

## ORIGINAL ARTICLE OPEN ACCESS

# Diagnosed Patients With Chronic Hepatitis B and Delta Virus in Italy in 2024: An Estimation From a National Real-World Database

Alessandro Loglio<sup>1</sup>  | Ivan Gardini<sup>2</sup> | Massimiliano Conforti<sup>2</sup> | Marco Bartoli<sup>2</sup> | Francesco Silvia<sup>2</sup> | Carmine Coppola<sup>3</sup> | Luchino Chessa<sup>4</sup> | Gianluca Svegliati-Baroni<sup>5</sup>  | Laura Schiada<sup>5</sup>  | Ivan Gentile<sup>6</sup>  | Biagio Pinchera<sup>6</sup>  | Maurizia Rossana Brunetto<sup>7</sup>  | Piero Colombatto<sup>7</sup> | Alessio Aghemo<sup>8</sup>  | Stella De Nicola<sup>8</sup> | Pierluigi Toniutto<sup>9</sup>  | Edoardo Giovanni Giannini<sup>10</sup>  | Antonio Colecchia<sup>11</sup>  | Dante Romagnoli<sup>11</sup>  | Loredana Sarmati<sup>12</sup>  | Francesca Romana Ponziani<sup>13</sup>  | Filomena Morisco<sup>14</sup>  | Calogero Cammà<sup>15</sup> | Giuseppe Cabibbo<sup>15</sup>  | Pietro Lampertico<sup>16,17</sup>  | Elisabetta Degasperis<sup>16</sup>  | Pietro Invernizzi<sup>18,19</sup>  | Antonio Ciaccio<sup>18</sup>  | Francesco Paolo Russo<sup>20</sup> | Antonio Massimo Ippolito<sup>21</sup>  | Grazia Anna Niro<sup>21</sup>  | Natalia Terreni<sup>22</sup> | Gerardo Nardone<sup>23</sup>  | Alba Rocco<sup>23</sup>  | Maria D'Antò<sup>24</sup> | David Sacerdoti<sup>25</sup>  | Donatella Ieluzzi<sup>25</sup> | Alessia Ciancio<sup>26</sup> | Adriano Pellicelli<sup>27</sup> | Alessandro Federico<sup>28</sup>  | Loredana Simone<sup>29</sup> | Vincenzo Messina<sup>30</sup>  | Ernesto Claar<sup>31</sup>  | Valerio Rosato<sup>31</sup>  | Gianpiero D'Offizi<sup>32</sup>  | Paolo Caraceni<sup>33,34</sup>  | Paolo Muratori<sup>35</sup>  | Cinzia Giaccherini<sup>36</sup> | Stefano Fagioli<sup>1,37</sup>  | Mauro Viganò<sup>1,37</sup> 

**Correspondence:** Mauro Viganò ([mvigano@asst-pg23.it](mailto:mvigano@asst-pg23.it))

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## ABSTRACT

**Background and Aims:** Hepatitis B (HBV) and Hepatitis Delta virus (HDV) infection have undergone significant changes in Italy over the past few decades, but reliable and updated prevalence of chronic hepatitis B (CHB) and Delta (CHD) data are lacking. The aim of the study was to describe the epidemiology of CHB and CHD in Italy in 2024, based on real-world data.

**Methods:** The number of patients with a healthcare expenditure exemption for CHB (016.070.32) and CHD (016.070.33) was obtained from 21 Regional Health Authorities. To understand how many CHB or CHD patients did not have these specific exemptions, a survey was conducted in 30 Gastroenterology, Hepatology and Infectious Diseases Units across the country.

**Results:** Health Authorities data reported 67 514 and 5216 subjects with an exemption for CHB and for CHD, respectively. However, among 6775 CHB and 504 CHD patients, only 60.3% and 55.7% of them had the specific exemption, respectively. Based on these results, we estimated 111 960 (95% CI: 109 780–114 240) CHB and 9360 (95% CI: 8690–10 150) CHD patients, with a prevalence of 0.22% and 0.019% of the adult overall population. Moreover, anti-HDV prevalence was 7.7% from this cohort.

**Conclusion:** Our study provides a plausible estimate of the current number of adult patients diagnosed with CHB and CHD in Italy and may be considered the basis for decision-making health policies.

**Abbreviations:** ALT, alanine aminotransferase; ASL, regional health authorities; CHB, chronic hepatitis B; CHD, chronic hepatitis D; HBIG, anti-HBs immunoglobulins; HCC, hepatocellular carcinoma; LT, liver transplantation; NA, nucleos(t)ide analogs; qHBsAg, quantitative hepatitis B surface antigen.

For affiliations refer to page 8.

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## Summary

- In Italy, there is no universal screening program for HBsAg nor a registry for patients diagnosed with HBV. Only specialists can issue the exemption for medical conditions; Regional Health Authorities have the total number of exemptions recorded for HBV and HDV.
- Not all patients diagnosed with HBV or HDV have a specific exemption for their liver disease, and some use instead exemptions relative to income, cancer or other comorbidities.
- Starting from the total number of exemptions for chronic hepatitis B (CHB) and Delta (CHD) in Italy, as requested from the Regional Health Authorities, and using surveys obtained from 30 specialised centres on a representative sample of people with HBV and HDV, we have estimated the number of adult patients with diagnosed HBV or HDV in Italy in 2024: 111 960 (95% CI: 109 780–114 240) and 9360 (95% CI: 8690–10 150), respectively.

## 1 | Introduction

Hepatitis B virus (HBV) is a significant global health problem. In 2022, the World Health Organization (WHO) made an estimation suggesting the presence of approximately 254 million people worldwide who were chronic carriers of the hepatitis B surface antigen (HBsAg). Data from 187 countries show that the estimated number of deaths from viral hepatitis increased from 1.1 million in 2019 to 1.3 million in 2022, and that 83% of these deaths were caused by HBV. Despite progress in preventing hepatitis infections, deaths are globally rising because far too few people with hepatitis are being diagnosed and treated [1].

In Italy, HBV infection has seen a significant decline over the past few decades, primarily due to effective vaccination programmes and improved public health measures [2, 3]. Of note, the vaccination campaign against HBV has been characterised by two phases. In the first phase (1984–1991), vaccination was recommended only for high-risk groups (e.g., intravenous drug users, household contacts of chronic HBV carriers, newborns of HBsAg-positive mothers, homosexuals, healthcare workers, haemophiliacs, poly-transfused patients and hemodialyzed patients). In the second phase (1991–nowadays), the recombinant vaccine targeted, by law, infants 2 months old and teenagers 12 years old (limited to the first 12 years of campaign), and this latter phase was pivotal in reducing new infections among younger populations [4, 5]. However, still today, HBV infection remains a public health problem also in our country, although confined to the cohort of long-term infected older patients with severe liver diseases and to young immigrants from endemic countries in which vaccination programmes are not in place [6–8]. A recent systematic review highlighted how the prevalence of HBV in the migrant population increased by 0.9% in the European Union and in the European Economic Area when comparing the period before and after 2017, from 4.9% (1.9%–8.4%) to 5.8% (2.5%–9.9%) [9].

Closely related to HBV is hepatitis Delta (HDV) infection, recognised as the most severe form of viral hepatitis and a major public health issue (30% progression to cirrhosis in 5 years from diagnosis) [10, 11]. High rates of HDV endemicity are found in both Eastern Europe and the Mediterranean basin, also due to the immigration flows from high endemicity areas [12]. Nowadays, across Europe, there is a remarkably high prevalence of HDV among HIV/HBV-coinfected subjects, individuals who inject drugs, immigrants and HBV-infected patients with advanced liver disease [13]. Although in Italy HDV is considered a vanishing disease, it still represents an important medical issue and maintains an impact on liver transplantation mainly due to a legacy of ageing native-Italian patients with advanced HDV liver disease and of migrants from HDV-endemic areas [14, 15].

In the absence of a national registry, in Italy there are no recent or updated epidemiological data on patients with a known diagnosis of HBV or HDV, and only estimates are available on the number of people who are unaware of the infection [16] or estimates obtained from mathematical models that have processed data from studies published in different historical periods. Nationwide, the most up-to-date estimates were published in 2023 by the Polaris Observatory from the analysis of studies published between 2016 and 2022, suggesting a 0.5% (0.3%–0.6%) prevalence of HBsAg in the Italian general population, corresponding to 303 000 (187 000–383 000) infected individuals [6]. The same analysis reported in Italy an adjusted HDV prevalence of 3.4% among HBsAg-positive individuals, with an adjusted 60.5% rate of HDV-RNA positivity [7]. Similarly, a recent systematic review and meta-analysis including 282 studies estimated, in Italy, a 3.2% (95% CI 0.2–13.2) anti-HDV prevalence among HBsAg-positive patients with an overall prevalence of 0.02% (95% CI: 0%–0.1%) in the entire population [17]. However, a recently published cross-sectional study among 4152 HBsAg-positive patients followed at tertiary referral centres reported a 10.2% anti-HDV positivity rate, showing that compared with HBsAg mono-infected patients, anti-HDV-positive patients were more often younger, non-Italians, with a history of drug use, had elevated alanine transaminase, cirrhosis or hepatocellular carcinoma (HCC) [18].

In Italy, disease-specific exemption is assigned by specialists to enable patients to avoid co-payment for medical appointments and most procedures related to their condition. For CHB and CHD, disease-specific exemptions are assigned by gastroenterologists, hepatologists, or infectious disease specialists registered to the Local Health Authority. Although the specific list of exempt laboratory and imaging tests may vary based on regional provisions and regulatory updates, they usually include upper abdomen ultrasound, laboratory tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, HBsAg, anti-HBs and serum HBV DNA.

In order to achieve the ambitious WHO goal of eliminating viral hepatitis by 2030, a precise estimate of patients with chronic HBV and HDV hepatitis is more necessary than ever. Therefore, the main aim of this study was to accurately derive the number of diagnosed patients with chronic hepatitis B (CHB) and Delta (CHD) in Italy from regional exemption databases.

## 2 | Materials and Methods

In 2015 and in 2018, the major Italian Patients Association for Liver Disease *EpaC* conducted two studies, with the aim to determine the number of people living with Hepatitis C Virus (HCV) infection in Italy, starting from the number of specific exemptions for the disease and using surveys to cover the gap of individuals without exemptions [19, 20].

The same approach was implemented for CHB and CHD in the present study. In the first trimester of 2024, we requested all Local Health Authorities of the 21 Regions/Autonomous Provinces of Italy to provide the number of individuals with a specific exemption for CHB (016.070.32) or CHD (016.070.33).

Through direct contact with Local Health Authorities, *EpaC* ETS Association obtained the overall number of exemptions for CHB and CHD. Active exemptions apply only to living patients; therefore, the reported number is very accurate and represents all patients under care within the National Health System. Once the total number of exemptions was obtained, a statistical calculation was performed to determine how many surveys were necessary to achieve a realistic proportion of how many patients with CHB and CHD do not have the disease-specific exemption. As a matter of fact, to adequately interpret the exemption data and reach the most realistic estimate of the number of CHB or CHD patients in Italy, it is essential to identify and determine the percentage of patients diagnosed with CHB or CHD who use other exemptions (e.g., income, disability, older age, another health conditions) already covering healthcare expenses, as well as patients who do not have any exemption at all.

To fill this gap, in the second trimester of 2024, a survey (text in [Supporting Information](#)) was conducted in 30 Gastroenterology, Hepatology and Infectious Diseases Units across the Country (10 in Northern Italy, 10 in Central Italy and 10 in Southern and major Islands). Given the clearly defined objective of the study—descriptive rather than comparative—all major geographical areas were included, along with both urban and rural centres, in order to capture differences potentially related to socio-healthcare contexts. Participating institutions included both secondary and tertiary care hospitals (university and community-based), with varying levels of experience in managing these specific conditions. Only centres with the capacity to maintain an up-to-date and accurate database were selected. To ensure adequate statistical power, a total of 30 centres (hepatology and infectious disease units) were involved—exceeding the minimum of 10–20 centres typically required for descriptive studies. All the centres selected based on the above criteria agreed to participate in the survey.

Each centre was asked to anonymously report how many patients were on regular follow-up for CHB or CHD (residing in 2024 and under regular follow-up at the center for at least 1 year), the percentage of HBsAg-positive patients tested for HDV, and how many of them had exemption code for the index disease, other or none. This retrospective approach (by consulting local databases, the “Fascicolo Sanitario Elettronico” (a national Italian database that also includes patients’ exemption statuses), or by directly inquiring with patients regarding existing exemptions)

enabled the collection of an updated overview of the active exemptions in 2024 across the participating centres.

Moreover, the survey differentiated the number of patients with active chronic B hepatitis versus those with inactive HBV infection (i.e., Phase 3 of chronic HBV infection, also known as HBeAg-negative chronic infection, previously termed the “inactive carrier” phase), since it is more likely that those patients, despite carrying HBV infection, were not in possession of the exemption code, due to the absence of active hepatitis. Each center asked for this information, ensuring patients privacy and providing only aggregated numbers. As the study includes only fully anonymised data from investigations, no ethical approval was required. Of note, all patients—Italian or foreign-born—who attend the centres receive disease exemption status if eligible (i.e., chronic hepatitis B or HDV), thanks to Italian public healthcare system policy. To be eligible for exemption, a foreigner must be a resident in Italy. Irregular immigrants are not included in the denominator of our study, as only residents—both Italian and foreign-born—living in Italy in 2024 were considered.

### 2.1 | Sample Size Calculation

A sample of patients with HBV followed in the 30 centres has been evaluated for the possession of the disease-specific exemption (016.070.32). As there are no administrative or literature data to indicate an expected percentage of HBV patients with or without this exemption, the sample size calculation would assume a 50% proportion, that is, that with the greatest uncertainty. Thus, assuming a confidence level of 95% and an expected proportion of 50%, at least 6147 surveys were needed to estimate the true HBV prevalence with a margin of error of 1.25% (48.75%–51.25%).

A similar procedure was also developed for patients with HDV specific exemption (016.070.33). Given the low prevalence of the disease, it is expected that the survey will reach a small number of patients with this condition, and therefore a larger, but consistent, margin of error is set for the sample size calculation. Once again, assuming a 95% confidence level and an expected proportion of 50%, at least 385 surveys were needed to estimate it with a margin of error of 5% (45%–55%).

### 2.2 | Statistical Analysis

After determining the observed proportion ( $p$ ) from the survey, the standard error (SE) was calculated to estimate the variability of  $p$ . Using the SE and the critical  $z$ -value for a 95% confidence level, the confidence interval (CI) for  $p$  was defined. The total population size ( $N$ ) was then estimated by dividing the number of CHB or CHD exemptions in Italy by the observed proportion  $p$ , with limits for  $N$  derived from the CI of  $p$ .

## 3 | Results

The official number of the adult population residing in Italy, generated by the Italian Statistical Institute on 1st January 2024, was 50040752 individuals, of which 4223241 (8.4%) foreigners (ISTAT website, Istituto Nazionale di Statistica, Roma. <https://>

The 30 Gastroenterology, Hepatology and Infectious Diseases Units reported 6775 surveys on CHB and 504 on CHD patients, respectively. The number of surveys evaluated therefore complied with the requirements for the sample size calculation (6147 and 385 subjects, respectively). Moreover, there was an equal distribution of surveys in Northern, Central and Southern Italy, with approximately 2100 HBV and 120 HDV reports for each macro-area. The median number of patients followed per center was 172 (range: 22–740) for CHB, 90 (9–550) for chronic HBV infection, and 17 (2–77) for CHD.

### 3.1 | HBV

Table 1 reports the overall number (67514) of patients having the exemption for CHB in Italy and the rates of HBV exemptions

according to the resident population in any Region. The distribution of CHB exemption across the three macro-areas of Italy (Northern, Central, Southern and major Islands) is reported in Table 2. The survey of 6775 patients with HBV showed that only 60.3% of patients had a disease-specific exemption. Based on this proportion, its standard error ( $SE = 0.006$ ), and the total number of exemptions for HBV ( $n = 67\,514$ ), we estimated that the total number of patients with diagnosed HBV in Italy is approximately 111 960, with a 95% confidence interval ranging from 109 780 to 114 240 (Figure 1). Therefore, the overall HBV prevalence in the adult population changed from 0.13% (based on disease-specific exemption code) to 0.22% (based on the correction factor derived from the surveys). Of the 6775 HBV patients followed in the 30 centres, 2044 (43%) were classified as “inactive carriers”; of these, 54.6% had the specific exemption for HBV. Table 3 summarises HBV exemption distribution according to the surveys: from about 70% of patients in Northern and Central Italy to 35% in Southern Italy and major Islands.

**TABLE 1** | Number of exemptions for chronic hepatitis B in 2024 on adult resident population in Italy and number of foreign residents (data provided by the 21 regions/autonomous provinces).

Italian region	Adult resident population at 1st Jan 2024	Adult foreign resident population (percentages on resident population)	Chronic hepatitis B exemptions (percentages on adult resident population)
Abruzzo	1 086 372	70 371 (6.48%)	1569 (0.14%)
Basilicata	459 402	20 816 (4.53%)	400 (0.10%)
Calabria	1 551 113	81 245 (5.24%)	610 (0.04%)
Campania	4 651 813	218 296 (4.69%)	2760 (0.06%)
Emilia Romagna	3 785 983	448 252 (11.83%)	6210 (0.16%)
Friuli Venezia Giulia	1 028 984	97 404 (9.46%)	1010 (0.10%)
Lazio	4 845 562	527 130 (10.88%)	3419 (0.07%)
Liguria	1 311 310	125 383 (9.56%)	1603 (0.12%)
Lombardia	8 458 530	944 461 (11.17%)	17 928 (0.21%)
Marche	1 268 619	108 831 (8.58%)	1225 (0.10%)
Molise	251 038	11 103 (4.42%)	202 (0.08%)
Piemonte	3 636 043	341 119 (9.36%)	3615 (0.10%)
Provincia Autonoma di Bolzano	438 642	45 649 (10.41%)	531 (0.12%)
Provincia Autonoma di Trento	456 557	37 776 (8.27%)	332 (0.07%)
Puglia	3 305 094	120 116 (3.63%)	5408 (0.16%)
Sardegna	1 371 711	44 677 (3.26%)	1693 (0.12%)
Sicilia	4 020 820	158 422 (3.94%)	3098 (0.08%)
Toscana	3 142 996	346 009 (11.01%)	6179 (0.20%)
Umbria	731 632	72 818 (9.95%)	963 (0.13%)
Valle D'Aosta	104 659	7011 (2.87%)	146 (0.14%)
Veneto	4 123 872	396 352 (9.61%)	8613 (0.21%)
Total	50 040 752	4 223 241 (8.44%)	67 514 (0.13%)

**TABLE 2** | Summary of hepatitis B exemptions by geographical macro-area.

	National	North	Center	South and Islands
Number of adult residents	50 040 752	23 344 580	11 075 181	15 610 991
Number of adult foreign residents (%)	4 223 241 (8.44%)	2 443 407 (10.47%)	1 125 159 (10.16%)	654 675 (4.19%)
Number of patients with HBV exemption	67 514	39 988	13 355	14 171
% HBV exemption on adult resident population	0.135%	0.171%	0.121%	0.091%

Note: North: V. D'Aosta, Veneto, Friuli V.G., Piemonte, Lombardia, Liguria, E. Romagna, P.A. Trento, P.A. Bolzano; Center: Lazio, Abruzzo, Umbria, Marche, Toscana; South and Islands: Sicilia, Sardegna, Calabria, Campania, Puglia, Basilicata, Molise.

### Patients living in Italy with chronic HBV o HDV in 2024

**Official Data from Local Health Authorities (including regularly residing foreign nationals)**

50,040,752 adult residents in Italy on 1<sup>st</sup> January 2024

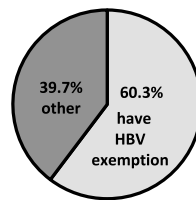
**67,514 exemptions for HBV**  
0.13% of residents

**5,216 exemptions for HDV**  
0.010% of residents

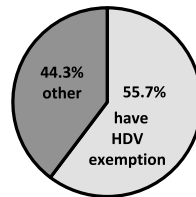
- Only regular residents are eligible for exemption
- Patients who already hold exemptions for other conditions are not granted additional exemptions for HBV or HDV

**Exemption held in 2024, Survey from 30 Centers**

Out of 6,775 HBV patients



Out of 504 HDV patients



**New data on patients with a diagnosed liver condition in Italy**

**111,960 HBV**  
(95%CI: 109,780-114,240)  
0.22% of adult residents

**9,360 HDV**  
(95%CI: 8,690-10,150)  
0.019% of adult residents

**FIGURE 1** | New estimates on diagnosed HBV and HDV patients living in Italy in 2024.

**TABLE 3** | Summary of HBV exemption distribution according to survey.

	National	North	Center	South and Islands
Total number of HBV patients in the surveys	6775	2483	2218	2074
HBV exemption (016.070.32)	4085 (60.3%)	1826 (73.5%)	1526 (68.8%)	733 (35.3%)
Other/no exemption	2690 (39.7%)	657 (26.5%)	692 (31.2%)	1341 (64.7%)

Note: North: V. D'Aosta, Veneto, Friuli V.G., Piemonte, Lombardia, Liguria, E. Romagna, P.A. Trento, P.A. Bolzano; Center: Lazio, Abruzzo, Umbria, Marche, Toscana; South and Islands: Sicilia, Sardegna, Calabria, Campania, Puglia, Basilicata, Molise.

### 3.2 | HDV

Table 4 reports the overall number (5216) of patients having the specific exemption for CHD in Italy and the rates of HDV exemptions, according to the regional residents' population. The distribution of CHD exemption across the three macro-areas of Italy is represented in Tables 5 and 6. The survey of 504 patients with CHD reported 55.7% of patients with a specific exemption for CHD. Based on this proportion, its

standard error (SE=0.022) and the total number of exemptions for HDV in Italy ( $n=5216$ ), we estimated that the total number of patients with diagnosed CHD in Italy is approximately 9360, with a 95% confidence interval ranging from 8690 to 10 150 individuals.

Therefore, the overall HDV prevalence changed from 0.010% (based on specific exemption code) to 0.019% (based on the correction factor derived from the surveys).

**TABLE 4** | Number of exemptions for chronic hepatitis D in 2024 on adult resident population in Italy and number of foreign residents (data provided by the 21 regions/autonomous provinces).

Italian region	Adult resident population at 1st Jan 2024	Adult foreign resident population (percentages on resident population)	Chronic hepatitis D exemptions (percentages on adult resident population)
Abruzzo	1 086 372	70 371 (6.48%)	77 (0.007%)
Basilicata	459 402	20 816 (4.53%)	54 (0.012%)
Calabria	1 551 113	81 245 (5.24%)	84 (0.005%)
Campania	4 651 813	218 296 (4.69%)	842 (0.018%)
Emilia Romagna	3 785 983	448 252 (11.83%)	320 (0.008%)
Friuli Venezia Giulia	1 028 984	97 404 (9.46%)	36 (0.003%)
Lazio	4 845 562	527 130 (10.88%)	226 (0.005%)
Liguria	1 311 310	125 383 (9.56%)	99 (0.008%)
Lombardia	8 458 530	944 461 (11.17%)	621 (0.007%)
Marche	1 268 619	108 831 (8.58%)	123 (0.010%)
Molise	251 038	11 103 (4.42%)	19 (0.008%)
Piemonte	3 636 043	341 119 (9.36%)	541 (0.015%)
Provincia Autonoma di Bolzano	438 642	45 649 (10.41%)	46 (0.010%)
Provincia Autonoma di Trento	456 557	37 776 (8.27%)	34 (0.007%)
Puglia	3 305 094	120 116 (3.63%)	850 (0.026%)
Sardegna	1 371 711	44 677 (3.26%)	98 (0.007%)
Sicilia	4 020 820	158 422 (3.94%)	327 (0.008%)
Toscana	3 142 996	346 009 (11.01%)	468 (0.015%)
Umbria	731 632	72 818 (9.95%)	47 (0.006%)
Valle D'Aosta	104 659	7 011 (2.87%)	14 (0.013%)
Veneto	4 123 872	396 352 (9.61%)	290 (0.007%)
Total	50 040 752	4 223 241 (8.44%)	5 216 (0.010%)

**TABLE 5** | Summary of hepatitis D exemptions by geographical macro-area.

	National	North	Center	South and Islands
Number of adult residents	50 040 752	23 344 580	11 075 181	15 610 991
Number of adult foreign residents (%)	4 223 241 (8.44%)	2 443 407 (10.47%)	1 125 159 (10.16%)	654 675 (4.19%)
Number of patients with HDV exemption	5 216	2 001	941	2 274
% HDV exemption on adult resident population	0.010%	0.0086%	0.0085%	0.0146%

Note: North: V. D'Aosta, Veneto, Friuli V.G., Piemonte, Lombardia, Liguria, E. Romagna, P.A. Trento, P.A. Bolzano; Center: Lazio, Abruzzo, Umbria, Marche, Toscana; South and Islands: Sicilia, Sardegna, Calabria, Campania, Puglia, Basilicata, Molise.

In the survey, centres were asked to report the percentage of HBsAg-positive patients who had been tested for HDV at their facility. Twenty-nine out of the 30 centres (97%) reported that all their HBsAg-positive patients had been tested for delta infection (HDV-Ab). Therefore, assuming that all HBsAg-positive patients have been tested for HDV, that

patients with HDV exemption are HBsAg positive, as well as patients with an HDV exemption do not have a concomitant HBV exemption, we can estimate that the prevalence of HDV among HBsAg-positive individuals in Italy is 7.7% ( $(\text{HDV}/\text{HBsAg} = 9360 \text{ CHD}) / (111\,960 \text{ CHB} + 9360 \text{ HBsAg-positive patients with HDV})$ ).

**TABLE 6** | Summary of HDV exemption distribution according to survey.

	National	North	Center	South and Islands
Total number of HDV patients in the surveys	504	186	199	119
HDV exemption (016.070.33)	281 (55.7%)	84 (45.2%)	127 (63.8%)	70 (58.8%)
Other/no exemption	223 (44.3%)	102 (54.8%)	72 (36.2%)	49 (41.2%)

Note: North: V. D'Aosta, Veneto, Friuli V.G., Piemonte, Lombardia, Liguria, E. Romagna, P.A. Trento, P.A. Bolzano; Center: Lazio, Abruzzo, Umbria, Marche, Toscana; South and Islands: Sicilia, Sardegna, Calabria, Campania, Puglia, Basilicata, Molise.

#### 4 | Discussion

Real-life prevalence data on HBV and HDV in Italy are still quite scarce due to the absence of a national screening program and a national registry for all HBsAg-positive subjects. From an epidemiological point of view, this lack of information is a limitation for the decision-making policy in terms of risk prevention, resource allocation and treatment with current and future antiviral drugs; moreover, it represents an obstacle to understand how far we are from reaching the 2030 WHO goal of HBV elimination.

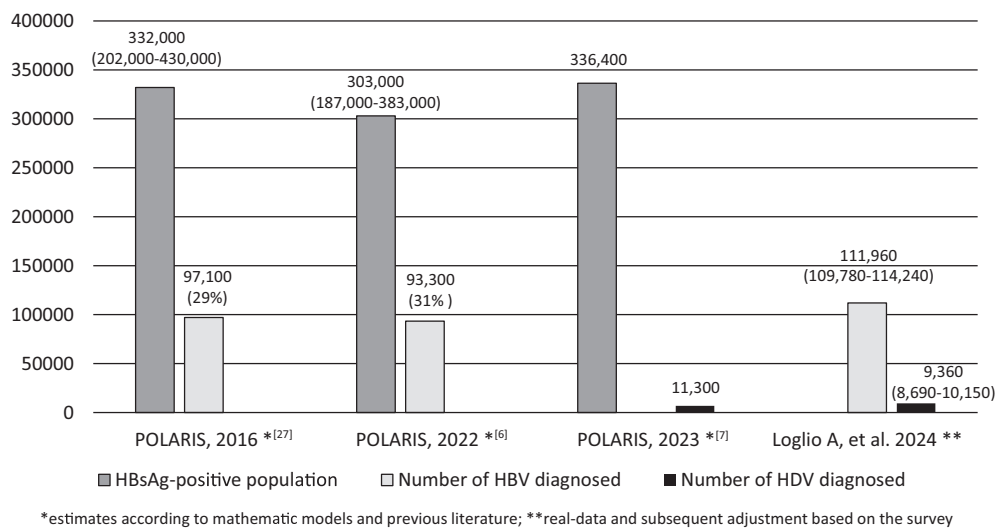
Nowadays, thanks to the HBV vaccination campaign started in 1991 for all newborns and 12-year-olds, all individuals born in Italy under the age of 46 are virtually considered “immune” to HBV. Moreover, thanks to third-generation nucleos(t)ides analogues (NAs) that effectively suppress viral replication, chronic HBV infection has progressively been perceived as less important and impactful on the healthcare system [21, 22]. However, with regard to compulsory HBV vaccination, after about 10 years (2002–2013) in which coverage in Italy remained above the percentage recommended by the WHO (i.e., 95%), in the following years there was a slight decline in coverage, reaching lower levels (94% in the 2019 birth cohort) ([epicentro.iss.it/vaccini/casi-evitabili-epatite-b](https://epicentro.iss.it/vaccini/casi-evitabili-epatite-b); access 28 February 2025). These subjects who have not been vaccinated despite the obligation, together with those outside the age of compulsory vaccination, remained at risk also due to the progressive increase in migration rates of patients coming from endemic countries. These latter subjects, combined with those already infected, represent an important reservoir with a significant impact on the Italian healthcare system, making their precise estimate urgent.

Our study provides the most updated and accurate data on HBV and HDV epidemiology in Italy because we based our analysis on the clear data of the disease-specific exemptions provided by all Local Health Authorities of the 21 Regions/Autonomous regions. We have identified that, in 2024, in Italy there were 111 960 (95% CI: 109 780–114 240) and 9360 (95% CI: 8690–10150) patients with diagnosed CHB and CHD, respectively, with a prevalence of 0.22% and 0.019% of the adult general population, respectively. Our data are lower than the 0.5% reported by the Polaris Observatory group for HBV, because it refers to all HBsAg-positive subjects, while our study only refers to diagnosed patients [6]. Moreover, our results are quite similar to the estimated 3.4% anti-HDV-weighted average prevalence among HBsAg-positive patients, which ultimately means an overall prevalence of 0.017% on the entire Italian population

[7]. However, data reported by the Polaris international study is an estimated prevalence obtained from mathematical models that process data from studies published in different historical periods. Therefore, these estimates integrate data from multiple sources, including seroprevalence studies, epidemiological surveys and health records. Consequently, they tend to have very wide confidence intervals. Conversely, our data is based on real numbers from disease-specific exemptions with a low margin of error, making them more accurate.

Recently, several real-world studies have been published on this topic. A retrospective study among 372 patients hospitalised for SARS-CoV-2 infection in Genoa reported a 0.5% (95% CI: 0.0006–0.02) rate of HBsAg prevalence [23]. Regarding HDV prevalence, a cross-sectional large multicenter study reported anti-HDV positivity rates exceeding 10.2% among patients followed up at tertiary referral centres [18], whereas two other studies in Central and Southern Italy reported lower seroprevalence rates (9% and 8.4%, respectively) [24, 25]. Interestingly, the anti-HDV prevalence slightly increased (10.7%) when the HBsAg reflex test strategy was used, as reported in a single center study conducted in 484 HBsAg-positive patients tested in 2022 [26]. Although not designed with this purpose and assuming that all HBsAg patients followed in the 30 specialised Centres were tested for HDV as per survey results, we can assume a 7.7% prevalence of HDV among HBsAg-positive patients. Of note, this number is similar to the 7% reported in a recent Italian single center long-term study [15]. Compared to the past, when anti-HDV testing rates were lower in Italy, it is likely that the joint recommendations issued in 2023 by SIMIT (Italian Society of Infectious and Tropical Diseases) and AISF (Italian Association for the Study of the Liver), as well as the 2023 EASL guidelines, which advocate testing all HBsAg-positive patients for HDV, have finally been implemented in clinical practice, at least in secondary and tertiary centres.

Finally, only data from individuals regularly residing in Italy are considered. As shown in the updated tables, the percentage of foreign residents in 2024 is higher in the northern regions and some central regions of Italy, and lower in the southern regions, likely due to employment factors. Irregular migrants, who may be infected with HBV or HDV and access healthcare services when needed, are not included in this study, as they do not have either exemption status or residency. In southern Italy, there are fewer foreign residents (Tables 1, 2, 4 and 5), and HDV patients are typically older Italians who often have other exemptions based on older age or lower income, unlike in the northern regions. In the latter, it is more common for individuals—often younger and possibly foreign-born—to have only an exemption



**FIGURE 2** | HBV and HDV epidemiology in Italy according to different periods and study population.

for CHD, without additional exemptions. In northern regions, it is more likely that HBV patients were diagnosed years ago and received the exemption code for the condition, and, as they aged, additional exemptions were not issued.

Although our study represents a considerable improvement over the previously available reports helping all the stakeholders to implement a more effective strategic plan with the aim to eliminate HBV and HDV, it also has some limitations. The major limitation is related to the fact that only diagnosed patients were counted, therefore excluding the hidden situation of those who do not know their HBsAg positivity. However, only a screening strategy in the general population could overcome this shortcoming, knowing that the infection can remain asymptomatic for many years, and early diagnosis before the development of severe complications is the only strategy that may identify infected individuals. Undoubtedly, these strategies would allow the identification of all infected subjects, even if this would be infeasible from an organisational point of view, and possibly screening on older age or risk groups could maximise the cost-effectiveness of the screening itself in interrupting transmission, especially among high-risk populations, and to ensure timely access to care and antiviral treatments. Another possible limitation is that only those who had access to a specialist Centre that issued the exemption were intercepted, and that the percentage of those with or without the exemption was assessed in specialist Centres and not among general practitioners. It is, in fact, known that HBsAg-positive patients, especially if “inactive carriers”, never referred to the hospital usually do not have exemption. Although the survey was not performed in all specialised centres across the Country and excluded some particular subpopulations (prisoners and illegal immigrants) we recognised that the number of involved sites is representative enough of the Italian reality in terms of level, distribution, specialisation and number of patients in care. Finally, since the mathematical estimates from the Polaris study suggested that only one-third of HBsAg-positive patients were diagnosed, we can infer from our study that the real number of HBsAg patients in Italy is approximately 335 880 (329 340–342 720). This number, based on real data rather than

estimates, is actually very similar to the one derived from the Polaris report [303 000 (187 000–383 000)] [6].

In conclusion, in a period where it is crucial to allocate national healthcare resources properly, it is important to rely on real and updated estimates of major liver diseases. Epidemiological studies used to estimate HBV burden in Italy so far suffered from significant biases: most of the studies were performed in the 1990s, and when new data are available, they usually come from small single-centre collections on small-sized groups of patients. This study, based on real-life data of HBV and HDV exemptions in Italy in 2024, provides more realistic prevalence estimates for HBV and HDV, demonstrating a 0.22% and 0.019% prevalence among the overall adult population, respectively (Figure 2 offers a comprehensive overview of both estimated data and real-world evidence related to this topic [6, 7, 27]). This information could help stakeholders to implement more effective strategies for eliminating HBV and HDV, because it could be used as a benchmark for monitoring trends over time and identifying unmet needs, to improve management as well as access to and flow of care.

#### Author Contributions

Conception and design: I.G., M.C., M.B., F.S., M.V., A.L., C.G. Acquisition of data, analysis and interpretation of data: A.L., I.G., M.C., M.B., F.S., C.C., L.C., G.S.-B., L.S., I.Ge, B.P., M.R.B., P.C., A.A., S.D.N., P.T., E.G.G., A.C., D.R., L.Sa, F.R.P., F.M., C.Ca, G.C., P.L., E.D., P.I., A.Ci, F.P.R., A.M.I., G.A.N., N.T., G.N., A.R., M.D., D.S., D.I., A.Cia, A.P., A.F., L.S., V.M., E.C., V.R., G.D., P.C., P.M., C.G., S.F., M.V. Drafting the article: A.L., I.G., M.C., M.B., F.S., M.V. Revising it critically for important intellectual content: A.L., I.G., M.C., M.B., F.S., C.C., L.C., G.S.B., L.S., I.Ge, B.P., M.R.B., P.C., A.A., S.D.N., P.T., E.G.G., A.C., D.R., L.Sa, F.R.P., F.M., C.Ca, G.C., P.L., E.D., P.I., A.Ci, F.P.R., A.M.I., G.A.N., N.T., G.N., A.R., M.D., D.S., D.I., A.Cia, A.P., A.F., L.S., V.M., E.C., V.R., G.D., P.C., P.M., C.G., S.F., M.V. All authors contributed to reviewing and approving the final version of the manuscript.

#### Affiliations

<sup>1</sup>Gastroenterology, Hepatology and Transplantation Division, ASST Papa Giovanni XXIII, Bergamo, Italy | <sup>2</sup>EpaC Ets, Italian Liver Patient

Association, Monza, Italy | <sup>3</sup>Unit of Hepatology and Interventional Ultrasonography, Department of Internal Medicine, OORR Area Stabiese, Gragnano, Italy | <sup>4</sup>Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy | <sup>5</sup>Liver Injury and Transplant Unit, Azienda Ospedaliero-Universitaria Delle Marche, Ancona, Italy | <sup>6</sup>Department of Clinical Medicine and Surgery, University of Napoli Federico II, Naples, Italy | <sup>7</sup>Department of Clinical and Experimental Medicine, University of Pisa and Hepatology Unit, University Hospital of Pisa, Pisa, Italy | <sup>8</sup>Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Milan, Italy | <sup>9</sup>Hepatology and Liver Transplantation Unit, Azienda Ospedaliero Universitaria, University of Udine, Udine, Italy | <sup>10</sup>Gastroenterology Unit, Department of Internal Medicine, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy | <sup>11</sup>Gastroenterology Unit, University Hospital of Modena and Reggio Emilia, University of Modena and Reggio Emilia, Modena, Italy | <sup>12</sup>Clinical Infectious Diseases, Department of System Medicine, Tor Vergata University, Roma, Italy | <sup>13</sup>Liver Unit, CEMAD-Centro Malattie Dell'apparato Digerente, Medicina Interna e Gastroenterologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy | <sup>14</sup>Gastroenterology Unit, Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy | <sup>15</sup>Section of Gastroenterology and Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy | <sup>16</sup>Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy | <sup>17</sup>CRC "A. M. And A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy | <sup>18</sup>Division of Gastroenterology, Center for Autoimmune Liver Diseases, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), IRCCS Fondazione San Gerardo Dei Tintori, Monza, Italy | <sup>19</sup>Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy | <sup>20</sup>Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Padova, Italy | <sup>21</sup>Division of Gastroenterology and Endoscopy, Fondazione IRCCS "Casa Sollievo Della Sofferenza" Hospital, San Giovanni Rotondo, Italy | <sup>22</sup>Gastroenterology Unit, Valduce Hospital, Como, Italy | <sup>23</sup>Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Naples "Federico II", Naples, Italy | <sup>24</sup>Hepatology Unit, Santa Maria Delle Grazie Hospital, Pozzuoli, Italy | <sup>25</sup>Liver Unit, Department of Medicine, University of Verona, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy | <sup>26</sup>Gastroenterology Unit, Città Della Salute e Della Scienza di Torino-Molinette Hospital, Turin, Italy | <sup>27</sup>Department of Hepatology and Transplant Unit, San Camillo Forlanini Hospital, Rome, Italy | <sup>28</sup>Hepatogastroenterology Division, Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples, Italy | <sup>29</sup>Department of Gastroenterology and GI Endoscopy, Arcispedale S. Anna Ferrara, Ferrara, Italy | <sup>30</sup>Infectious Diseases Unit, AORN Sant'anna e San Sebastiano, Caserta, Italy | <sup>31</sup>Liver Unit, Ospedale Evangelico Betania, Naples, Italy | <sup>32</sup>Infectious Diseases Hepatology Unit-National Institute for Infectious Diseases L. Spallanzani – IRCCS (INMI), Rome, Italy | <sup>33</sup>Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy | <sup>34</sup>Unit of Semeiotics, Liver and Alcohol-Related Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy | <sup>35</sup>Division of Internal Medicine, Morgagni-Pierantoni Hospital, Forli, Italy | <sup>36</sup>FROM, Fondazione per la Ricerca Ospedale di Bergamo ETS, Bergamo, Italy | <sup>37</sup>Gastroenterology, Department of Medicine, University of Milano Bicocca, Milan, Italy

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## Conflicts of Interest

Alessandro Loglio: Speaker bureau and received grants from Gilead Sciences and Roche. Laura Schiada: travel grants from Astra Zeneca,

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** liv70336-sup-0001-supinfo.pdf.