) replication. Hepatitis B e antigen (HBeAg) and HBV deoxyribonucleic acid (DNA) are the indicators of HBV replication. ASC, asymptomatic carrier; CI, confidence interval; HCC, hepatocellular carcinoma; OR, odds ratio.

The implementation of a global HBV vaccination program may be a cost-effective approach in this respect. Previous studies and mathematical modeling suggest that an HBV vaccination coverage above 80% is sufficient for eventual eradication of both HBV and HDV infection [3, 24]. However, early childhood HBV vaccination coverage is still low (globally only 39% in 2015), especially in African and Southeast Asia [7], and it is estimated that more than 100 million people are annually de novo infected with HBV [25, 26]. Thus, more efforts in this respect are necessary.

An important finding of our study is the dichotomy in outcome between simultaneous coinfection with HBV/HDV and a later HDV superinfection. The majority of the HBV-HDV-coinfected patients spontaneously recover, whereas a substantial proportion of superinfected patients progress to chronic disease (Supplementary Data). The implication of this result is that treatment of HBV carriers is important, to prevent later chronic HDV infection. It is unfortunate that only 10% of HBV infections are diagnosed, and only 5% receive antiviral therapy, also because of the relatively high costs associated with HBV-directed antiviral therapy [23]. We find clinical evidence that HDV and HBV actively interact with each other, resulting in 3 replicative patterns, but most patients are HDV dominant (Supplementary Data). Mechanistically, this may be partially explained by a previous experimental study that HDV replication can suppress HBV replication by interfering with HBV messenger RNA synthesis and stability [11]. Furthermore, HDV infection can induce the production of both type I and type III interferons (IFN-β and IFN-λ), both of which inhibit HBV infection, whereas HDV is resistant to self-induced innate immune responses [27, 28].

Hepatitis D virus infection is associated with progression to severe liver disease, but, intriguingly, different liver diseases associated with HBV infection show a distinct relationship to HDV status. Among acute HBV patients—although the vast majority of the data were collected from the studies published before year 2000—the rate of HDV infection is much higher in FH (26.75%) compared with that in less symptomatic cases of

AH (11.70%) (Figure 3A) [29–31]. Among chronic HBV patients, HDV infection is also much more often observed in more severe symptomatic than less symptomatic cases, and this is further supported by the pooled OR (Figure 3). Together, HDV prevalence is particularly high in symptomatic HBV patients, especially patients with FH and cirrhosis, than less symptomatic or asymptomatic cases. More than half (52%) of the patients suffering from acute HDV infection develop chronicity, and the majority (76%) of these chronically infected patients progress to CH. In turn, half (54%) of the CH patients progress to cirrhosis within 3 to 5 years [10, 32–34], and thus disease progression is much more aggressive in patients with HDV infection compared with those suffering from HCV or HBV infection alone [35, 36]. These results may correspond to previous findings that HDV replication synergistically activates HBV X (HBx)-mediated transforming growth factor-β and c-Jun signaling cascades, both linked to fibrosis (Supplementary Data) [37, 38]. Counterintuitively, however, protective effects have been associated with an HDV-positive status on the outcome of liver transplantation for cirrhosis or HCC [39].

There are several limitations of our study. First, we failed to collect sufficient data regarding antiviral treatment. Second, we mainly included publications in English, but we also included the literatures published in Chinese language. This improves results because China bears a large part of the global HBV burden, but available English publications are mainly from Taiwan, and the prevalence of HDV may be different from the mainland and Taiwan. Third, HDV is currently classified into 8 genotypes [40], and different genotypes maybe lead to distinct clinical outcomes, but we did not include this aspect in the analysis because available data are limited. Fourth, we performed the estimates both among the general population and HBsAg-positive population. Interpretation of results relating to the latter is directly influenced by the HBV burden reference, but this itself is uncertain with estimates ranging from 250 million to 500 million [41]. We used the most frequently cited reference burden of 367 million and estimated the infection of HDV as 48 million, but HDV estimates range from 32 million to 61 million when referring to different HBV estimates (Supplementary Figure 12). Finally, the interpretation of our estimates may be affected by the study quality, data source, and study population included, resulting in variations that may increase the heterogeneity in our analysis (Supplementary Data). Thus, our current estimates will likely evolve as more high-quality epidemiological data become available.

CONCLUSIONS

In summary, we now provide a high-confidence estimate of global HDV prevalence, although our results also show the need for high-quality epidemiological surveys for HDV in low-income and lower-middle-income countries. Our results quantify the effect of HDV infection in the context of HBV infection and highlight the risk of HDV superinfection in this context. Overall, our study shows that the global HDV burden is substantial, whereas its association to rapid progression to severe liver disease calls for more efforts with respect to screening, prevention, and treatment.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Lempp FA, Ni Y, Urban S. Hepatitis delta virus: insights into a peculiar pathogen and novel treatment options. Nat Rev Gastroenterol Hepatol **2016**; 13:580–9.
2. Stockdale AJ, Chaponda M, Beloukas A, et al. Prevalence of hepatitis D virus infection in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health **2017**; 5:e992–1003.
3. Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. Gut **2019**; 68:512–21.
4. Shen DT, Ji DZ, Chen HY, Goyal H, Pan S, Xu HG. Hepatitis D: not a rare disease anymore: global update for 2017–2018. Gut **2019**:pii: gutjnl-2019-318691.
5. Wedemeyer H, Negro F. Devil hepatitis D: an orphan disease or largely underdiagnosed? Gut **2019**; 68:381–2.
6. Stockdale AJ, Kreuels B, Henrion MR, Giorgi E, Kyomuhangi I, Geretti AM. Hepatitis D prevalence: problems with extrapolation to global population estimates. Gut **2019**:pii: gutjnl-2018-317874.
7. Soriano V, Young B, Reau N. Report from the International Conference on Viral Hepatitis - 2017. AIDS Rev **2018**; 20:58–70.

8. Colombo M, Cambieri R, Rumi MG, Ronchi G, Del Ninno E, De Franchis R. Long-term delta superinfection in hepatitis B surface antigen carriers and its relationship to the course of chronic hepatitis. Gastroenterology **1983**; 85:235–9.
9. Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). Gut **2000**; 46:420–6.
10. Romeo R, Del Ninno E, Rumi M, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology **2009**; 136:1629–38.
11. Sureau C, Negro F. The hepatitis delta virus: replication and pathogenesis. J Hepatol **2016**; 64:102–16.
12. Wedemeyer H, Yurdaydin C, Hardtke S, et al. Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial. Lancet Infect Dis **2019**; 19:275–86.
13. Yurdaydin C, Abbas Z, Buti M, et al. Treating chronic hepatitis delta: the need for surrogate markers of treatment efficacy. J Hepatol **2019**; 70:1008–15.
14. Negro F. Hepatitis D virus coinfection and superinfection. Cold Spring Harb Perspect Med **2014**; 4:a021550.
15. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet **2011**; 378:571–83.
16. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis **2016**; 16:797–808.
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ **2009**; 339:b2535.
18. Stevens GA, Alkema L, Black RE, et al.; The GATHER Working Group. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. Lancet **2016**; 388:e19–23.
19. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat **1950**; 21:607–11.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials **1986**; 7:177–88.
21. Perez-Vargas J, Amirache F, Boson B, et al. Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo. Nat Commun **2019**; 10:2098.
22. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health **2017**; 5:e1192–207.
23. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol **2018**; 3:383–403.
24. Goyal A, Murray JM. The impact of vaccination and antiviral therapy on hepatitis B and hepatitis D epidemiology. PLoS One **2014**; 9:e110143.
25. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet **2017**; 390:1211–59.
26. GBD 2018 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet **2018**; 392:1789–858.
27. Suslov A, Heim MH, Wieland S. New insights into HDV-induced innate immunity: MDA5 senses HDV replication. J Hepatol **2018**; 69:5–7.
28. Zhang Z, Filzmayer C, Ni Y, et al. Hepatitis D virus replication is sensed by MDA5 and induces IFN-β/λ responses in hepatocytes. J Hepatol **2018**; 69:25–35.
29. Amoroso P, Giorgio A, Fico P, et al. Delta infection in the Naples area. Epidemiologic and clinical significance. J Hepatol **1986**; 2:11–8.
30. Bensabath G, Hadler SC, Soares MC, et al. Hepatitis delta virus infection and Labrea hepatitis. Prevalence and role in fulminant hepatitis in the Amazon Basin. JAMA **1987**; 258:479–83.
31. Anand AC, Gandhi BM, Acharya SK, Irshad M, Joshi YK, Tandon BN. Hepatitis δ virus infection in India. J Gastroenterol Hepatol **1988**; 3:425–9.
32. Govindarajan S, De Cock KM, Redeker AG. Natural course of delta superinfection in chronic hepatitis B virus-infected patients: histopathologic study with multiple liver biopsies. Hepatology **1986**; 6:640–4.
33. Calle Serrano B, Großhennig A, Homs M, et al. Development and evaluation of a baseline-event-anticipation score for hepatitis delta. J Viral Hepat **2014**; 21:e154–63.
34. Wranke A, Serrano BC, Heidrich B, et al. Antiviral treatment and liver-related complications in hepatitis delta. Hepatology **2017**; 65:414–25.
35. Arzumanyan A, Reis HM, Feitelson MA. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. Nat Rev Cancer **2013**; 13:123–35.
36. Shirvani-Dastgerdi E, Schwartz RE, Ploss A. Hepatocarcinogenesis associated with hepatitis B, delta and C viruses. Curr Opin Virol **2016**; 20:1–10.
37. Roberts AB, Thompson NL, Heine U, Flanders C, Sporn MB. Transforming growth factor-beta: possible roles in carcinogenesis. Br J Cancer **1988**; 57:594–600.

38. Choi SH, Jeong SH, Hwang SB. Large hepatitis delta antigen modulates transforming growth factor-beta signaling cascades: implication of hepatitis delta virus-induced liver fibrosis. Gastroenterology **2007**; 132:343–57.
39. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med **1993**; 329:1842–7.
40. Miao Z, Zhang S, Ma Z, et al. Recombinant identification, molecular classification and proposed reference genomes for hepatitis delta virus. J Viral Hepat **2019**; 26:183–90.
41. Basnayake SK, Easterbrook PJ. Wide variation in estimates of global prevalence and burden of chronic hepatitis B and C infection cited in published literature. J Viral Hepat **2016**; 23:545–59.