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MINIREVIEWS

Epidemiological and clinical aspects of hepatitis B virus infection in Italy over the last 50 years

Caterina Sagnelli, Antonello Sica, Massimiliano Creta, Armando Calogero, Massimo Ciccozzi, Evangelista Sagnelli

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Abstract

A relevant gradual reduction of both the incidence rate of acute hepatitis B (AHB) and prevalence of chronic hepatitis B has occurred in Italy in the last 50 years, due to substantial epidemiological changes: Improvement in socioeconomic and hygienic conditions, reduction of the family unit, accurate screening of blood donations, abolition of re-usable glass syringes, hepatitis B virus (HBV)-universal vaccination started in 1991, use of effective well tolerated nucleo(t)side analogues able to suppress HBV replication available from 1998, and educational mediatic campaigns against human immunodeficiency virus infection focusing on the prevention of sexual and parenteral transmission of infections. As an example, AHB incidence has gradually decreased from 10/100000 inhabitants in 1985 to 0.21 in 2020. Unfortunately, the coronavirus disease 2019 (COVID-19) pandemic has interrupted the trend towards HBV eradication. In fact, several HBV chronic carriers living in the countryside have become unable to access healthcare facilities for screening, diagnosis, clinical management, and nucleo(t)side analogue therapy in the COVID-19 pandemic, mainly for anxiety of becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), movement restrictions, and reduced gains from job loss. In addition, one-third of

healthcare facilities and personnel for HBV patients have been devolved to the COVID-19 assistance.

Key Words: Hepatitis B virus; Hepatitis B virus epidemiology; Acute hepatitis B; COVID-19

Core Tip: An impressive reduction in the spread of hepatitis B virus (HBV) infection has been observed over the past 5 decades in Italy. This review article analyzes, in Italy, the effects of various events on HBV endemicity: Reduction of the impact of several risk factors, HBV-universal vaccination started in 1991, the nucleo(t)side analogue therapy started in 1996, the increased immigration flows from countries at high HBV endemicity, and the restrictions generated by the coronavirus disease 2019 (COVID-19) pandemic. Particular attention has been directed at the negative effects of the COVID-19 pandemic that threaten to interrupt the favorable trend towards HBV eradication.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem with 3.61% of the world population chronically infected and 890000 deaths per year for cirrhosis, liver failure, or hepatocellular carcinoma (HCC)[1,2]. Despite the availability of an effective recombinant HBV vaccine from 1991[3] and of effective well-tolerated nucleo(t)side analogues since 1998, the rate of individuals persistently infected with HBV does not decrease worldwide and, unfortunately, it is increasing in some developing countries[4]. Several factors support the level of endemicity of HBV infection: (1) Most patients with chronic infections are asymptomatic and undiagnosed for years[5]; (2) 70% of the individuals with chronic HBV infections live in developing areas where HBV vaccination does not have the character of universality, with 95.3 million in Western Pacific areas and 75.6 million in Africa, where there is a prevalence of hepatitis B surface antigen (HBsAg) chronic carriers of 5.26% and 8.83%, respectively[6]; and (3) Nucleo(t)side analogues suppress but do not eradicate chronic HBV infection. Instead, in the last 30 years, a trend to HBV eradication has been observed in northern America, western Europe, and Japan [7].

As far as Italy, HBV endemicity has progressively decreased over the last 50 years, due to universal HBV vaccination since 1991, the improvement in socioeconomic conditions correlated to better standard of hygiene, substantial reduction of the family unit, and continuous mediatic human immunodeficiency virus (HIV) campaigns organized and financed by the Italian government[8].

Italy is experiencing a continuous migratory flow, more frequently from eastern Europe and sub-Saharan Africa for 20 years and today migrants represent about 9% of the resident population. As an effect of immigration, some HBV genotypes previously rare in Italy are currently responsible for about 40% of acute hepatitis B (AHB) cases[9-12]. There is the fear that the continuous immigrant flows from countries with high or intermediated HBV endemicity will adversely affect the low endemicity level of Italy. As an example, of 882 asymptomatic undocumented migrants or refugees observed in southern Italy in 2015, 78 (9%) were HBsAg positive. This rate was 14% in 444 sub-Saharan Africa subjects, 6% in 198 eastern Europe subjects, and 2%-3% in the 240 migrants from northern Africa, Bangladesh, India, Pakistan, or Sri Lanka, percentages much higher than the 0.8% registered in the people born and living in Italy[13]. The regional office of the World Health Organization (WHO) for Europe reported that a high percentage of immigrants are not vaccinated against HBV upon their arrival in host countries[14] and therefore at risk of becoming infected even in geographic areas with a low HBV endemicity level; accordingly, in Italy one fifth of the new AHB cases are represented by the immigrant population.

Like for numerous other sectors of medicine, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic reduced care levels also for HBV-related diseases. A recent web-based survey performed in Italy registered that a quarter of healthcare centers and personnel dedicated to liver diseases had been intended for coronavirus disease 2019 (COVID-19) and that 23% of cases with chronic hepatitis B (CHB) undergoing HBV suppression with nuclo(t)side analogues have suffered interruptions of therapeutic plans[15]. There is therefore a suggestion for the healthcare institutions of Italy not to neglect the need of patients with HBV infection throughout this long terrible COVID-19 pandemic, not to lose in short time the advantages obtained with decades of considerable efforts and economic

commitment.

EPIDEMIOLOGICAL AND CLINICAL CHANGES OF AHB IN ITALY OVER LAST FIVE DECADES

HBV is a non-cytopathic virus that induces liver cell necrosis through cytolytic action of human cytotoxic T cells made able to recognize the viral antigens expressed on the surface of infected hepatocytes from a previous pre-sensitization to HBV. The degree of immune response depends on the age of the host at the acquisition of HBV infection, being absent or low in infants and young children who often develop an asymptomatic acute hepatitis frequently progressing to an HBsAg chronic carriage, but high in young adults and adults who usually develop a self-limiting symptomatic acute hepatitis, progressing to chronicity in only 2%-5% of cases. Fulminant hepatitis occurs in only 1%-3% of cases, more frequently in adolescents and young adults, with a mortality rate of 70%, and in most cases requiring liver transplantation[16-19]. In its classic form, AHB begins with generic symptoms such as fever, malaise, headache, nausea, anorexia, vomiting, and diarrhea, followed by jaundice common in adults and rare in children. The aminotransferases serum levels are usually normal or moderately increased in children and high in adults, reflecting the extension of liver damage. High serum titers of IgM to hepatitis B core antigen identify HBV as the etiological factor, simultaneously with serum HBsAg positivity. Hepatitis B e antigen (HBeAg) and serum HBV DNA are signs of high infectivity; they can be found in the early stage of the disease and are no more detectable in the elimination phase of the virus, event accompanied by seroconversion to anti-HBe. A Cochrane's review of seven randomized controlled trials involving a total number of 597 participants found that antiviral treatment has no benefit for AHB[20], since any evolution to chronicity is strongly determined by the reactivity of the patient's immune system. Some more severe cases, however, may require supportive therapy.

All yearly AHB cases occurred in Italy in the sixties were registered by the Italian Institute of Statistic (ISTAT) under one single entry, with an incidence rate of 98 cases per 100000 inhabitants, followed by a subsequent gradual decline to 20 cases per 100000 inhabitants until 1987[8]. Reliable data on AHB incidence in Italy are reported since 1985, when the surveillance of the integrate epidemiological system of acute viral hepatitis (SEIEVA) registered 12 cases per 100000 inhabitants. This incidence gradually decreased in subsequent years, driven by two important events: (1) The beginning in 1985 of mediatic HIV educational campaigns that advised the condoms for sexual intercourses at risk and to avoid syringe sharing[21]; and (2) since 1991, the national universal HBV vaccination continued so far without interruption; currently all Italian people aged 0 to 41 have been vaccinated[22]. The AHB incidence in 1987 decreased to 10.4 cases per 100000 inhabitants, 5.4 in 1990, 0.9 in 2012, 0.6 in 2016, and 0.21 in 2020 (Table 1).

These data testify the strong contribution of the HBV vaccination to reduction of AHB incidence, but it is equally evident that this reduction had already begun before the universal HBV vaccination campaign had started in 1991. The reason for this is that other factors have contributed to the decrease of AHB incidence in Italy, such as the obligation to test blood donations for HBV markers and not to transfuse the samples testing positive, improvement of socioeconomic and hygienic conditions, and some behavioral changes that have led to the reduction of domestic contacts with a chronic HBsAg carrier and not to use non-disposable or improperly sterilized instruments for medical and surgical practice, piercings, tattoos, manicures, pedicures, acupuncture, and barber's shop[23-25]. Vertical transmission of HBV is no longer a route of HBV transmission in Italy from 1991, due to the mandatory screening for HBV infection among women in pregnancy or at delivery, and to the mandatory, in babies born of HBsAg-positive mothers, active and passive immune prophylaxis. Two routes of HBV transmission remain active, the parenteral one because of the exchange of syringes or other objects between intravenous drug users and the sexual one because of the unusual use of condom in sexual intercourses. It should also be underlined that the impact of these two risk factors on HBV endemicity has progressively lowered, due to the positive effect of universal HBV vaccination which currently covers the Italian population aged 0-41.

Analyzed by the age classes, 0-14 years, 15-24 years, and 25 years or more, the data registered by SEIEVA in 1985 showed 6 subjects with AHB per 100000 inhabitants in age class 0-14, 41 in age class 15-24, and 7 in age class 25 or more. The progressive decline was observed in subsequent years in all the three age classes: (1) In 1990: 1, 17, and 4 cases per 100000 inhabitants, respectively; (2) in 1995: 1, 6, and 3 cases, respectively; (3) in 2000: 0.1, 2, and 2 cases, respectively; (4) in 2005: 0, 5, and 1.8 cases, respectively; and (5) in 2011: 0, 0.5, and 1.2 cases per 100000 inhabitants, respectively[26] (Table 1).

Patients with acute viral hepatitis B registered by SEIEVA from 2009 to 2020 were allocated in five age classes (0-14, 15-24, 25-34, 35-54, and 55 or more), with an incidence close to zero in age classes 0-14 and 15-24 and with a continuous downtrend in older age classes up to 2020[26] (Table 1). The cases of AHB in SEIEVA in the period 1991-2019 have been also analyzed by their geographical distribution[26,27], northern + central Italy *vs* southern Italy + main islands (Sicily and Sardinia), a distribution reflecting historical events and the behaviors of the respective inhabitants (Figure 1).

Table 1 Incidence rate of acute hepatitis B in Italy: Cases per 100000 inhabitants per year, according to age classes

Age classes	1985	1990	1995	2000	2005	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
0-14	6.00	1.00	1.00	0.10	0.00	0.00	0.00	0.00	0.04	0.10	0.03	0.05	0.00	0.00	0.03	0.03	0.00
15-24	41.00	17.00	6.00	2.00	5.00	0.50	0.50	0.45	0.40	0.30	0.28	0.30	0.20	0.15	0.32	0.08	0.08
> 25	7.00	4.00	3.00	2.00	1.80	-	-	-	-	-	-	-	-	-	-	-	-
25-34	-	-	-	-	-	1.20	1.20	1.20	0.80	0.70	0.46	0.33	0.30	0.23	0.34	0.26	0.26
35-54	-	-	-	-	-	1.90	1.80	2.00	1.70	1.90	1.76	1.40	1.10	1.04	0.76	0.69	0.34
> 55	-	-	-	-	-	0.70	0.50	0.50	0.60	0.70	0.51	0.46	0.60	0.48	0.39	0.38	0.20
Total	12.00	5.00	3.00	2.00	1.30	1.00	0.90	1.00	0.85	0.90	0.80	0.70	0.60	0.51	0.44	0.38	0.21

Figure 1 shows a clear trend towards an overtime reduction of the total number of cases in Italy, and moderate changes in cases distribution, increased in northern and central regions and decreased in southern and island areas[26,27].

In Italy, the uninterrupted flux of migrants over the last 20 years brought that about 9% of resident population are composed of immigrants, more frequently from eastern Europe and sub-Saharan Africa. Out of the 4981 AHB cases reported to SEIEVA from 2004 to 2019 by 10 of the 20 Italian regions, 849 (17.0%) occurred in immigrants, of whom 53.4% had come from eastern Europe, 14.6% from Asia, 21.6% from Africa, 8.9% from central/southern America, 0.1% from North America, and 0.1% from Oceania. The comparison between the AHB incidence rates among people born in Italy and foreigners, reported by the "Strong Migratory Pressure Countries", report among foreigners values up to 4 times higher until 2008, a difference progressively decreased from 2009 to 2019, when the standardized rates were 0.4 per 100000 for Italians, and 0.6 for foreigners[26,27].

In Italy, the uninterrupted flux of migrants modified the AHB molecular evolution, where, for decades, genotype D was observed in 95% of patients. Coppola *et al*[28] showed that in 123 AHB-patients, a significant increase in HBV genotypes non-D, from 11% in 1999-2003 to 41.1% in 2004-2008, associated with unsafe sexual habits. In good agreement, Ferraro *et al*[10] showed a high rate of cases with acute hepatitis B due to HBV genotypes non-D in Sicily in 2012 (44% genotype A, 3% genotype E), infected mainly through unsafe sexual intercourses.

In 2015, Zuccaro *et al*[11] reported that HBV genotypes non-D were responsible of nearly half of 103 consecutive cases of acute hepatitis B, mainly HBV genotypes A and F, associated with unsafe sexual exposure. In addition, mutations of antiviral resistance or viral mutants in the antigenic determinant "a" of HBsAg have been reported in AHB-patients[28].

Even clinical presentation and outcome of AHB have changed over time in Italy since, in abolishing the circulation of the virus in subjects aged 0-41, the universal HBV vaccination has confined acute hepatitis B to older ages when the disease is more severe[28,29].

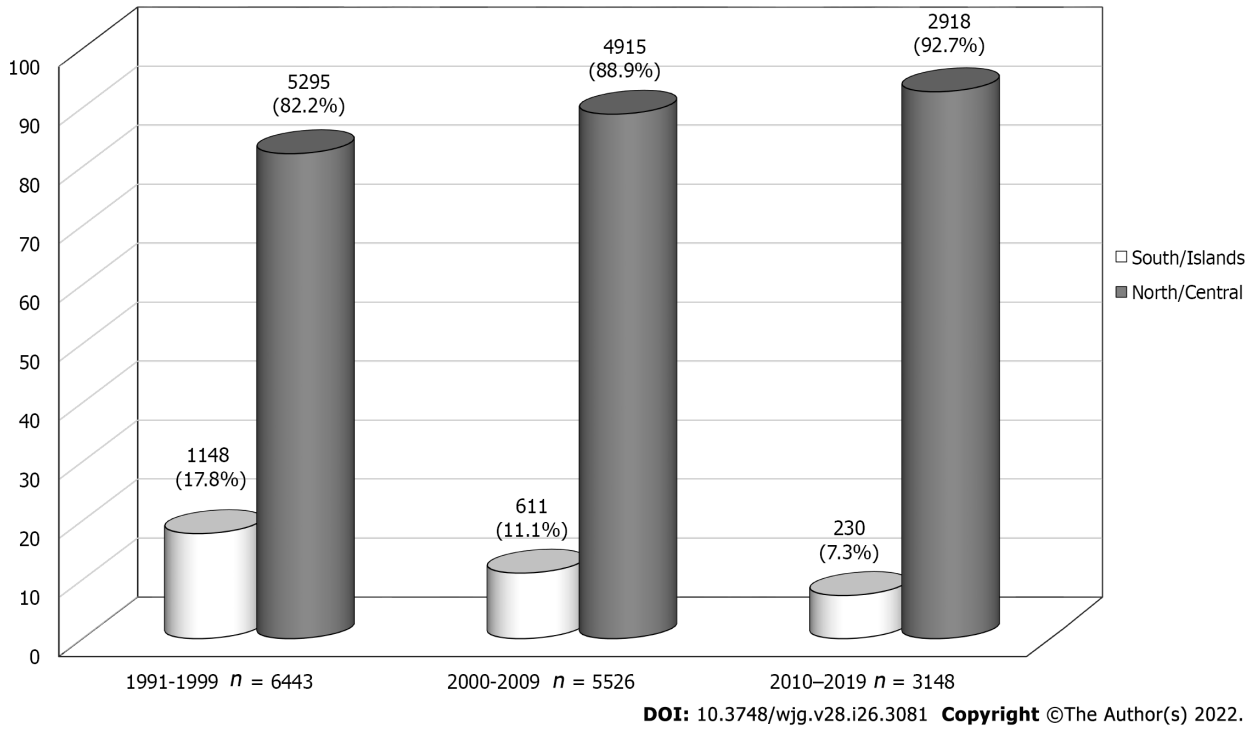

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Figure 1 Geographic distribution of 15117 new cases of acute hepatitis B registered in the surveillance of the integrate epidemiological system of acute viral hepatitis (SEIEVA) system from 1991 to 2019, according to the time of occurrence.

EPIDEMIOLOGICAL AND CLINICAL CHANGES OF CHB IN ITALY IN THE LAST 50 YEARS

The worldwide prevalence of subjects with chronic HBV infection is estimated at around 5%, with wide differences from a geographic area to another, 0.1%-2.0% in northern America and northwestern Europe, 1.0%-8.0% Japan and African countries overlooking the Mediterranean sea, and 8.0%-20.0% in Southeast Asia/sub-Saharan regions[16,17]. HBV genotype A prevails in northern America and northwestern Europe, HBV genotypes B and C in Asia, genotype D in southern Europe, northern Africa, India, and Middle East, HBV genotype E in western Africa, HBV genotype F in southern/central America, HBV genotype G in the USA and France, and genotype H in Mexico and some countries of South America[30]. CHB, defined as the persistence of HBsAg in serum for more than 6 mo, is a dynamic process which develops through five main phases: (1) "Immune tolerant" phase with mild/absent necroinflammation with normal/low aminotransferase levels, high HBV DNA levels, and HBeAg positivity, with no/slow evolution to fibrosis; (2) "immune reactive phase" characterized by liver necroinflammation, increased or fluctuating aminotransferase serum values, low or intermediate HBV-DNA level, HBeAg positivity, and progression to liver fibrosis or cirrhosis; (3) "inactive HBV carrier state" with low/absent necroinflammation, low/normal aminotransferase serum levels and with very low or undetectable serum HBV DNA, commonly, seroconversion to anti-HBe; (4) "HBeAg-negative CHB" characterized by mild to severe necroinflammation, fluctuating serum levels of aminotransferases and HBV-DNA, linked to e-minus HBV variant unable to express HBeAg[31]; and (5) "occult HBV infection" with HBsAg negativity and low HBV replication with detection of HBV DNA in the liver cells and also in serum (some cases) which clinical impact needs further investigation[32,33].

A complete clinical history should always be the first approach to patients with chronic hepatitis B, including family history, alcohol consumption analysis, metabolic risk assessment, and vaccinations performed. Physical examination should be complete and especially directed at identifying signs indicative of cirrhosis[1]. The laboratory tests useful to define the degree of viral replication and the stage of chronic hepatitis include the search for HBeAg/anti-HBe in serum, HBV DNA load, the blood count, the detection of aminotransferases, total bilirubin, and alkaline phosphatase serum values, and any other tests eventually necessary for the patient under examination[1].

For untreated adult patients, the 5-year cumulative incidence of developing cirrhosis varies between 8% to 20% across studies, and the risk of HCC from 2% to 5%[1]. Among the instrumental investigations, liver biopsy is needed to evaluate the degree of inflammation and fibrosis, a technique, however, sometimes burdened by serious complications, while transient elastography is considered sufficient for the evaluation of fibrosis alone; hepatic ultrasound is of great use for monitoring the clinical course of liver cirrhosis and, in particular, for the early identification of intrahepatic nodules of HCC. Better definition of HCC can be obtained with computed tomography and magnetic resonance imaging.

Drugs recommended and most frequently used to treat CHB are nucleus(t)side analogues tenofovir disoproxil fumarate or tenofovir alafenamide and entecavir, chosen in relation to their high genetic barrier, antiviral potency, and excellent profiles of resistance, tolerability, and safety[1,34]. The duration of treatment remains indefinite because these drugs suppress HBV replication but do not eradicate viral infection and reactivation of both viral replication and chronic disease occurs frequently upon treatment suspension, sometimes with a serious clinical impact[1,34].

At the end of 1970s, the HBV endemicity was considered intermediate, with a prevalence of HBsAg chronic carriers nearly 3%[35,36] and with an increasing gradient from North to South of Italy, where 5% of people were HBsAg positive[37,38]. At that time, the main routes of transmission were vertical transmission at delivery, intravenous drug use (IVDU), and living with an HBsAg chronic carrier, mainly between siblings.

As a result of the reduced HBV circulation, the percentage of HBsAg chronic carriers has decreased overtime in Italy. An impressive decline in HBsAg prevalence in children and teenagers has been observed even before the universal HBV vaccination had been introduced. As an example, the rate of HBsAg positivity decreased from 2.2% in 1980 to 0.8% in 1988 in schoolchildren aged 7-12 years in the city of Naples[39]. This decline has been confirmed in subsequent studies in pregnant women tested at the delivery[40], and in young adults at their enrolment in the army[41].

The rate of HBsAg positivity in patients with chronic hepatitis of all etiologies, either inpatients or outpatients of numerous Italian liver units, was: 61% in 1975[42], 44% in 1980, 34% in 1989[43], and 12.2% in 2001[43-45]. At present, only 0.8% of subjects born in Italy are HBsAg positive, also thanks to the universal HBV vaccination. Additional evidence of efficacy of HBV vaccination in Italy was the increase in the mean age of patients with CHB, from 30.8 years in 1980-1989[42] to 57.3 years in 2019[46].

The positive effects of HBV vaccination to reduce levels of HBV endemicity were also observed in countries with a high level of endemicity. About that, it seems interesting to evaluate the data reported by some authors from China, a nation that like Italy has achieved a remarkable socio-economic improvement in the last decades, where an extensive vaccination campaign against HBV infection has been conducted. A national cross-sectional epidemiological study performed in China in 1992 reported a 9.8% rate of HBsAg chronic carriers[47]. A reduction of this prevalence to 7.2%, due also to a series of measures implemented by the Chinese government, has been reported by Tedder *et al*[48] in 2006. A tendency to a further decline has been shown by a meta-analysis by Wang *et al*[49] who, analyzing the data published in 27 studies from January 2013 to December 2017, estimated a 6.89 HBsAg prevalence in the Chinese population, with more than 90% of HBV infected subjects aging more than 20 years[49]. The data reported by the above-mentioned studies indicate that even starting from very high level of endemicity, the correct application of general and special prophylactic measures, including a wide vaccination campaign against HBV, can yield significant results.

Italy, as mentioned above, has now a country of migration from geographical areas with high or intermediate HBV endemicity in the last two decades. Currently, nearly 9% of the 60 million of inhabitants are immigrants, of whom the major part has not received HBV vaccination and 250000 are estimated to be HBsAg chronic carriers with a 30% rate of HBeAg positivity[50]. The integration of immigrants is proceeding slowly, and it is unlikely that their continuous flow could not impair the favorable results obtained in Italy in the last five decades. El-Hamad *et al*[23] observed 3.728 migrants, mainly undocumented, 12.4% from northern Africa, 21.4% from sub-Saharan Africa, 16.8% from Asia, 44% from eastern Europe, and 5.4% from Central/South America, have come to Italy from 2006 to 2010. The mean rate of HBsAg positivity was 6%, different in the various geographic groups as well as the prevailing HBV genotype, both reflecting those of the country of origin. Coppola *et al*[13] studied 882 undocumented migrants/refugees who lived in the South Italy (period of study January 2012-June 2013), of whom 9% were HBsAg positive. This percentage was 14% in 444 individuals from sub-Saharan Africa, 6% in 198 individuals from Eastern Europe, and 2%-3% in the remaining 240 migrants from other geographic areas[13]. Zermiani *et al*[51] found a 3.5% HBsAg positive rate in migrant female sex workers. A cross-sectional Italy study[50] carried out in 3760 HBV chronic carriers from February to July 2008, reported that 37.1% (932 cases) were migrants from Far East, 35.4% from eastern Europe, 17.5% from sub-Saharan Africa, 5.5% from northern Africa, and 4.5% from other sites. HBV genotype D was detected in 40% of migrants and in 87% of subjects born in Italy. Migrants more frequently than subjects born in Italy were HBV-inactive carriers and less frequently showed CHB, cirrhosis, and HCC.

Sagnelli *et al*[52] evaluated 53 HBsAg chronic carriers with genotype E, immigrated in Southern Italy, of whom 47 (88.7%) were from sub-Saharan Africa, 4 (7.5%) from eastern Europe, and 1 (1.9%) from Asia. The molecular epidemiology study disclosed four statistically supported clusters and traced the genetic evolution and phylogenesis. In addition, phylogenetic analysis on a time scale considering the year of arrival in Italy showed that 52 immigrants had contracted genotype E infection in their country of origin before they arrived in Italy[52].

CONCLUSION

In Italy, the level of HBV endemicity has progressively decreased over the last 50 years. The main

contribution to the downward trend of AHB incidence and of the prevalence of their chronic sequelae is mainly attributable to improvement in socioeconomic and hygienic conditions, the effective educational HIV infection campaigns, and the HBV vaccination since 1991 continued without interruptions until now[43]. There was a consequent strong reduction in the impact of major risk factors for HBV infection acquisition. Vertical transmission from HBsAg positive mother to their newborn babies is just a memory, due to mandatory determination of serum HBsAg in pregnant women, and to passive and active immunization of babies born of HBsAg positive mothers. Besides, the impressive reduction in size of families, particularly in the South Italy regions and islands, has strongly impaired HBV transmission through household contacts with HBsAg-positive chronic carriers. A strong contribution to the significant reduction of HBV endemicity in Italy has been also given by the mandatory screening of blood donations for HBV markers and by the remarkable reduction or abolition of improperly sterilized instruments for medical, surgical, and cosmetic procedures. Also, the role of IVDU has progressively reduced by extension of vaccination to persons aged up to 41. Currently, sexual transmission plays the major role in HBV transmission in Italy, due to infrequent use of condom in unsafe sexual activity[53].

As a consequence of the reduced impact of risk factors for HBV infection acquisition, the prevalence of HBV chronic carriers in the general population has undergone an impressive continuous decrease and to date is 0.8%; similarly, the current AHB incidence B has been reduced to 0.21 per 100000 inhabitants, higher in males than in females, most of cases occurring in Italian citizens with unsafe sexual habits aged over 41 and in unvaccinated migrants[27]. In this regard, most immigrants who come to Italy are not vaccinated against hepatitis B and are three times more likely to acquire HBV infection than Italian citizens[13,26,52,53]. The WHO Regional Office for Europe strongly motivated the national health authorities of the host countries to set up national hepatitis B vaccination protocols for all unvaccinated migrants and instruct local health authorities how to apply them[14]. It should be also emphasized that HBsAg positive migrants should be entrusted to local healthcare facilities for further diagnostic information and clinical therapeutic follow-up.

Like for numerous other sectors of medicine, SARS-CoV2 pandemic has reduced care level also for HBV related diseases. In this period, nearly half people worldwide have not been able to enter clinical center for HBV prevention, diagnosis, and treatment due to breakdowns or other restrictions on the movement imposed by individual governments, absence, or reduction of earnings due to loss of work activities and for the subject' fear to acquire SARS-CoV-2 infection in clinical environments[54]. Furthermore, the activity of clinical structures dedicated to HBsAg positive patients has been greatly reduced, with a sharp contraction in the number of beds for hospitalization, day hospital facilities and healthcare personnel, devolved to assistance for SARS-CoV-2 patients. In Italy, recent web-based survey performed by the Italian Association for the Study of the Liver (AISF) registered that a quarter of hepatology centers have been transformed into divisions for the management of COVID-19 patients and also a quarter of other health services for liver outpatients have been suspended[15]. A continuous clinical/therapeutic follow up has been provided only to 32.5% of patients with decompensated cirrhosis and to 18% of those with HCC; in addition, 23% of CHB patients treated with nuclo(t)side analogues have undergone temporary interruptions of therapy[15]. In this regard international guidelines give clear indications on how to apply therapy with entecavir or tenofovir for an effective long-term suppression of viral replication in CHB patients: Start therapy at first diagnosis, and then continue without interruption to avoid serious and sometimes life-threatening virus reactivations[55,56].

The percentage of subjects vaccinated against COVID-19 in developing countries is decidedly low. In addition, many children have not yet been vaccinated and a minority of adults has refused vaccination in countries with a high socioeconomic level. All this has favored the development of viral variants more and more infectious that is leading the pandemic to its fifth wave. Nevertheless, by reducing SARS-CoV-2 circulation, COVID-19 vaccination is exerting a favorable effect on CHB management, whose consistency, however, is not yet fully assessable because liver units and transplant centers are still suffering severe limitations. Furthermore, most of the damages produced by COVID-19 to patients with liver diseases will come both from the delays in screening, diagnosis and start of treatment and from the interruptions of clinical activities for outpatients, damages not yet calculable. However, the consequences of the first 3 waves of the COVID-19 pandemic have been analysed by Tapper *et al*[57] who reported that all screening procedures were significantly delayed and that this has resulted in a substantial increase in early diagnoses in the advanced stages of liver diseases or at the onset of complications. Analysing the events following the pandemic waves, these Authors identified three phases: The first one taking place in lockdown and other social distances, characterized by high priority for the needs of COVID-19 patients and a strong delay for elective and routine activities regarding other pathologies; the second one following abolition of physical distancing, with a rapid increase in morbidity and decompensation of non-COVID-19 diseases and by a crowding of health facilities forced to solve old and new problems; a long third stage heavily burdened by consequences of delays in diagnosis and start of treatment and by the interruptions of clinical-therapeutic follow-up[57]. More tuned with the problems of HBsAg positive subjects, Mandel *et al*[58] analysed the effect of three waves of COVID-19 pandemic on HBV testing volume in Ontario, a state of Canada with a high socioeconomic level. Test volume for HBV DNA decreased by 37% during the first pandemic wave, by 27% in second one and by 20% in the third one, reflecting reduction in HBsAg testing, 33%, 18% and 15%, respectively. These reductions are most likely due to both an adaptation of citizens to subsequent pandemic waves,

and a favorable effect of an overtime increase in COVID-19 vaccination coverage.

In numerous developing countries, the COVID-19 pandemic is also severely damaging the programs of the HBV-vaccination, as demonstrated by an analysis by the Institute for Health Metrics and Evaluation which showed in 2020 a dropped of vaccination activity to 1990s levels[59].

In clinical practice, telemedicine was increased over the past 20 years[60], with a sharp increase in 2020 and 2021 due to social distancing measures mandatory to curb COVID-19. Consent to the use of telemedicine was expressed by American Association for the Study of Liver Diseases and EASL-ESCMID experts who recommended it in COVID-19 emergency for the care of chronic hepatitis patients, those on waiting for liver transplantation, and those already transplanted[61,62]. On the strength of the experiences gained in waves of COVID-19, telemedicine can usefully be introduced in programs of prevention and screening, diagnosis, clinical, and therapeutic follow-up of HBV patients, with particular advantage for those living in rural areas and for those who have serious trouble getting to a liver unit.

The COVID-19 has caused quickly significant damage to hepatitis B setting that has lost some of the beneficial impact of several scientific research on clinical practice and on technological application, and huge economic investments. Local health authorities should monitor the damages inflicted to HBV patients by COVID-19 pandemic and work to reduce and, when possible, abolish them. Also, a greater spread of telemedicine could reduce the impact of COVID-19 pandemic.

To prevent onset of new SARS-CoV-2 variants highly infectious, nations with high economic levels should contribute to increase the coverage of COVID-19 vaccination in low- or moderate-income nations; the development of new low-cost vaccines suitable for countries with limited health resources will be of help in solving this problem. As far HBV infection, the HBV-universal vaccination must continue worldwide without interruption and health authorities should extend their HBV vaccination protocols to all unvaccinated migrants.

FOOTNOTES

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