Editorial

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The burden of hepatitis D – defogging the epidemiological horizon

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In 1977 Mario Rizzetto and colleagues described a new antigen, termed delta, in the liver of hepatitis B patients with liver damage.[1] Three years later, with John Gerin, he published a study showing that a small RNA was associated with the delta antigen in infected chimpanzees.[2] Subsequently, it became evident that infection with the hepatitis D virus (HDV) causes the most severe form of viral hepatitis. Numerous studies published during the 1980s and 1990s showed more severe courses of acute infections and higher prevalences of advanced cirrhosis in patients coinfected with HBV and HDV.[3] The interest in hepatitis D was limited thereafter as HDV coinfections seemed to decline with the introduction of vaccines against HBV and treatment options were limited with no direct-acting antivirals against HDV on the horizon – in contrast to hepatitis B and C. Only interferon alpha had some efficacy against HDV, but cure rates were low and late relapses were reported several years after initially successful interferon therapies.[4] Thus, the clinical benefit of interferon treatment has been questioned and the clinical consequence of diagnosing hepatitis D seemed to be minor. In addition, the epidemiology of HDV infection worldwide was obscure. While in distinct regions such as Mongolia, Pakistan or the Western Amazonian area far more than 15–20% of HBsAg carriers showed antibodies against HDV, screening for anti-HDV seemed to be rather useless in some European countries and the United States, with prevalence rates of less than 1% among HBV-infected individuals. Both, the FDA and EMA granted hepatitis D an orphan disease status, but a reasonable estimate on the overall disease burden caused by HDV infection was lacking.

However, there has been a remarkable re-emerging interest in hepatitis delta during recent years. Several pivotal new insights into HDV virology, immune control of HDV infection and defining clinical benefits of interferon therapy were published during the last 18 months. For example, it has been suggested that HDV may be transmitted with envelopes other than HBsAg including HCV envelope proteins.[5] The importance of HDV-specific CD8+T cells and distinct innate immune cell populations such as mucosa-associated invariant T cells has been highlighted by other groups.[6–8] For clinical practice, important studies became available defining distinct subgroups with better responses to peginterferon alfa therapy[9] and highlighting the clinical benefit of HDV RNA suppression.[10] Moreover, the distinct course of liver disease and response to interferon treatment of HDV genotype 5 infection – which is highly prevalent in sub-Saharan Africa – became evident in 2 reports recently published in the *Journal of Hepatology*.[11,12] Finally, new drugs against HDV are currently being explored in phase II and III clinical trials which led to a controversial discussion on treatment endpoints.[13,14] On May 28 2020, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorization for bulevirtide, the most advanced new compound to treat hepatitis D. Thus, new drugs for this most severe form of viral hepatitis are no longer on the horizon, the door is almost open for many patients.

In light of these exciting new developments, it is even more important to have a reliable estimate on the global prevalence of HDV infection and the associated clinical disease burden. Two systematic reviews on this issue were recently published.[15,16] Both studies screened a large number of studies and came up with surprisingly high numbers of individuals presumably being infected with HDV. The first study by Chen and colleagues suggested that up to 70 million people worldwide may be infected with HDV[15] while the other paper proposed a pooled prevalence of HDV of about 0.8% among the general population and 13% among HBV carriers, corresponding to 48–60 million infections globally.[16] These studies led to a controversial discussion with several letters to the editor highlighting potential limitations. Can it be true that almost as many people are infected with HDV as with HCV? Did we really underestimate the global frequency of hepatitis D in a such dramatic way for decades? The problem with systematic reviews is that these studies can be only as good as the selected input studies are. And with HDV infection there are several pitfalls to be considered, including lack of population-based studies, a major referral bias in experienced treatment centers, non-standardized HDV RNA assays with poor sensitivities and unclear effects of treatment interventions for both HDV but also for the underlying HBV infection. Still, both systematic reviews highlighted that HDV infection is a particular problem in patients with liver cirrhosis and among distinct risk groups such as people who inject drugs and HIV-coinfected individuals.

The HDV field was struggling with this discussion for some months but fortunately a very well performed additional systematic review and meta-analysis published in this issue of the *Journal of Hepatology* throws a little more light on the matter.[17]

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Alexander Stockdale and the group of Anna Maria Geretti went through the published literature again. They considered many issues that were raised regarding the previous systematic reviews and came up with an estimate of 12 million people worldwide having experienced HDV infection. This number sounds much more reasonable and would be in line with previous rough estimates. The authors differentiated between the general HBsAg-positive cohort and patients attending hepatology clinics which, not unexpectedly, had a 4-fold higher risk of testing anti-HDV positive. Higher frequencies of HDV infection were determined for injecting drug users, commercial sex workers, men who have sex with men, haemodialysis recipients, and patients with HCV and HIV coinfection. The authors also provide very nice maps with distinct HDV genotypes and regional hotspots which not only included Mongolia but also countries like Moldova and some Western African nations. The enormous heterogeneity of HDV seroprevalence must be considered when screening programs are implemented. Thus, there will be no "one strategy fits all" approach to target HDV infection in different countries. Importantly, heterogeneity was observed even within closely related geographic areas, likely highlighting the importance of distinct local risk factors in spreading HDV. Another interesting point is that the population attributable fraction of HDV to cirrhosis and hepatocellular carcinoma (HCC) among HBsAg-positive people was calculated. By applying random-effects models the authors suggest that HDV causes 18% of cirrhosis and 20% of HCC associated with hepatitis B.

Even though the HDV fog thins out a bit with the study by Stockdale *et al.*, there are still major epidemiological clouds, raising uncertainties on the true disease burden caused by HDV worldwide. The authors were not able to identify reliable data for large countries like India, Russia, Mexico and several African countries. Moreover, temporal trends could not be considered as only very few studies provided seroprevalence data over time. Will HDV still be a problem in the 2020s or do the high numbers simply reflect old studies which are no longer relevant? Earlier studies suggested that HDV may disappear from some populations with the introduction of HBV vaccination and anticipated even complete control of HDV infection,[18] but global migration prevented the achievement of this goal. In most European countries, the vast majority of patients with hepatitis D were born in other regions and the extent of migration has not been considered in most studies. Finally, prevalence estimates were based mainly on detection of antibodies against HDV. However, 20–50% of anti-HDV positive patients may have undetectable HDV RNA which could either indicate resolved HDV infection or very low HDV viremia, which is usually associated with a benign course of liver disease.[10] Stockdale *et al.* tried to address this issue and found that HDV RNA detection was lower in general populations relative to hepatology clinic populations. Still, reliable, sensitive and standardized HDV RNA assays became available only recently and future studies need to follow this important point.

All previous systematic reviews highlighted that HDV infection is associated with a severe course of liver disease. Patients with HBV-related liver cirrhosis have a particularly high prevalence of anti-HDV. However, there had been some debate as to what extent HDV also increases the risk of HCC beyond more frequent and earlier progression to liver cirrhosis. The group of Franco Negro from Geneva addressed this issue and performed another systematic review and meta-analysis.[19] The authors could identify an increased HCC risk for anti-HDV-positive patients with a pooled odds ratio of 1.28 compared to HBV monoinfection. Several additional interesting findings of the study should be noted. First, the increased risk for HCC was evident only in recent studies published since 2010. If this is a true finding or can be explained by limitations and heterogeneities of earlier studies remains an open issue. Second, the association between HDV infection and HCC could be confirmed only in studies published from Asia but not elsewhere. Whether host, environmental or viral factors can explain this finding is unclear. Few studies are available where HBV and HDV genotypes where determined but HDV genotypes have been associated with distinct outcomes. However, the role of HDV genotypes on the risk of HCC has not been investigated yet. Third, the association with HCC was stronger in the absence of heterogeneity and highest in patients with HIV coinfection (OR 7.13). The increased HCC risk in HIV-infected individuals may indicate a synergistic role of HIV, HBV and HDV in the development of HCC or a defective immune response in HIV-positive patients. However, the observation may also demask a bias as most HIV patients received antiviral therapy including drugs with potent activity against HBV. Thus, the underlying HBV infection was controlled in HIV-positive patients which may not always have been the case in HIV-negative cohorts.

In conclusion, the systematic reviews and meta-analyses published in this issue of the *Journal of Hepatology* convincingly address key questions on the epidemiology and natural history of HDV infection that have been ongoing for several decades. Even though the seroprevalence of HDV may be not as high as recently suggested, hepatitis D is without any doubt a severe liver disease. The increased risk of developing HCC should not be neglected.

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Conflict of interest

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Supplementary data

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