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Hepatitis Delta Virus Epidemiology in the Industrialized World

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Abstract

Within the hepatitis virus landscape, one incomplete virus, the hepatitis delta virus (HDV), appears to differ from hepatitis B and C viruses in the context as it still may not infrequently lead to complications of chronic liver disease and continues to be associated with significant liver-related mortality even when patients have received available treatment for it. Breakthrough therapies are so far lacking for HDV-infected patients and treatment has not changed since the discovery of HDV in 1977 and consists mainly of interferons. While there was little interest on the global epidemiology of HDV until recently, this has changed in the past 2 years and we are currently observing a stream of papers on the global epidemiology of HDV and commentaries about why prevalence estimates appear to differ so dramatically. This may be related to the fact that reliable data are not available for most of the countries. However, in the industrialized world, data on the epidemiology of HDV are expected to be of better overall quality. Hence, this review was undertaken to provide a detailed overview on the epidemiology of HDV infection in industrialized countries using data from representative larger countries. In industrialized countries, with maybe the exception of China, HDV infection is a disease of high-risk groups. Migrant groups and people who inject drugs are the most encountered high-risk groups. This review summarizes the dynamics of their contribution to the HDV epidemiology in industrialized countries of the west and the east. ***(AIDS Rev. 2020;22:203-212)***

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Key words

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Introduction

Viral hepatitis is considered an important and universal health problem. The World Health Organization (WHO) recognized this in 2016 based on mortality figures between the years 2000 and 2015 which basically showed that malaria, tuberculosis, and HIV were on the decline in mortality figure estimates and viral hepatitis had surpassed all of them as a mortal disease on a global scale[1]. Almost 95% of hepatitis deaths were estimated to be due to hepatitis B or hepatitis C. This led to a paradigm shift within the WHO with the consequence of an ambitious strategic target of elimination of viral hepatitis as a major public health threat by 2030[2]. Underdiagnosis and consequent undertreatment are important barriers to achieve the ambitious goals of the WHO, in particular in developing countries. However once diagnosed, basically every single patient can be effectively treated with currently available treatment options for hepatitis B and C avoiding development of complications of liver disease and mortality from liver disease.

Within the hepatitis virus landscape, one incomplete virus, the hepatitis delta virus (HDV), appears to differ from hepatitis B and C viruses in this context as it still may not infrequently lead to complications of chronic liver disease and continues to be associated with significant liver-related mortality even when patients have received available treatment for it. This is clearly shown in the HIV literature, where HDV-HIV coinfection appears to have surpassed HIV-HBV or HIV-hepatitis C virus (HCV) coinfection as a cause of liver-related mortality due to the availability of very effective treatment options for the latter two conditions[2,3]. This was mainly possible with the introduction of nucleos(t)ide analogs for hepatitis B in the past two decades[4] and the recent availability of direct acting antivirals for hepatitis C[5]. Such breakthrough therapies are so far lacking for HDV infected patients and treatment has not changed since the discovery of HDV in 1977[6] and consists mainly of interferons[7]. Interferons may affect favorably the natural history of chronic hepatitis delta[8,9] but is effective only in a minority of patients[7].

The fact that HDV remains as the main viral hepatitis agent with potential dreadful consequences and the recent clinical studies with new agents have raised interest in hepatitis D[10]. In this context, the global epidemiology of HDV has been revisited with two large studies suggesting that the conventional estimates of the global HDV prevalence[11] represent an underestimation[12,13]. Both studies were critically assessed[10,14,15]. Besides these three commentaries, the two studies have now been challenged by a very recent study which basically argues that the old WHO estimates may be correct[16].

A study on global epidemiology has to be based on published data and published data differ in overall quality from sample size to use of state of the art statistical models for optimal sample selection. Further for some countries and regions, data availability is the problem in others the weightiness of hot spots of HDV endemicity. All these factors may affect given prevalence figures in a study on global epidemiology. In the industrialized world, data on the epidemiology of HDV are expected to be scientifically sound and homogenous, and the above-mentioned concerns may thus be overcome. This review was, therefore, undertaken to have a detailed perspective on the epidemiology of HDV infection of industrialized countries of Europe, the Far East, Australasia, and North America. While giving a general perspective, we looked at epidemiological dynamics in large representative countries in these regions.

Epidemiology of HDV in the industrialized world

Conventionally, HDV epidemiology has been described as occurring in three epidemiological patterns: (i) as an endemic disease occurring in a large proportion of chronic HBsAg carriers; (ii) as an epidemic disease striking isolated HBsAg-positive communities; and (iii) as a disease occurring only in high-risk groups[17]. Endemic HDV disease today is seen in former Soviet republics, West Pacific islands, Mongolia, Pakistan, Afghanistan, countries of sub-Saharan Africa, Mediterranean, and East European countries such as Turkey, Romania, and Albania, and areas close to the Amazon river in South America[11,18]. Epidemic disease has been described in South America[19].

The third pattern is observed in areas where HDV is rare such as West Europe and North America or in industrialized countries. High-risk groups were described in the late 1980s as intravenous drug addicts (or with today's definition people who inject drugs [PWIDs]) and patients frequently exposed to blood products[17]. Since then, HBV/HDV exposure through blood products is negligible. PWIDs still constitute an important risk factor, but another risk factor added today is migration of people from HBV/HDV endemic areas. International migration showed a sharp increase

Table 1. Estimated number of international migrants according to the UN as of 2017, and migrants as the percentage of the total population in industrialized countries (Adapted from United Nations, International Migration Report 2017[22])

Major area, region, or country	Number of international migrants (thousands)		Migrants as percentage of total population	
	2000	2017	2000	2017
World	172.604	257.715	2.8	3.4
High-income countries	100.405	164.847	9.6	14.1
Middle-income countries	64.042	81.440	1.4	1.4
Low-income countries	7.733	10.915	1.8	1.6
West Europe				
Sweden	1.004	1.748	11.3	17.6
United Kingdom	4.730	8.842	8.0	13.4
Germany	8.893	12.165	11.0	14.8
France	6.279	7.903	10.5	12.2
Spain	1.657	5.947	4.1	12.8
Italy	2.122	5.907	3.7	10.0
Netherlands	1.566	2.057	9.8	12.7
Switzerland	1.571	2.506	21.9	29.6
North America				
USA	34.814	49.777	12.3	15.3
Canada	5.512	7.861	17.9	21.5
Oceania				
Australia	4.386	7.036	23.0	28.8
Asia				
China	508	1.000	0.0	0.1

after 1985[20] and continue to rise in the 21st century[21,22]. The estimated number of international migrants rose from 173 million in 2000 by more than 50% and reached 258 million in 2017 (3.4% of the world population) and 272 million in 2019 (Table 1)[21,22]. The number of PWIDs is estimated from 10.6 million to more than 15 million (0.2% of the world population) (Table 2)[23,24]. Overall, it suggests that PWID on a global scale represents roughly 5% of the high-risk group pool, in particular when immigrants are considered. Immigrants reside mainly in high-income countries and represent more than 10% of the general population in industrialized countries except China (Table 1) and Far East countries (data not shown). In addition, other high-risk groups worth mentioning may be individuals with high-risk sexual behavior and incarcerated people.

HDV in immigrant populations

Migration of individuals from high endemic areas to low endemic areas might affect the disease burden of specific pathogens[25]. Due to a lack of universal standards for screening, vaccination, and treatment of viral hepatitis, the burden of chronic liver disease and hepatocellular carcinoma continues to increase among migrant populations globally[26]. Migration to West Europe and North America occurs mainly from countries with high prevalence for viral hepatitis[26,27]. In 2019, the EU and the US were home to 82 million and 59 million foreign born migrants, respectively[21]. According to a recent systematic review[28], the highest infectious disease prevalence reported in refugees and asylum seekers is latent tuberculosis (9-45%) followed by hepatitis B virus infection (12%).

Data on published HDV prevalence studies among immigrants in representative industrialized countries are shown in table 3. Among them, Far East countries represented here by China display an epidemiological pattern which differs from the rest of the countries in West Europe, North America, and Australasia. In China, immigrants are not a risk group in contrast to the above-mentioned other regions. However, based on

Table 2. Estimates of people who inject drugs (PWIDs) and HBsAg prevalence in PWIDs in representative industrialized countries (2A) and world regions (2B) (Adapted from Degenhardt et al.[23])

2A			
Country	**Prevalence (range)**	**Number of PWIDs (range)**	**HBsAg prevalence (range)**
Australia	0.60 (0.43, 0.76)	93.000 (68.000, 118.000)	3.8 (2.4, 5.3)
England	0.59 (0.55, 0.63)	210.500 (196.500, 225.000)	NK
France	0.20 (0.16, 0.23)	82.000 (66.500, 97.000)	0.8 (0.3, 1.6)
Italy	0.83 (0.57, 1.14)	341.500 (235.500, 467.500)	5.1 (0.9, 9.3)
Germany	0.24 (0.03, 0.45)	131.500 (14.000, 249.500)	0.7 (0.3, 1.0)
Sweden	0.13 (0.03, 0.62)	8.000 (2.000, 38.500)	1.9 (0.2, 6.6)
Spain	0.03 (0.01, 0.05)	10.500 (3.500, 17.500)	1.8 (0.4, 5.2)
USA	1.04 (0.57, 1.88)	2.248.500 (1.236.500, 4.074.000)	4.8 (3.0, 7.2)
Canada	1.22 (1.04, 1.40)	308.000 (262.000, 354.500)	NK
China	0.25 (0.19, 0.31)	2.564.000 (1.964.000, 3.164.000)	23.4 (10.4, 36.4)
2B			
Region	**PWID population prevalence (95% UI)**	**Estimated number of PWIDs (95% UI)**	**Estimated HBV prevalence among PWIDs (95%UI)**
West Europe	0.34% (0.23-0.47)	1.009.500 (686.500-1.386.500)	3.2% (0.9-5.6)
East and Southeast Asia	0.25% (0.19-0.31	3.990.00 (3.041.000-4.955.000)	20% (9.8-30.2)
North America	1.06% (0.62-1.83)	2.557.000 (1.498.500-4.428.000)	4.8% (3.0-7.2)
Australasia	0.59% (0.42-0.75)	115.500 (83.000-148.000)	3.6% (2.2-5.1)
Global	0.33% (0.21-0.49)	15.648.000 (10.219.000-23.737.500)	9.1% (5.1-13.2)

HBV: hepatitis B virus; NK: not known; PWIDs: persons who inject drugs; UI: uncertainty interval.

the three different studies on the global epidemiology of HDV, it is estimated that 0.25-0.45% of the general population of China or West Pacific region are HDV infected[12,13,16]. With a population of 1.39 billion people, even 0.25% is a huge number in a country which was considered hypoendemic for HDV.

Among West European countries, relatively good epidemiological data are available from some countries, in particular from Spain and Italy whereas in others data are scant. Three well-conducted studies from Spain give good clues of the evolution of the dynamic epidemiology of HDV. The pioneer study by Navascues et al.[29] from 1995 reported the HDV burden in Spain explicitly in the time frame between 1979 and 1992 based on data of one tertiary liver center in Northwest Spain.

Among 696 HBsAg-positive patients, anti-HDV was positive in 67 (9.6%). Of the 696 patients, 387 were inactive HBsAg carriers and HDV was found in none of them, whereas HDV was found in 67 of 389 (21.7%) patients with hepatitis B-induced chronic liver disease. These data are consistent with the natural history of HDV known for its progressive and aggressive form when an HBsAg carrier is superinfected with HDV, the most noticeable and common form of chronic hepatitis D[30]. Of the 67 HDV-positive patients, 59 (88%) reported intravenous drug use (IDU), and 4 patients (6%) reported a history of blood transfusion or hemo-

Table 3. Hepatitis delta virus prevalence studies in industrialized countries

Author, year (reference)	Country	Population	Prevalence
Aguilera et al.,[32] 2018	Spain	HBsAg-positive patients, tertiary out clinic Northwest Spain	4% anti-HDV antibody, 13/19 (70%) were PWIDs
Coghill et al.,[47] 2018	Queensland, Australia	All tested for HDV in state wide Queensland Pathology database (Auslab.)	4.1% seroprevalence associated with overseas births, mainly Africa
Cross et al.,[44] 2008	South London, UK	962 HBsAg positive referred to King's College Hospital	8.5% positive for HDV antibody, majority is foreign born
El Bouzidi et al.,[45] 2015	London, UK	Cross-sectional data from four London hospitals, HBsAg-positive individuals	4.5% HDV prevalence
Geata et al.,[35] 2000	Italy	14 referral units Italy	8.3% positive for HDV antibody among HBsAg-positive patients
Heidrich et al.,[41] 2009	Hannover, Germany	2,363 HBsAg-positive patients	11% anti HDV positive
Jackson et al.,[46] 2018	West of Scotland	People newly diagnosed for HBV	1.6% in Glasgow immigrants from East Europe, and people who inject drugs amount for most cases
Ji et al.,[43] 2012	Sweden	Chronic hepatitis B-infected patients using the Swedish hospital discharge register and outpatient registry	3.80% HDV prevalence
Kucirka et al.,[53] 2010	USA	AIDS Linked to the Intravenous Experience (ALIVE) cohort among HBsAg-positive individuals	50% HDV prevalence among chronic HBsAg-positive PWIDs
Kushner et al.,[50] 2015	USA	Nationwide retrospective study (Veterans Health Administration) of all HBsAg positive	3.4% HDV positive (out of only 8.5% of HBsAg positives that were tested for HDV)
Liao et al.,[63] 2014	Guangdong province, China	Retrospective study on 6604 CHB infected patients	6.5% tested positive for IgM anti-HDV
Lin et al.,[55] 2015	Taiwan	Prospective, multicenter cohort study of 2562 HBsAg-positive patients	HDV prevalence among HIV-infected PWIDs was 74.9%, HIV uninfected PWIDs was 43.9%, HIV MSM 11.4%, HIV-infected heterosexuals 11.1%, and general HBsAg positive only 4.4%
Mahale et al.,[54] 2018	San Francisco, USA	PWID HBsAg positive	HDV present in 35.6%
Ordieres et al.,[31] 2017	Spain	Tertiary referral hospital 1215 patients with CHB	8.2% immigrants and PWIDs
Patel et al.,[51] 2019	USA	National Health and Nutrition Examination Survey (NHANES)	42% anti-HDV among adult HBsAg carriers
Piccolo et al.,[38] 2010	Italy	Large cohort of HBsAg-positive patients	5.4% anti-HDV-positive mostly in non-EU from East Europe
Reinheimer et al.,[42] 2012	Frankfurt, Germany	HBsAg-positive patients University Hospital Frankfurt am Main	Seroprevalence of anti-HDV 7.4% among immigrants born abroad
Servant et al.,[39] 2014	France	National epidemiological donors database	1.98% HDV Ab positive, immigration from endemic countries
Shen et al.,[64] 2012	China	1486 HBsAg positive (inactive) patients	1.2% anti-HDAg positive
Stroffolini et al.,[37] 2017	Italy	Cross-sectional study, 16 referral centers across the country	Among HBsAg positive, 11.9% were anti-delta positive
Stroffolini et al.,[33] 2020	Italy	HBsAg-positive patients, nationwide survey (9 tertiary centers)	Anti-HDV overall 9.9%

CHB: chronic hepatitis B; HBsAg: hepatitis B surface antigen; HDAg: hepatitis D antigen; HDV: hepatitis delta; PWIDs: people who inject drugs.

philia. There is no mention of immigrants in this pioneer study from Spain[29]. In a more recent study from the same center, Ordieres et al.[31] described the epidemiology of HDV in 1215 HBsAg-positive patients over a course of 30 years. In the period between 1983 and 1997, anti-HDV prevalence is 9.4% which decreases to 6.1% in 1998-2012 period. While in the first period, HDV was observed exclusively in Spaniards (74/74, 100%), in the period between 1998 and 2012 this dropped to 50% (13/26), and half of HDV patients were immigrants. Similarly, the origin of HDV cases, the HBV population, consisted 98% of Spaniards (770/786) in the period before 1998 but this decreased to 68% after 1998 (294/429). However, these data have been challenged from another tertiary referral center located in the same region of Spain[32]. They reported that after 2000, among 478 HBsAg-positive cases, only 12% were immigrants and among 19 anti-HDV positive cases (4% of the HBsAg-positive cohort), 16 (84%) were Spaniards[32].

In Italy, as shown recently by Stroffolini et al.,[33] anti-HDV prevalence progressively decreased from 23% in 1987[34] to almost 9% in 1997 at which point it was asked if HDV was actually vanishing from Italy[35]. However, since than in several reports, HDV prevalence did not further decrease and stayed around 9-10%[33,35-37]. In 2001, anti-HDV prevalence in HBsAg-positive patients was 7.4% among native Italians and 12.2% among immigrants[36]. In a 2010 report, relevant prevalence figures for Italian versus immigrants were 4.2 and 17%[38] and this year (2020) in a nationwide survey of 9 tertiary centers,[33] it was 6.4 and 26.4%, respectively. Italy and Spain compared to other West European countries appear to have recognized the migration factor in HDV rather recently, in line with the sharp increase in immigrants since 2000 (Table 1).

In France, Servant-Delmas et al. reported[39] a seroprevalence of close to 2% and suggests similar to Le Gal et al.[40] that HDV cases are mainly immigrants from Africa. Heidrich et al.[41] reported among 2363 HBV patient's anti-HDV positivity in 10.9% in Germany. Only 20% were German, pointing to the role of immigration, now more from East Europe and former Soviet republics and less from Turkey in variance with the past. Similar results came from a more recent study by Reinheimer et al.[42], with an anti-HDV seroprevalence of 7.4%.

Similarly, in a study from Sweden[43] analyzing the Swedish hospital discharge and outpatient registries, from Januray1997 to the end of 2008, they identified 9160 chronic hepatitis B patients of whom 84% were foreign born. From the 9160 chronic hepatitis B patients, 650 (7.1%) were coinfected with HDV. A study from London, England[44] reported that among the 962 HBsAg-positive patients referred to the King's College Hospital, 8.5% were seropositive for HDV. About 82% were foreign born, most from South or East Europe or Africa. In a more recent study again from London, out of 3543 HBsAg carriers, 158 (4.5%) were anti-HDV positive. Detailed data available from 55 patients on clinical follow-up revealed that 50 (91%) were foreign born[45]. Finally, in a study from Scotland, in two cohorts of 991 and 141 HBV patients, respectively, HDV coinfection was found in 1.6% and 4.9%, respectively. Of 23 HDV patients, 12 were native English and 11 were immigrants[46].

There appears to be two epidemiological studies from Australia in the past decade[47,48]. Both studies underline the importance of immigration. In the first study, HDV status was assessed in Victoria between 2000 and 2009[46]. Out of 2595 people who had serological testing for HDV, 110 (4.8%) were found positive. While in the period from 2000 to 2004, 37.5% of HDV-positive patients were immigrants, in the period from 2005 to 2009 their contribution to HDV positivity rose to 53.2%[48]. In a more recent study from Queensland, Australia[47], that used the state-wide pathology database, the anti-HDV seroprevalence was similar with 4.1% and again the majority (75%) were born outside Australia, being mainly from Africa. Similar to the European example, in a study from 1986 on HDV epidemiology in Australia, there is no mention of immigration[49].

In the US, the burden of HDV has been addressed by two important studies, one retrospective and one prospective[50,51]. A large nationwide retrospective study[50] of all veterans who tested positive for HBsAg in the US reported that only 8.5% were tested for HDV, and 3.4% tested positive for HDV. Conversely, a study using a multistep probability cluster sampling scheme through the National Health and Nutrition Examination Survey[51], reported an HBsAg and anti-HDV prevalence of 0.36 and 0.15, respectively, among 16,143 individuals ages 18+. Among the 113 HBsAg-positive cases, 43 (42%) were anti-HDV positive and among this latter group, 79% were foreign born. The HDV seroprevalence figures were higher than expected and the authors suggested that AASLD guidance[52] on serological HDV testing of high-risk groups should be changed and encompass every HBsAg-positive individual, a view we also have shared and recommended[10].

HDV prevalence among PWID population

PWIDs are commonly exposed to both B and D viruses. The UNODC/WHO/UNAIDS/World Bank joint

estimate is that the number of PWIDs in 2016 was 10.6 million (range: 8.3-14.7 million) which corresponds to 0.22% of the global population aged 15-64 years[24]. Subregions with the largest number of PWID are East and Southeast Europe – IDU in this region is estimated to be 3.8 times the global average- IDU figure estimate for the US is also high with 2.5 times the global average whereas in East and Southeast Asia, IDU is estimated as being below the global average[24]. However, because of the population size, the latter region accounts for 30% of the global total of PWID. Almost half of all PWID worldwide are estimated to live in just three countries: China, Russia, and the US. A global prevalence study[23] on IDU and prevalence of HIV, HBV, and HCV in PWID reported that in the US and China, HBsAg prevalence among PWID is 4.8 (3.0-7.2), and 23.4% (10.4-36.4), respectively (Table 2A). In West Europe, this estimate is 3.2% (0.9-5.6) (Table 2B). Regions with high estimated HBV prevalence rates are East and Southeast Asia accounting for 20% (9.8-30.2) and East Europe accounting for 7.9% (5.7-10.0) of HBV prevalence rates[23]. In this study, globally, 9.1% of PWID were estimated to be HBsAg positive (Table 2B).

HBV and HDV seroprevalence among PWID is dynamic and, in general, has changed in recent years, but the pace and the direction of these dynamic changes are not uniform (data of some representative countries of the industrialized world are summarized in Table 3). In the US, anti-HDV prevalence among PWID with chronic hepatitis B in Baltimore has increased from 29% in the 1988-1989 time frame to 50% in 2005-2006[53]. In a more recent study among 73 HBsAg-positive PWID in San Francisco, anti-HDV prevalence was 36%[54]. Similarly, in a relatively recent publication from Taiwan, among PWID anti-HDV prevalence was 44%[55]. However, in two recent studies from Italy and Spain, a totally different picture emerged despite being within the same time frame. While in the study from Spain in the period between 1993 and 1996, among 209 IDUs, HBsAg prevalence was 35% and anti-HDV was positive in 53% of hepatitis B patients[32], in the 2011 and 2014 period out of 47 available IDUs, only two were HBsAg positive as well as anti-HDV positive. Similarly, in a study conducted in 2009 in a national sample containing 543 IDUs in Italy, HBsAg seropositivity was found in a merely 2.8% of PWID compared to 64% anti-HCV seroprevalence[56]. Of 15 HBsAg-positive cases, three were coinfected with HDV. Low HBV vaccination coverage in the 2005-2006 Baltimore cohort in the US[53], decrease in protective immunity against HBV in IDUs reported from Taiwan[55], efficient harm reduction programs[57], decrease in IDU in Spain and Italy[57,58], and decreased circulation of HDV (and HBV) among IVUs may to some extend explain this geographical differences. Besides, harm reduction programs such as clean needles, opioid substitution therapy, and vaccination against HBV should to be the reasonable solution. Still, it is quite surprising that the significant drop in HBsAg prevalence among the IDU population in Italy was possible despite a low vaccination coverage rate of 34% in the IDU cohort[56], and the very high HBV and HDV prevalence among PWID in Taiwan was possible despite the implementation of a very successful infant vaccination program in 1986 in this country[59]. In Europe, the impact of long-term widespread use of tenofovir as part of an antiretroviral treatment regimen in HIV patients including IDUs (see below) need to be considered. It may have acted as protection against HBV and indirectly against HDV acquisition[60,61].

PWID represent one of the most marginalized people. Homelessness, incarceration, high-risk sexual behavior, and unsafe injecting practices are common which further leads to increased exposure of PWID to HIV, HCV, and HBV[23,24]. This is one important reason why one in eight PWID is living with HIV[24]. Similarly, HCV infection was found to be associated with HDV or it was an independent risk factor for HDV in several studies from the West as well as the Far East[32,41,44,47,55]. HCV in PWID shares with HDV the same transmission route and hence this is to be expected. However, in regions where IDU is rare, association of HDV with HCV is not observed, and in such regions, HDV is acquired mainly by horizontal transmission[41,62]. Another important finding in these studies is that HIV was found to be an independent risk factor associated with HDV infection[55]. In the multicenter cohort study from Taiwan involving 2562 HBsAg-positive individuals, prevalence rates of HDV infection among HIV-infected IDUs, HIV uninfected IDUs, HIV-infected men who had sex with men, HIV-infected heterosexuals, and the general population of HBsAg-positive subjects were 75%, 44%, 11%, 11%, and 4.4%, respectively. These data reiterate the importance of IVDU as an important risk factor for HDV infection but also underlines the importance and place of high-risk sexual behavior. High-risk sexual behavior alone is a known risk factor for HDV transmission. However, accumulated evidence suggests that its risk of transmitting HDV is not as strong as is IDU.

Finally, PWID and China need mentioning. The WHO estimates that HBsAg prevalence in Chinese PWID is

more than 20% (Table 2A). There are also data on non-IDU population and in two separate studies, HDV prevalence among HBsAg carriers was reported as 6.5% and 1.2%[63,64]. The former figure may be biased toward more severe cases. In the recent global studies on HDV epidemiology, HDV prevalence among HBsAg carriers is reported between 4.1 and 5.6%[12,16].

Discussion

HDV in industrialized countries was perceived as restricted to high-risk groups. With the exception of China, this perception captures the real-world scenario in industrialized countries. China has a large population where HDV in high-risk groups such as PWID can be potentially very important as reflected by the estimated very high HBsAg prevalence rate of the WHO. On the other hand, China may have low or intermediate HDV endemicity (0.25-0.69% in the general population) but due to its high population, the "non-high-risk" HDV cohort may contribute significantly to the global HDV burden. China aside, HDV in the industrialized world is a disease of high-risk groups. The high-risk group of PWID continues to be important but overall its importance is to some extent diminished and immigration appears to have emerged as the most important risk factor in the 21st century for propagation of HDV in the industrialized world. However, risk factors are interrelated. While in some immigrant exporter countries or regions such as Mongolia, Pakistan, and Africa, high HDV endemicity may be linked to horizontal and non-IDU parenteral exposure, in others such as those coming from East Europe or Russia or former Soviet republics IDU without any precautions may have contributed to HDV positivity[65]. In this context, the importance of precautions, that is, harm reduction programs such as clean needle and syringe and opioid substitution therapy to the IDU community is striking as can be seen in the examples of Italy and Spain where despite the lack of HBV vaccination in a substantial proportion of patients, HBV/HDV transmission has drastically declined[56,57].

Despite the reports of the increase of HDV among immigrants, the causes of this increase among foreign born, which policies to change to get these patients tested as well as monitored and treated, have not been assessed. This could also be an indication that screening, monitoring, and treatment for HBV alone are not being properly practiced among migrants and refugees in these countries. Vaccinating newly arrived refugees as well as positive tested family members of vulnerable populations might be the only option to have control or even decrease new cases of infections in their own (native) populations. Especially with the current migration crises happening in countries of the European Union in 2020, the authorities and UN as well as the WHO need to prioritize vaccinating vulnerable and susceptible population/children for HBV even if, this might be put on hold, or experience some delays of implementing due to the current coronavirus pandemic[66].

According to the WHO's vaccine services for refugees and migrants 2019 report[67], effective strategies for making routine delivery of immunization services for refugees and migrants as part of mainstream health services are, to a great extent, congruent with the elements of an effective national program. In 2019, Turkey continued to be the country hosting the largest number of refugees in the world (4 million), with 1.4 million being under age of 15, and around 800,000 between ages 15 and 24[68]. In a study by Kose et al.[69] from 2017, among Syrian refugee children ages 0-18, 4.2% were tested HBsAg positive. In 2017, the Turkish Ministry of Health, with support from UNICEF, WHO, and local non-governmental organizations, conducted a mass countrywide vaccination campaign, at which HBV vaccine was included, to more than 400,000 refugee and migrant children. Through a major coordinated effort with a team of more than 5000 people, including trained Syrian refugee doctors and nurses, vaccines were provided to children in their homes and communities, as well as in health centers[67,70]. Screening the at-risk groups and vaccinating those kids that test antibody negative and educating family about transmission and care options for those that tested positive should be implemented to refugees or immigrants. Turkey has been providing each Syrian refugee the same health insurance opportunities as Turkish citizens[67].

A study by van der Veen et al.[71] shows that cultural values and social cognitive factors are related to HBV screening intention among Turkish migrants in the Netherlands, and various culturally tailored programs[72], such as the ones for screening Chinese migrants in the Netherlands[73] and in the US[74].

Migrants are unfortunately disproportionately impacted by chronic viral hepatitis sequel[26], and it is important to point out the patient, provider, and system-related barriers for monitoring, treatment, and HCC surveillance[75] in migrant populations. A few cost-effectiveness studies have shown that screening immigrants from intermediate and high prevalence countries for CHB are cost effective and can reduce liver-related mortality and morbidity[76-78]. A mathematical model and cost-effectiveness analysis by Goyal and Murray[79] was

developed to capture the dynamics of the spread of HBV and HDV in moderate (China) and high (Amazon Basin) HDV endemic areas. The study concluded that it would cost $1400 per QALY (compared to doing nothing) to implement testing with HBV adult vaccination, diagnosis with antiviral treatment for HBV infection, diagnosis with antiviral treatment for HBV-HDV infection, and an awareness campaign[79].

A recent study by Besombes et al.[80] reported that transmission probability of HDV within household is higher than previously thought and higher compared to other viral infections, including HBV. These differences highlight an opportunity for more effective implementation of public health interventions in particular in regions where universal HBV vaccination coverage is still low or birth dose vaccination is significantly delayed[81]. As such, HDV prevention might need to be and can be handled separately from HBV prevention[82]. Educating families about transmission have access to care options for those that test positive, might be a solution to decrease the burden of HDV as well.

Conclusions

The pace of the decrease in HDV prevalence observed in the last decade of the 20th Century in HDV endemic and industrialized countries appears to have diminished. The decrease in HDV prevalence was mainly due to the successful introduction of universal infant vaccination against HBV in the vast majority of countries worldwide, and the positive impact of the HIV epidemic in better implementation of preventive measures, particularly the widespread use of disposable needles and syringes. Traditionally, HDV in the industrialized world was confined to high risk groups, such as patients exposed to blood products and people with intravenous drug use (IVDU) and promiscuous behavior. Exposure to blood products is no longer a risk factor today. The latter two behaviors still constitute an important risk in acquiring HDV much more so with IVDU than through sexual promiscuity. However, even the impact of IVDU may be diminishing as seen in examples from Europe thanks to harm reduction programs and HBV vaccination. The most important risk factor for HDV acquisition today in the industrialized world is immigration from HDV endemic areas.

The prospect for the future is that immigration from countries with low socioeconomic level to rich countries will continue and increase. Industrialized countries have so far neglected the problem but need to come up with rationale health strategies encompassing issues such as screening, prevention and treatment of affected people. This may be the only way for controlling new infections.

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