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Hepatitis B virus/hepatitis D virus epidemiology: Changes over time and possible future influence of the SARS-CoV-2 pandemic

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Abstract

Hepatitis D virus (HDV) is a defective liver-tropic virus that needs the helper function of hepatitis B virus (HBV) to infect humans and replicate. HDV is transmitted sexually or by a parenteral route, in co-infection with HBV or by super-infection in HBV chronic carriers. HDV infection causes acute hepatitis that may progress to a fulminant form (7%-14% by super-infection and 2%-3% by HBV/HDV co-infection) or to chronic hepatitis (90% by HDV super-infection and 2%-5% by HBV/HDV co-infection), frequently and rapidly progressing to cirrhosis or hepatocellular carcinoma (HCC). Peg-interferon alfa the only recommended therapy, clears HDV in only 10%-20% of cases and, consequently, new treatment strategies are being explored. HDV endemicity progressively decreased over the 50 years from the identification of the virus, due to improved population lifestyles and economic levels, to the use of HBV nucleos(t)ide analogues to suppress HBV replication and to the application of universal HBV vaccination programs. Further changes are expected during the severe acute respiratory syndrome coronavirus-2 pandemic, unfortunately towards increased endemicity due to the focus of healthcare towards coronavirus disease 2019 and the consequently lower possibility of screening and access to treatments, lower care for patients with severe liver diseases and a reduced impulse to the HBV vaccination policy.

Key Words: Hepatitis B virus/hepatitis delta virus; SARS-CoV-2; COVID-19; Hepatitis delta virus infection; Hepatitis D; Hepatitis delta virus epidemiology

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Core Tip: There has been a tendency to a reduction in hepatitis D virus (HDV) endemicity in most countries in recent decades, mostly due to an improvement in population lifestyles and economic levels, to an extensive use of hepatitis B virus (HBV) nucleos(t)ide analogues to suppress HBV replication and to the application of universal HBV vaccination programs. However, an increase in HDV endemicity is expected during the severe acute respiratory syndrome coronavirus-2 pandemic since healthcare is mostly diverted towards coronavirus disease 2019, with a reduced attention to liver disease, screening, access to treatment, care for patients with severe liver disease and the HBV vaccination policy.

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INTRODUCTION

A new antigenic reactivity was identified in hepatocytic nuclei by immunofluorescence technique on paraffinized liver sections of hepatitis B surface antigen (HBsAg) positive patients by Rizzetto *et al*[1] in the early 1970s in Turin, Italy, and called Delta. The Authors understood that this new reactivity was different from that expressed by the hepatitis B virus (HBV) core antigen (HBcAg) and hypothesized that it could be part of a new virus; with a careful interlacing of antisera on cryostat-cut biopsy sections, Delta reactivity was identified as a new antigen localized in the nucleus of the hepatocytes and yielding a fluorescent staining similar but not equal to HBcAg[1]. In Bethesda, United States, Rizzetto *et al*[2] developed a radioimmunoassay for the delta antigen-antibody system in serum and performed transmission studies in chimpanzees demonstrating the existence of a new a liver tropic virus [hepatitis D virus (HDV)][2]. Further studies mentioned below defined HDV as a defective virus that needs a helper function of HBV to infect humans and replicate.

This virus consists of the HDV antigen (HDAg, small and large antigen) and a circular single-strand RNA (HDV-RNA). It uses a human RNA polymerase II and a rolling-cycle mechanism like that of plant viroid to replicate. Being a defective virus, HDV needs the S-HBsAg, M-HBsAg and L-HBsAg proteins of HBV to produce its envelope and propagate. Coated with the HBV envelope, HDV uses the pre-S1 domain of L-HBsAg to bind NCTP (sodium taurocholate co-transporting polypeptide) and enter differentiated hepatocytes[3].

Eight genotypes of HDV have been identified at present, distributed differently in the world: Type 1 is present worldwide and prevalent in western Europe and North America, type 2 mainly in the Far East, Egypt and Iran, type 3 in the Amazon Basin, type 4 in Japan and Taiwan, types 5 to 8 in Africa but now spreading also in Western regions due to immigration flows[4]. In Western countries, HDV infection at present occurs mostly in elderly adults with chronic HBV infection or in young immigrants from endemic areas[5].

HDV is parenterally and sexually transmitted in co-infection with HBV or by super-infection in HBV chronic carriers. Both types of transmission cause acute hepatitis, self-limited with a clearance of both viruses in 95% of subjects simultaneously infected, while in the case of HDV super-infection in HBV chronic carriers the disease progresses to chronicity in nearly 90% of cases[6].

Acute hepatitis delta is clinically indistinguishable from other types of acute viral hepatitis and is usually mistaken for HBV acute hepatitis if the specific diagnostic tests [search for HDV RNA and immunoglobulin M (IgM) to HDV-Ag] are not performed. HDV super-infection in HBsAg chronic carriers causes massive acute exacerbation with a fulminant clinical course in 7%-14% of patients, two thirds of whom die of liver failure. The outcome is less severe in subjects acquiring HBV and HDV in co-infection. They may develop fulminant hepatitis in 2%-3% of cases and progression to chronicity in 1%-5%.

Chronic HDV infection is the most severe and rapidly progressive form of chronic hepatitis, leading to cirrhosis in 70% of patients within 5-10 years[7]. Furthermore, as compared with HBV mono-infection, HBV/HDV co-infection increases the risk up to three times of cirrhotic patients developing hepatocellular carcinoma[4,8,9].

Despite the importance of HDV infection, no treatment has been so far approved by the Food and Drug Administration. However, treatment with pegylated interferon alfa (Peg-IFN) is recommended by the major scientific societies for the study of the liver because it may clear HDV infection in 10%-20% of patients and may reduce liver fibrosis and the risk of hepatic decompensation and mortality. Because of its limited efficacy, its significant side effects, and the prolonged time of administration (1-2 years) Peg-IFN was used also in combination with ribavirin and/or HBV nucleoside analogues, but no improvement was obtained. Therefore, new treatment strategies are now under study with the use of peginterferon lambda, bulevirtide (entry inhibitor that targets NCTP), nucleic acid polymers (HBsAg secretion inhibitors), and lonafarnib (virus assembly inhibitor)[10].

In end-stage liver disease, HCC and fulminant hepatitis, liver transplant is the only therapeutic option. Comparing HBV mono-infected patients with the HBV/HDV co-infected, the latter show a better outcome if reinfection is prevented by the continuous administration nucleos(t)ide analogues and of hepatitis B immune globulins[11,12].

The epidemiology of HDV infection has changed a lot in nearly every country since its first identification 55 years ago[13-20]. This is related to changes in population lifestyle habits, variations in economic levels, extension of the use of HBV nucleos(t)ide analogues to treat HBV chronic carriers and, most importantly, to the effectiveness of universal vaccination campaigns against HBV infection in most countries. Further changes are expected in this era of the coronavirus disease 2019 (COVID-19) pandemic, which might involve, among others, a lower possibility of screening and access to treatment and a reduced effectiveness of the vaccination policy against HBV infection and of the management of patients with severe chronic hepatitis.

These epidemiological changes have great impact on the health quality of life of human beings and are the subject of this review.

HBV/HDV EPIDEMIOLOGY BEFORE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 PANDEMIC

The epidemiology of HDV infection has been mainly studied by assessing the prevalence of subjects with HDV infection among HBV chronic carriers because acute HDV hepatitis, either acquired in co-infection with HBV or by HDV super-infection in HBV chronic carriers, easily identifiable during outbreaks, often remains undiagnosed when it occurs in single subjects. In fact, the clinical presentation of HBV and HDV acute hepatitis is similar, and only specific tests (anti-HDV IgM and quantitative HDV RNA), infrequently performed in general practice, allow the differentiation between these etiologies. These tests, however, do not provide accurate results in epidemiological studies on chronic HDV infection, because their titers, elevated in acute phase of the infection, decrease markedly in the chronic phase. In addition, HDV RNA is typically determined home made only in some specialized laboratories and its quantification is not standardized. For these reasons, commercial standardized kits to detect serum anti-HD IgG have been used in almost all epidemiological studies on HDV chronic hepatitis.

HDV has spread all over the world, with a global disease burden around 62-72 million HBV/HDV co-infected subjects[13] and with an HDV seroprevalence among HBV carriers widely varying in different geographic areas[14,15].

EPIDEMIOLOGICAL INFORMATION OF HDV/HBV ACUTE HEPATITIS

Outbreaks of fulminant hepatitis have occurred in the Amazon Basin. in French Guyana, in Yucpa Indians of Venezuela from 1934 to 1955, and in the Central African Republic in 1997 as documented by the presence of Delta antigen in hepatocytic nuclei of autoptic liver specimens; small but similar outbreaks have occurred from 1955 to 1985 in northern Colombia and designated as hepatitis of Santa Marta (de Sierra Nevada)[16-24].

In patients with fulminant hepatitis, morphologic studies showed marked liver steatosis with characteristic "morular hepatocytes", cells with small droplets of fat and

central pycnotic nuclei. Worthy of note, some similarities in the clinical presentation of fulminant hepatitis Delta with that of yellow fever has led to the hypothesis that some of the outbreaks occurring in the past in the Amazon basin and attributed to yellow fever, may have been due to HBV/HDV co-infection[25].

In the mid-1980s, several cases of severe acute liver failure were described in Bangui, in the Central African Republic, associated with an HDV outbreak. At least 124 cases of fulminant hepatitis were observed among 154 jaundiced patients, 88% of whom died[23]. The disease was associated with specific pathological lesions (spongicyte-associated hepatitis) involving lympho-plasmocytoid infiltrates, eosinophilic necrosis and massive macro- or micro-vacuolar steatosis[23] resembling the "morula-like" cells previously described in South American HDV outbreaks[24-26]. In Italy, two collections of sera from patients with acute hepatitis B collected in Naples in 1972 and 1974 were retrospectively evaluated and for the first time the IgM antibody to HDV (anti-HDV IgM) was detected in over 90% of cases. Most anti-HDV IgM-positive patients were also anti-HBc IgM-positive, suggesting an outbreak of HBV/HDV coinfection in Naples in those years[27].

THE INCIDENCE OF ACUTE HDV HEPATITIS IN HOSPITALIZED PATIENTS

Italy was estimated by a system of hospital surveillance in the period 1987-2010[28]. The incidence of primary HDV infection in the general population progressively decreased from 3.2/100000 inhabitants in 1987 to 0.2/100000 in 2010. The decrease in the incidence of HDV acute hepatitis and the parallel similar trend observed for HBV acute hepatitis in the same study were most likely an effect of the mass vaccination, which in 2010 had covered all Italian citizens aged from 0 to 31 years. In this period, however, three peaks of HDV epidemic were registered, in 1990 and 1993 in the age groups 14-25 and 25 or more and in 1997 only in the 15-24 age group, all due to the spread of HDV infection among intravenous drug users[29]. Apart from intravenous drug use (IVDU), other putative risk factors associated with the development of HDV acute hepatitis were family contacts with a chronic HBsAg carrier, promiscuous sexual activity, and cosmetic treatments with percutaneous exposure in 1992-1994, whereas those identified from 2008 to 2010 were dental therapy, cosmetic treatment with percutaneous exposure and promiscuous sexual activity.

Between December 2004 and January 2005, out of 110 patients with acute hepatitis in 8 city hospitals of Mongolia, 1.8% had HDV etiology by co-infection with HBV and 27.3% by HDV super-infection[30]. Again, in Mongolia from January 2012 to December 2014, 546 consecutive patients with acute hepatitis were observed, of whom 6% had HDV etiology by co-infection with HBV and 10.8% by HDV super-infection[31].

In Spain, 398 patients with HDV infection were observed from 1983 to 2008, 182 with acute hepatitis, of whom 84% by co-infection and 16% by super-infection, and 216 had chronic HDV infection[28]. The number of patients with acute hepatitis Delta strongly decreased across this study, while the number of those with chronic Delta infection showed a small decline. In addition, patients observed in the 1983-1995 period compared to those examined from 1996-2008 were significantly younger, born in Spain, mainly intravenous drug users, and more frequently had acute hepatitis. In this study, the percentage of immigrants (prevalently from Africa and Eastern Europe) increased from 1% of the first period to 28% in the second.

EPIDEMIOLOGICAL INFORMATION OF HDV/HBV CHRONIC INFECTION

In 2018, the World Health Organization considered these geographic areas HBV/HDV endemic regions: Central and West Africa, Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Chinese Taipei, the Pacific Islands (Kiribati and Nauru), the Middle East and Eastern Europe, Eastern Mediterranean regions, Turkey, the Amazonian Basin, and Greenland[32].

To offer the readers an overview of the worldwide variability of the prevalence of anti-HDV among HBV chronic carriers, we report data recorded at different times in some countries: 10.6%-37.5% in India (1985-2005)[33,34], 3.5%-13.1% in China (1987-1993)[35,36], 17.7% in Tunisia (1987-1994)[37], 8.3%-23.0% in Italy (1987 and 1997)[13, 38], 21.8%-65.5% in Thailand (1988)[39], 48%-5.7% in Iran (1991-2005)[40], 8%-10.9% in Germany (1992-2006)[41], 16.6%-58.6% in Pakistan (1994 to 2001)[42], 8.6% in Saudi Arabia (1996-1997)[43], 4.4%-15.3% in Taiwan (1997-2012)[13,44], 56.5% in Mongolia

(2004)[13,44], 41.9% in Brazil (2005-2006)[45], 7%–45.5% in Turkey (2006-2009)[46], and 9.9% in Egypt (2013)[13,44] (Table 1).

A lower prevalence was reported for non-endemic areas, ranging from 6% in Japan (1991)[47], 2% in Jordan (1978-1985)[48], 4.1%–4.8% in Australia (1997-2016)[49,50], 4.2% in Greece (1997)[51], and 2.6%–8.5% in England (2000-2006)[13,44]. Notably, in the United States, the prevalence of HDV among HBV chronic carriers has been reported to range from 2% in native citizens to 50% in some foreign populations[52-54] (Table 1).

There was a gradual reduction in the percentage of HBsAg-positive subjects and a parallel decrease in the prevalence of cases with HBV/HDV chronic infection in several countries in the last 3 decades, primarily due to the application of universal vaccination programs. As an example, the prevalence of HDV infection in HBsAg-positive chronic carriers was very high in some Mediterranean countries (Greece, southern Spain, southern Italy) 5 decades ago[55], a prevalence that gradually declined, like in Italy, where the prevalence of HDV infection in HBV chronic carriers decreased from 24% in 1990 to 8.5% in 2006[38].

About 35 million people are infected with human immunodeficiency virus (HIV) in the world and among these the percentage of those with HBV/HDV co-infection varies from 1.4% to 19.7% in relation to the epidemiological diversity of these infections in individual nations[56-60]. Considering the high number of subjects with triple HBV, HDV and HIV infections, it is highly likely that some of them have contracted severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, asymptomatic or symptomatic, although there are no data in the literature to the best of our knowledge.

REASONS FOR REDUCED PREVALENCE RATE OF HDV/HBV CHRONIC INFECTION

The impact of risk factors for acquiring HBV infection has changed over the past five decades around the world. Vertical transmission is no longer a risk factor for the transmission of HBV infection, due to the introduction of mass passive/active immunization of newborn babies. Furthermore, the impact of risk factors for HBV transmission through household contacts with HBsAg infected subjects has dropped in Western countries with the application of universal HBV vaccination and the reduction in family size. The epidemiological impact of other risk factors, such as the use of improperly sterilized medical and surgical instruments, transfusion of contaminated blood and blood products, the use of glass syringes and for men shaving at a barber's shop have dramatically decreased worldwide. IVDU and sexual transmission of HBV infection plays a major role in HBV transmission nowadays due to the exchange between drug addicts of syringes or other objects used for the preparation of drugs and to the infrequent or incorrect use of condoms in unsafe sexual activity. A marginal role is still played by cosmetic treatment with percutaneous exposure (piercing, tattooing, manicure, pedicure, and acupuncture) and dental treatment[61].

The current residual reservoir of HDV in Western countries comprises aging patients with advanced liver disease, young immigrants with chronic hepatitis Delta from areas where HDV infection remains endemic and drug users. The increase in the spread of HDV has recently been observed in some countries of Western Europe mostly regarding IV drug users and immigrants from Eastern Europe and Sub-Saharan Africa[44,62]. The recently increased HDV prevalence observed in the United Kingdom, France, and Germany reflects the increased prevalence in young immigrants from regions at high HBV/HDV prevalence. A high prevalence has been reported for immigrants from Equatorial Guinea living in Spain (20.9% among 1220 HBV chronic carriers).

Drug use remains a major risk factor, as seen by a study performed in Baltimore (United States) showing 50% HBV/HDV co-infection in IV drug users[54].

In some other geographic areas, however, the prevalence of HDV infection in HBV chronic carriers has remained high in the last two decades, such as in some eastern countries of the Mediterranean basin, the Middle East, central and northern Asia, western and central Africa, the Amazonian basin (Brazil, Peru, Venezuela, and Colombia), some Pacific islands[63] and Vietnam[64]. In a recent study in the western Brazilian Amazon region, 41.9% of HBV chronic carriers were found to be coinfecting with HDV, with a prevalence of over 60% among individuals aged 20–39 years[45], suggesting the likelihood of sexual transmission. In a 2013 study from West Africa (Mauritania), 30% of HBV chronic carriers had the anti-HDV antibody[65] and among

Table 1 Worldwide variability of anti-hepatitis D virus in hepatitis B surface antigen chronic carriers

Country	Anti-HDV in HBsAg chronic carriers, % (years of study)	Ref.
India	10.6 (1985); 37.5 (2005)	[33,34]
China	3.5 (1987); 13.1 (1993)	[35,36]
Tunisia	17.7 (1987-1994)	[37]
Italy	23.0 (1987); 8.3 (2006)	[13,38]
Thailand ¹	8.3; 11.1; 65.5 (1988)	[39]
Iran	48.0 (1991); 5.7 (2005)	[40]
Germany	8.0 (1992); 10.9 (2006)	[41]
Pakistan	16.6 (1994); 58.6 (2001)	[42]
Saudi Arabia	8.6 (1996-1997)	[43]
Taiwan	4.4 (1997); 15.3 (2012)	[13,44]
Mongolia	56.5 (2004)	[13,44]
Brazil	41.9 (2005-2006)	[45]
Turkey	7 (2006); 45.5 (2009)	[46]
Egypt	9.9 (2013)	[13,44]
Japan	6.0 (1991)	[47]
Jordan	2.0 (1978-1985)	[48]
Australia	4.1 (1997); 4.8 (2016)	[49,50]
Greece	4.2 (1997)	[51]
England	2.6 (2000); 8.5 (2006)	[13,44]
United States	2.0 (1950); 50.0 (2016)	[52-54]

¹65.5% in intravenous drug abusers, 11.1% in chronic active hepatitis, and 8.3% in cirrhosis patients.

HDV: Hepatitis D virus; HBsAg: Hepatitis B surface antigen.

these, 62.2% were HDV-RNA-positive[66-68]. A recent study from Iran showed that in Zahedan, 17% of HBV chronic carriers were anti-HDV-positive[69]. A meta-analysis showed that 14.8% of asymptomatic HBsAg-positive patients in the eastern Mediterranean region were coinfecting with HDV and that cirrhosis was common in these patients[70]. A study from Vietnam showed an anti-HDV prevalence of 10.7% in HBV chronic carriers[64], a prevalence much higher than expected based on previous reports[71]. These studies confirm the continuing high prevalence of HDV infection in the Amazonian basin, the Middle East, the eastern Mediterranean region, and western Africa, and show an unexpectedly increased prevalence in Vietnam. Instead, a low anti-HDV prevalence in HBV chronic carriers was reported from Egypt (4.7%)[72] and India (4.8%)[73,74].

The reports on the epidemiology of HDV infection are numerous, but at the same time are inadequate to have a complete overview of the spread of the Delta infection around the world[75,76].

First, HDV acute infection is infrequently recognized outside the outbreaks and the rate of chronic forms are likely to be underestimated for the unsatisfactory use of laboratory tests to identify HDV infection in HBsAg chronic carriers. In a nationwide study in the United States only 8.5% of the 25603 HBV patients investigated were ever tested for HDV. Manesis *et al*[51] reported that only one third of Greek patients with HBV chronic hepatitis have been tested for HDV infection[51]. Similarly, El Bouzidi *et al*[77] reported that only 40% of British patients with HBV chronic infection have been tested for anti-HDV[77]. In addition, most epidemiologic studies used anti-HDV to identify the seroprevalence of HDV infection, whereas HDV RNA was performed in some other studies to confirm the etiology and was used for epidemiological investigations.

Second, studies from the same country have reported a discrepant prevalence, probably due to significant geographic variations even within the same country. For

example, a meta-analysis from Turkey reported an anti-HDV seroprevalence of 4.8% in west Turkey, and 46.3% in south-east Turkey[78].

Finally, the time when the epidemiological survey was carried out is of considerable importance, due to the frequent variations over time in the lifestyle habits of the population of a geographic area and, even more, in the progress of anti-hepatitis B vaccination in the same area. As an example, HDV seroprevalence in chronic HBV carriers has largely declined in Italy over the last 50 years (from 23% in 1987, to 14% in 1992 and to 8.3% in 1997), indicating a substantial, progressive reduction in the endemicity level, due to improved socioeconomic conditions and the associated increase in the standards of hygiene, to a substantial reduction in family size, and, most importantly, to the mass vaccination campaign against HBV started in 1991[79-82]. More recent data, however, suggest that the prevalence of HDV in Italy has remained stable at nearly 8%[83].

Overall, HDV infection is still a major burden for public healthcare management in many countries. In recent times we have accumulated evidence that the prevalence of HDV has remained stable or has increased in many endemic and non-endemic geographic areas, due to an increase in migratory flows and to the persistent impact of other relevant risk factors like IVDU, intra-family spread and unsafe sexual activity, homosexual, and heterosexual[13,38,44,84,85]. Furthermore, outbreaks of HDV acute hepatitis are still occurring[80]. In this regard, it is useful to recall the important role of sex workers in the spread of HBV and HDV infections, as well as HIV and other sexually transmitted diseases. The prevalence of HBsAg among migrant sex workers in Chiangmai, Thailand, was 11.4%, but none of them showed anti-HDV antibodies [86].

Of note, most of these sex workers were migrants from Myanmar, born before the introduction of the universal HBV vaccination program in their native country. A meta-analysis on five studies, 4 from China and one from Vietnam, showed that Commercial sex workers have a greater risk to be anti-HDV positive than the external comparator population from the same geographic areas, with a pooled OR of 18.7 (95%CI: 6.70-51.17). In the same meta-analysis, a pooled OD ratio of 16.00 (95%CI: 3.94-64.92) indicates that MSM from Italy and Indonesia are at a greater risk to be anti-HDV positive than the comparator population from the same geographic areas, asymptomatic HBsAg carriers for Italy and normal subjects for Indonesia. No positive case was observed in MSM from a Burkina Faso study analyzed in the same contest [44].

SARS-COV-2 PANDEMICS: REDUCED OPPORTUNITY FOR SCREENING, MANAGEMENT, AND TREATMENT

Much of the assistance not linked to the SARS-CoV-2 pandemic has been severely compromised and/or downsized during this pandemic, a drastic reduction also affecting liver diseases. In Italy, 26% of hepatology wards have been converted to SARS-CoV-2 wards and another 33% have suffered a substantial reduction in the availability of beds. Screening and day hospital activities for liver diseases have been significantly reduced and the start of treatments for “new” HBV chronic hepatitis have been postponed in 23% of the open liver units[87]. Overall, hepatology activities, including the management of patients with compensated or decompensated liver disease, liver transplantation or HCC have been significantly reduced and/or suspended[34].

In April 2020, health centers in Burkina Faso, Gambia, and Tanzania, respectively, recorded a 71%, 83% and 95% decline in the numbers of “new” patients attending liver clinics, compared to the numbers recorded at the beginning of the same year, mainly due to the patient’s fear of accessing health services[88].

A limitation or closure of health centers offering harm reduction services (such as needle exchange and opioid replacement therapy) due to SARS-CoV-2 pandemic have been reported from South Africa, with an increased risk in overdose and transmission of blood-borne infections[89].

In other countries in Sub-Saharan Africa, essential diagnostic tests to manage chronic hepatitis, rapid tests for HBsAg, alanine aminotransferase and hematological tests, have always been available but there has been a serious shortage of nucleic acid tests to detect HBV and HDV replications; therefore, people newly identified as HBsAg carriers may have missed the opportunity to be evaluated for viral load, connected to treatments, and finally treated[89]. For Sub-Saharan African countries, there has also been a strong reduction in tenofovir supply[89], with an increased risk

of an exacerbation of liver cell necrosis, the onset of drug resistance and transmission of HBV infection.

In Japan, Singapore and the United States, the number of physical examinations for HBV chronic hepatitis decreased significantly in 2020, compared to 2019, especially for more elderly subjects[90].

Numbers from England give clear information on the influence of the SARS-CoV-2 pandemic on screening for liver diseases, 2478 tests in 2019 and 1224 in 2020[91].

COVID-19 has also led to an increase in economic and public health disparities. The pandemic has caused a global recession, driving millions of people below the poverty line, not only in countries with low economic levels[92]. In the United States, 6.2 million people have lost their health insurance since the start of the pandemic, due to job losses, leading to a greater risk of acquiring viral hepatitis as well as other infectious diseases[93].

The World Hepatitis Alliance conducted a worldwide survey to assess the impact of the SARS-CoV-2 pandemic on patients with viral hepatitis: Job loss during this pandemic resulted in a strong impact on household monetary income in low- and middle-income countries, with a frequent lack of access to drugs. Indigenous communities in some developing countries were the most affected both by traffic restrictions with the inability to reach healthcare centers and to the difficulties in earning a living and paying for a physical examination[93,94].

In high-income countries, remote assistance through telemedicine and other virtual platforms has been strongly encouraged to maintain continuity of care[95]. However, in sub-Saharan Africa, many patients and healthcare providers do not have access to telemedicine solutions[88].

There is also an increased risk of HBV vertical transmission during the SARS-CoV-2 pandemic, due to a higher frequency of home births without prophylactic measures [92]. Childhood prophylaxis against HBV infection performed at birth is estimated to have prevented 310 million new HBV infections between 1990 and 2020[96], including 14 million HBV/HDV infections[44]. Preliminary data from the Institute for Health Metrics and Evaluation indicate that global levels of vaccination coverage progressively increased from 1990 to the beginning of 2020, but during 2020 it fell to the levels of the 1990s[97]. The reduction in vaccination coverage may lead to a high increase in the incidence of HBV infection in childhood, and to an increased risk of acquiring HDV infection in subsequent years.

CONCEIVABLE DEVELOPMENTS IN HBV/HDV EPIDEMIOLOGY DUE TO THE SARS COV-2 PANDEMIC

The SARS-CoV-2 pandemic has had a negative impact on the global health system and on the development of assistance programs for other diseases. Considering that 290 million people live with chronic HBV, it is easy to calculate that the unidirectionality of healthcare towards SARS-CoV-2 has strongly damaged the programs for screening, management, and treatment of HBV and HDV associated diseases worldwide.

No epidemiological data on HBV/HDV coinfection during the SARS-CoV-2 pandemic is available at present and few data on HBV infection are reported in the literature, although HBsAg positive subjects are at high risk of acquiring SARS-CoV-2 infection. Guan *et al*[98] reported a 2.1% HBsAg positivity in 1099 SARS-CoV-2 Chinese patients[98] while Chen *et al*[99] found a 4% HBsAg prevalence in 274 SARS-CoV-2 Chinese patients[99]. Instead, the HBV prevalence was 0.1% in 5700 (8/5700) SARS-CoV-2 patients in the United States[100].

Even in the absence of data on the epidemiology of HBV/HDV co-infection during the SARS-CoV-2 pandemic, mostly due to the short period elapsed, it seems useful to make some predictions based on the sudden great variation in lifestyle worldwide, imposed by the spread of this life-threatening pandemic.

The multiplicity of factors, favoring or hindering the spread of HBV and HDV infections, mostly created by the measures put in place by the Political or Healthcare Authorities of different countries to hinder the spread of SARS-CoV-2, makes it difficult to predict the epidemiological variations of these two infections in the coming years. In fact, the restrictions in movement imposed in many countries may have decreased HBV transmission due to the reduction, outside the family, of physical contact between infected subjects and those exposed. These restrictions, however, have induced a depression in large segments of the population, which has led to an increase in alcohol consumption, drug use and unprotected sex. Another adverse effect of the restrictions is the increased risk of child deliveries at home, which may involve the

lack of screening for HBV infection for mothers and an inadequacy in the prophylaxis of the newborn.

In addition, a significant part of the resources usually reserved for the different fields of medicine have been devolved to the screening of SARS-CoV-2 infection and to the assistance of COVID-19 patients. As a result, there has been a downsizing of care for liver diseases: A lower number of hepatic wards and day hospitals, a lower number of beds in hepatic wards still open, difficulty in managing patients with serious liver diseases and the recipients of liver graft. In addition, screening for HBV and HDV infections have been significantly reduced, and the start of treatment for “new” patients frequently postponed. Another important role in the reduction of healthcare facilities for liver patients was played by their fear of contracting SARS-CoV-2 infection in healthcare structures and in centers giving assistance to drug addicts. Moreover, many “new” cases of HDV infection may have gone undiagnosed, since the determination of HBV DNA, HDV DNA and IgM to HD-Ag has undergone a significant reduction in several countries for the considerable commitment of many laboratories in the diagnosis of SARS-CoV-2 infection and for the fear of patients attending them. Therefore, several HBsAg carriers and HBV/HDV patients may not have been identified, and if identified may not have received appropriate treatment.

The sum of these contrasting effects exerted by the measures restricting mobility on the spread of HBV and HDV infections makes it difficult to predict the extent and modalities of their spread in coming years. However, we have no doubt in advancing pessimistic forecasts, because in the continuing course of the SARS-CoV-2 pandemic, foreseeable for about another 2 years, all the negative elements reported above will remain, while the positive effects of movement restriction will gradually decrease, because such restrictions, already not respected in many countries, will be even less so in the future. We only trust in a more rapid and intense production of vaccines against SARS-CoV-2 infection and in universal vaccination campaigns for a future return to normality[101].

CONCLUSION

The impact of the SARS-CoV-2 pandemic on essential health services is of great concern. In fact, it is feared that most improvements in public health achieved in recent years could be wiped out, with negative repercussions on the provision of health services to the public, with a consequent reduction in the prevention of infectious diseases, diagnostic efficacy, and the application of therapeutic and rehabilitative treatments, and overall, of healthcare promotion. The reduction of essential healthcare services, due to the focus towards COVID-19, risks having serious negative effects on the health of the most vulnerable populations, such as children, the elderly, patients with chronic diseases, viral (HBV, HDV and hepatitis C virus hepatitis, HIV infection), inflammatory, degenerative, oncological, cardiac, autoimmune, *etc.*

The COVID-19 pandemic has required the use of enormous healthcare resources and, consequently, reduces the care of patients with other diseases, particularly those who need continuous clinical monitoring to avoid clinical deterioration such as patients with chronic HBV/HDV infection. For these patients, there has already been, and will occur even more in the next few years, a lack of diagnosis for some, delayed access to treatment or lack of continuity of antiviral therapy for others, and finally a lack in the surveillance for the possible emergence of liver cirrhosis and HCC and the need for liver transplantation. When the COVID-19 emergency draws to a close, there will be a resumption of health activities for all diseases neglected during the pandemic, including screening for HBV and HDV infection, and a false increase in the prevalence of these infections will occur because of the effect of the recovery of cases undiagnosed in 2020, 2021 and, for some countries with reduced vaccination activity against COVID-19 even in some subsequent years.

We remind those in charge of treating hepatitis B and those who have the related administrative responsibility that the interruption of drugs suppressing HBV replication in patients with HBV chronic hepatitis frequently leads to the exacerbation of liver cell necrosis, with a risk of death from acute liver failure. Furthermore, patients with chronic HBV/HDV infection are at risk of developing cirrhosis, HCC, and serious decompensation of the disease, and therefore require close clinical, biochemical and ultrasound monitoring, now made difficult by the COVID-19 emergency.

There is also the need for strategic adjustments to ensure specialist healthcare services to identify, monitor and treat patients with chronic HBV infection and those

with HBV/HDV coinfection.

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