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ORIGINAL ARTICLE

Acute Delta Hepatitis in Italy spanning three decades (1991–2019): Evidence for the effectiveness of the hepatitis B vaccination campaign

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Abstract

Updated incidence data of acute Delta virus hepatitis (HDV) are lacking worldwide. Our aim was to evaluate incidence of and risk factors for acute HDV in Italy after the introduction of the compulsory vaccination against hepatitis B virus (HBV) in 1991. Data were obtained from the National Surveillance System of acute viral hepatitis (SEIEVA). Independent predictors of HDV were assessed by logistic-regression analysis. The incidence of acute HDV per 1-million population declined from 3.2 cases in 1987 to 0.04 in 2019, parallel to that of acute HBV per 100,000 from 10.0 to 0.39 cases during the same period. The median age of cases increased from 27 years in the decade 1991–1999 to 44 years in the decade 2010–2019 ($p < .001$). Over the same period, the male/female ratio decreased from 3.8 to 2.1, the proportion of coinfections increased from 55% to 75% ($p = .003$) and that of HBsAg positive acute hepatitis tested for by IgM anti-HDV linearly decreased from 50.1% to 34.1% ($p < .001$). People born abroad accounted for 24.6% of cases in 2004–2010 and 32.1% in 2011–2019. In the period 2010–2019, risky sexual behaviour (O.R. 4.2; 95%CI: 1.4–12.8) was the sole independent predictor of acute HDV; conversely intravenous drug use was no longer associated (O.R. 1.25; 95%CI: 0.15–10.22) with this. In conclusion, HBV vaccination was an effective measure to control acute HDV. Intravenous drug use is no longer an efficient mode of HDV spread. Testing for IgM-anti HDV is a grey area requiring alert. Acute HDV in foreigners should be monitored in the years to come.

KEYWORDS
epidemiology, hepatitis B vaccination, hepatitis delta, surveillance

Abbreviations: CI, confidence interval; HAV, hepatitis A virus; anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, delta virus hepatitis; IDUs, intravenous drug users; IgM, immunoglobuline M; OR, odds ratio; RNA, riboNucleic Acid.

See the SEIEVA collaborating group in Appendix.

1 | INTRODUCTION

Hepatitis Delta infection (HDV), firstly discovered in Italy in 1977[1] is a defective, single stranded RNA virus that requires hepatitis B surface antigen (HBsAg) envelope for assembly and transmission. HDV infection can occur either simultaneously with hepatitis B virus (HBV) infection (coinfection) or in chronic carriers of HBsAg (superinfection). Therefore, the hepatitis B vaccine protects against *de-novo* infection with both viruses, but does not protect chronic hepatitis B virus carriers against superinfection with the hepatitis delta virus.

Initial studies have shown that about 5% of chronic HBV carriers worldwide were also infected with HDV.[2] Recent studies have shown that the prevalence of HDV is twice as high as previous estimations.[3] A more recent study suggests that the latter prevalence is actually a large overestimation, being 4.5% among all HBsAg positive people and 16.4% among those attending Liver units.[4]

In the last 20 years, vaccination against HBV decreased the spread of HDV in industrialized countries. nevertheless HDV is returning to western Europe through immigration from HDV endemic areas.[5] Currently, the infection still has a great medical impact in Central-Western Africa,[6] Asia and South America where the HBV partner is not controlled.[5] Pakistan and Mongolia are the areas with the highest prevalence of HDV infection[7] worldwide. The exact burden of hepatitis Delta in several African and Amazon countries cannot be exactly assessed because of lack of availability of markers for testing subjects for this infection.

In Italy, several studies have shown a decreasing prevalence of Delta infection among chronic HBsAg carriers from 23.4% in 1987[8] to 8.3% in 1997[9]; thereafter it remained stable around 10.0% during the first two decades of the third millennium.[10–13] In the last survey,[13] HDV prevalence among Italians further decreased to 6.4%; instead it was 26.4% among foreigners, outlining that migration flow counterbalances the residual cohort of long-term native infections acquired during the 1970s and 1980s.

Although the prevalence of HBV infection in the world has been extensively studied, updated incidence figures of acute Delta hepatitis are lacking. Data from the national surveillance system of acute viral hepatitis (SEIEVA) have shown a decrease in the incidence of acute HDV in Italy from 3.2 cases per 1,000,000 inhabitants in 1987 to 1.2 cases per 1,000,000 inhabitants in 1992[14] and a further decrease to 0.5 cases per 1,000,000 inhabitants in 2004.[15]

In this paper, we present findings on the incidence of and risk factors for acute HDV infection spanning a period of three decades (1991–2019) in Italy.

2 | MATERIALS AND METHODS

2.1 | Participants

SEIEVA is an enhanced surveillance system coordinated by the Italian National Institute of Health and established in 1985.[16] The number of Italian health Units that voluntarily participate in the system has progressively increased, with 82.4% of the Italian population being under surveillance in 2019.

Case definition of acute hepatitis is based on clinical, biochemical and serological criteria. Clinical and biochemical criteria include the occurrence of an acute illness compatible with hepatitis together with an increase in serum alanine aminotransferase levels (> 10 times the upper limit of normal). Serological criteria, used to distinguish the different types of acute viral hepatitis, are as follows: acute hepatitis A virus (HAV) infection is defined by IgM anti-HAV positivity, regardless of other viral markers; HBV hepatitis is defined by IgM hepatitis B core antibody (anti-HBc) and HBsAg positivity, and IgM anti-HAV negativity; hepatitis C virus (HCV) is defined by IgM anti-HAV and IgM anti-HBc negativity and anti-HCV and/or HCV-RNA positivity (since 1992). Cases of acute hepatitis with HBsAg positivity, IgM anti-HDV positivity and IgM anti-HAV negativity are classified as HDV hepatitis. If IgM anti-HBc is also present, the case is considered HBV-HDV coinfection; if IgM anti-HBc is absent, the case is considered to be HDV superinfection in a chronic HBsAg carrier. Assays to detect viral hepatitis markers are performed in the local laboratories using standard methods.

2.2 | Data collection

Patients who receive a diagnosis of acute viral hepatitis are interviewed by either a public health inspector or a physician of the health local unit using a standard 2-page questionnaire. Information regarding sociodemographic characteristics and exposure to potential risk factors are collected. The interviewer is blinded with respect to the type of viral hepatitis, to avoid bias in the identification of risk factors. The results of assays to detect hepatitis markers were recorded on the questionnaire after the interview; the completed questionnaires were forwarded to the coordinating centre at the Italian National Institute of Health.

2.3 | Incidence rates estimate

Incidence rates are estimated using the new reported cases for each type of hepatitis as the numerator and the population of the local health units participating in the surveillance system at various points of time as denominators. No changes were done in the notification system during the study period. Most patients with symptomatic acute hepatitis are admitted to hospitals and virtually all cases of hepatitis in hospitalized patients are recorded by local health units.

2.4 | Case control study

To estimate the association linking acute HDV cases with characteristics of subjects and potential sources of exposure, cases of hepatitis A reported during the same time period to the SEIEVA were used as controls.

2.5 | Statistical analysis

Differences in proportions were tested by a chi-squared test. A *p*-value <.05 was considered to be significant. The adjusted Odds Ratios (OR) for the association of characteristics of subjects with acute HDV was evaluated by a multiple logistic regression analysis model. In the model sex, age, area of diagnosis, intravenous drug use, household contact with an HBsAg+ chronic carrier and risky sexual exposure were the independent variables and acute HDV was the outcome variable.

3 | RESULTS

3.1 | Incidence rate and characteristics over time

The incidence rate of acute HDV per 1 million of inhabitants declined from 3.2 cases in 1987 to 0.04 cases in 2019. This decrease closely parallels that of acute HBV per 100,000 inhabitants from 10.0 cases in 1987 to 0.39 cases in 2019 (Figure 1).

The main features of Delta hepatitis cases over three decades are reported in Table 1. An impressive shift over time in the proportion of cases by age group is observed: in the decade 1991–1999, acute HDV peaked (89.4%) in subjects ≤40 years of age, while in the decade 2010–2019 it peaked (53.6%) in those 41–60 years old ($p < .001$). Similarly, the median age of cases increased from 27 to 44 years ($p < .001$). The proportion of cases significantly increased from 72.8% to 89.3% in North/Centre ($p = .002$). HDV cases among people born abroad were 24.6% in 2004–2009 and 32.1% in 2010–2019 (*p* value not significant); out of these 23 cases, 16 came from Eastern Europe, 2 from Asia, 3 from Africa and 2 from Central-South America (data no shown). Coinfection cases linearly increased over time from 55% to 75% ($p = .003$). A significant decreasing trend of subjects reporting intravenous drug use ($p < .001$) and household contact with an HBsAg+ carrier ($p = .001$) was observed. Risky sexual exposure remained stable over time. The median peak of ALT value remained stable over 2000 units. The mean days of hospitalization decreased from 20 days in 1991–1999 to 9.5 days in 2010–2019 ($p < .001$). The death rate from acute HDV was 0.3% in 1991–1999 and 3.6% in 2010–2019 ($p < .05$).

3.2 | Comparison by type of infection

In order to provide and update the findings based on larger sample size, comparisons by infection type were made for the period 2000–2019. Coinfections were 2.2 fold (121 vs. 56) more frequent than superinfections. Coinfections predominated in North/Centre (89.3% vs. 75.0%), while the reverse occurred in South/Islands (25.0% vs. 10.7%; $p = .023$).

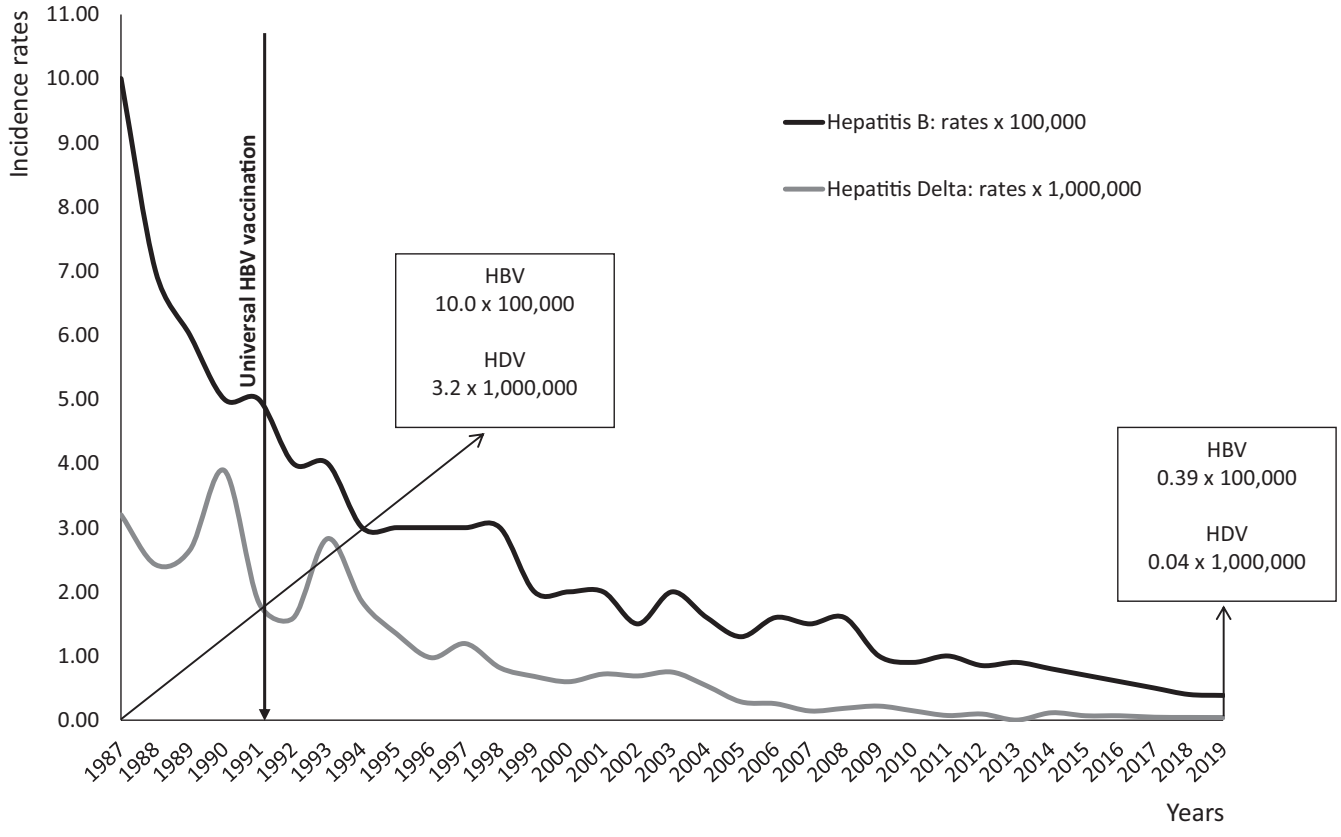

FIGURE 1 Incidence rates of acute hepatitis B (cases × 100,000 inhabitants) and acute Delta hepatitis (cases × 1,000,000 inhabitants) in Italy. SEIEVA 1987–2019

TABLE 1 Main features of acute Delta hepatitis cases in Italy 1991–2019 by decades

Characteristics	1991–1999 *N* = 320 *n* (%)	2000–2009 *N* = 149 *n* (%)	2010–2019 *N* = 28 *n* (%)	*p*-value for trend
Sex ratio (M/F)	3.8	4.1	2.1	.457
Age distribution:				
≤40 year	286 (89.4)	105 (70.5)	11 (39.3)	<.001
41–60 years	27 (8.4)	36 (24.2)	15 (53.6)	
≥61 years	7 (2.2)	8 (5.4)	2 (7.1)	
Median Age (range)	27 (1–80)	35 (7–92)	44 (19–86)	<.001
Area of diagnosis:				
North/Center	233 (72.8)	125 (83.9)	25 (89.3)	.002
South/Islands	87 (27.2)	24(16.1)	3 (10.7)	
Area of birth[a]:				
Italy		43 (75.4)	19 (67.9)	.460
Abroad		14 (24.6)	9 (32.1)	
Coinfections	176 (55.0)	100 (67.1)	21 (75.0)	.003
Superinfections	144 (45.0)	49 (32.9)	7 (25.0)	
I.V. Drug use	163 (45.5)	44 (30.8)	1 (4.2)	<.001
Household contact of an HBsAg+ carrier	36 (16.8)	7 (7.0)	1 (4.8)	.010
Sexual exposure[b]	96 (37.6)	36 (28.6)	8 (33.3)	.158
Icterus	272 (89.2)	124 (87.9)	22 (78.6)	.175
Hospitalization rate	307 (96.9)	132 (91.7)	25 (92.6)	.027
Mean days staying in hospital	20 (1–85)	14 (3–45)	9.5 (3–22)	<.001
Death	1 (0.3)	2 (1.3)	1 (3.6)	.048

Note: SEIEVA.

[a]Information available since 2004.

[b]Two or more sexual partners or lack of condom use in case of occasional sexual intercourse.

The same pattern by area of birth is observed: coinfections were more frequent among Italians (80.7% vs. 57.1), while superinfections were more frequent among people born abroad (42.9% vs. 19.9%; $p = .022$). All the 3 deaths occurred in coinfected cases (Table 2).

3.3 | Comparison by area of birth

Information on area of birth was available since the year 2004. As compared to Italian subjects, foreigners were more likely to be 40 years of age or younger (82.6% vs. 51.6%: $p < .01$); none of them reported intravenous drug use or household contact with an HBsAg+ chronic carrier. No difference was observed by sex, area of diagnosis and sexual exposure (Table 3).

3.4 | Risk factors

The analysis of risk factors was performed by decade. In the last decade (2010–2019), after adjustment for the confounding effect of all the variables considered, age >40 years (OR 3.34; CI 95% = 1.30–8.62) and risky sexual behaviour (OR 4.21; CI 95% = 1.39–12.81) were independently associated with the likelihood of acute HDV; conversely, intravenous drug use (OR 1.25; CI 95% = 0.15–10.22), and household contact with an HBsAg positive carrier (OR 4.67; CI 95% = 0.60–36.35) were no longer associated (Table 4).

3.5 | Testing for HDV

The proportion of HBsAg positive acute hepatitis (including acute HAV and acute HCV cases) tested by IgM anti-HDV was 50.1% in 1991–1999, 37.5% in 2000–2009, and 34.1% in 2010–2019 ($p < .001$) (data not shown). During the period 2010–2019, 1,160 (34.1%) out of 3390 HBsAg positive acute hepatitis cases were tested for HDV, without significant differences in demographic features and reported risk factors of subjects based on IgM anti-HDV testing (Table 5).

4 | DISCUSSION

This is the only worldwide study providing incidence rates of acute HDV over a long period of time in a country. The high proportion of

TABLE 2 Characteristics of acute Delta hepatitis cases by coinfection or superinfection in Italy

Characteristics	Coinfection cases *N* = 121 *n* (%)	Superinfection cases *N* = 56 *n* (%)	*p*-value
Sex ratio (M/F)	3.8	3.3	.700
Age distribution:			
≤40 year	38 (67.9)	78 (64.5)	.825
41–60 years	16 (28.6)	35 (28.9)	
≥61 years	2 (3.6)	8 (6.6)	
Median Age (range)	36 (20–92)	35 (7–77)	.235
Area of diagnosis:			
North/Center	108 (89.3)	42 (75.0)	.023
South/Islands	13 (10.7)	14 (25.0)	
Area of birth[a]:			
Italy	46 (80.7)	16 (57.1)	.022
Abroad	11 (19.3)	12 (42.9)	
Icterus	105 (89.7)	41 (78.9)	.086
Median alanine aminotransferase (range)[b]	2062.5 (347–6503)	2157 (504–8703)	.622
Hospitalization rate	108 (93.1)	49 (89.1)	.382
Mean days staying in hospital	14 (3–45)	12 (3–40)	.396
Death	3 (2.5)	0 (0.0)	.553

Note: SEIEVA 2000–2019.

[a]Information available since 2004.

[b]Information available since 2003.

TABLE 3 Comparison of acute Delta hepatitis in Italy by area of birth. SEIEVA 2004–2019

Characteristics	Italians *N* = 62 *n* (%)	Foreigners *N* = 23 *n* (%)	χ^2 *p*-value
Sex ratio (M/F):	3.1	2.3	.559
Age:			
≤40 years	32 (51.6)	19 (82.6)	.010
≥41 years	30(48.4)	4 (17.4)	
Median Age (range)	40 (19–92)	30 (21–57)	<.001
Area of diagnosis:			
North/Center	52 (83.9)	23 (100.0)	.056
South/Islands	10 (16.1)	0 (0.0)	
I.V. Drug use	16 (27.6)	0 (0.0)	.004
Household contact of an HBsAg+ carrier	3 (6.7)	0 (0.0)	>.999
Sexual exposure[a]	9 (17.0)	7 (33.3)	.208

[a]Two or more sexual partners or lack of condom use in case of occasional sexual intercourse.

the Italian population covered by the surveillance system, having a nationwide extension, provides a valid picture of HDV incidence in the country.

The dramatic decline of acute HDV in Italy, parallel to that of HBV, reflects the impact of universal hepatitis B vaccination on both infections. The vaccination campaign started in Italy in 1991 for all infants 3 months old and for children 12 years old (limited to the first 12 years of campaign for the latter group). Currently all Italian subjects ≤40 year of age are vaccinated against HBV. Immunization of teenagers was an important target because it afforded protection before the onset of risk taking behaviours such as sexual activity and drug use, more likely starting in the teenage years.

The decreased pool of chronic HBsAg carriers deprived HDV of the biological substrate necessary for its spread. Further evidence for the effectiveness of HBV vaccination in preventing

TABLE 5 Frequencies of socio-demographic characteristics and reported risk factors among acute B hepatitis cases according to the performance of testing for IgM anti-HDV assay

Characteristics	HBsAg+ acute hepatitis tested for anti-HDV *N* = 1160 *N* (row %)	HBsAg+ acute hepatitis no tested for anti-HDV *N* = 2230 *N* (row %)	χ^2 *p*-value
Sex:			
Male	856 (33.6)	1,693 (66.4)	.292
Female	296 (35.6)	536 (64.4)	
Age:			
≤40 years	420 (33.9)	818 (66.1)	.834
≥41 years	736 (34.3)	1,411 (65.7)	
Area of diagnosis:			
North/Center	1,069 (34.2)	2,058 (65.8)	.892
South/Islands	91 (34.6)	172 (65.4)	
Area of birth:			
Italy	938 (34.4)	1,791 (65.6)	.702
Abroad	222 (33.6)	439 (66.4)	
Risk Factors			
I.V. Drug use			
No	1,035 (34.1)	1,996 (65.9)	.811
Yes	34 (33.0)	69 (67.0)	
Household contact of an HBsAg+ carrier			
No	779 (34.5)	1,476 (65.5)	.696
Yes	81 (35.8)	145 (64.2)	
Sexual exposure[a]			
No	763 (34.2)	1,469 (65.8)	.791
Yes	290 (33.7)	571 (66.3)	

Note: SEIEVA 2010–2019.

[a]Two or more sexual partners or no condom use in case of occasional intercourse.

acute HDV hepatitis are the overtime reduced proportion of subjects with superinfection (which requires the presence of an HBsAg carrier) from 45% in the period 1991–1999 to 25% in the decade 2010–2019, the higher frequency of superinfection among people born abroad (42.9%) than among Italians (19.9%) and the shift of median age of cases from 27 to 44 years during the same periods of time.

The role played by people born abroad deserves attention. The proportion of acute HDV cases among foreigners increased from 24.6% in 2004–2010 to 32.1% in 2010–2019, occurring more likely than among Italian natives in the age group 0–40 years of age (82.6% vs. 51.6% $p = 0.010$). These findings confirm the results of a recent study among chronic HBsAg carriers showing that people born abroad were six times more likely to be anti-HDV positive and had a younger median age (46 vs. 57 years; $p < .01$) than Italians.[12] Taken together, these findings outline that migratory flow represents a new wave of HDV infection in Italy.

The increase overtime in death rate from acute HDV, despite being statistically significant ($p < .05$), cannot be considered clinically meaningful because of the low number of deaths.

The current minimal spread of HDV in Italy has generated a changing pattern of the main modes of its transmission.

Soon after the discovery of HDV, drug users sharing needles were recognized as the major victims of this infection.[7] The significant contribution of drug users to the burden of HDV infection has been clearly shown in a recent review including data on the prevalence of HDV in the global population. In this study, intravenous drug use was found to be driving the HDV spread in HBsAg positive subjects: HDV prevalence in drug users was more than three times higher than in subjects without any risk factor (37.6% vs. 10.6%).[3] In Taiwan, intravenous drug users (IDUs) have become the most important risk group and a reservoir for HDV infection, even after the implementation of a nationwide vaccination program for 30 years.[17] Conversely, in Italy intravenous drug use is no longer an efficient mode of HDV transmission. This finding may reflect the avoidance of sharing drug use equipment and/or the low proportion of IDUs still susceptible to the virus because they have already been exposed or previously vaccinated against HBV. The key explanation may be the start of HBV vaccination in 1991 even for teenagers, which has generated an early immune cohort

of young adults, who are the people at highest risk of intravenous drug use.

Even household contact of an HBsAg positive subject is no longer associated with acute HDV infection. This finding is in contrast with the corresponding figures of a previous survey among acute HDV in Italy[14] and with past evidence that the virus may be transmitted through person-to-person contact in the family setting.[18] The current low circulation of the virus has likely hampered its force of spread in this setting.

Higher HDV seroprevalence has been reported in individuals with risky sexual behaviour either homosexual or heterosexual.[19] The association, found even in the present survey, might be higher than that detected, because of the use of HAV cases as a control group. The HAV epidemic among homosexuals, which occurred in Italy as well as in several European countries during 2016–2017,[20] may have generated an underestimate of the true association linking sexual exposure and acute HDV.

The progressive declining proportion over time of acute HBsAg positive hepatitis cases tested for IgM anti-HDV raises some concern and generates an underestimate of the true incidence of acute Delta hepatitis. Similar low rates of testing for HDV have been reported even among subjects with chronic HBsAg infection. HDV serology was performed in 35.3% of HBV cases in Southern Italy,[21] in one-third of cases in Spain,[22] and from 7.8%[23] to 42.0%[24] of cases in the United States. These low rates of testing reflect the reduced degree of alertness in the developed world. The perception that hepatitis Delta as a relatively uncommon disease since the late 1990s is the main reason for the diminished tests for specific HDV markers. The results of our surveillance evidence the major weak points in the HDV testing. The majority (67.0%) of drug addicts, who bear the highest medical brunt of Delta infection in the western world, were left unchecked; similar high rates of lack of testing were observed in other risk groups, such as household contacts of an HBsAg carrier (64.3%) and risky sexual behaviour (66.3%). This grey area should be addressed by future studies.

Some potential limits of this study need commenting on. We are aware that the incidence rates of acute HDV herein reported underestimate the true incidence of the infection. SEIEVA, as a surveillance system based on voluntary reporting of acute hepatitis cases, may lack sensitivity because of underreporting, occurrence of subclinical infections and low rate of HDV testing for acute HBsAg positive hepatitis. Because the system was unchanged during the study period, its low sensitivity may affect the point yearly incidence but not the secular incidence trend of HDV infection. However, the low turnover of HDV in the community today may lead to less severe cases than in the past; hence subclinical infections and consequent underreporting may have increased in recent years.

The use of hepatitis A cases as a control group to estimate the strength of association between HDV infection and characteristics of subjects might be a matter of concern. Although HAV cases may differ from HDV cases by age, sex and geographical area, the potential confounding effect of these socio-demographic variables has been removed by the use of multiple logistic regression analysis.

On the other hand, this study is characterized by a further strong point that is worth underlining. In case-control studies, comparability between cases and control is the crucial point and it is more important than representativeness. In this study, hepatitis A and hepatitis Delta cases both were subjects identified by the same surveillance system and thus exposed to the same selective factors, if any.

In conclusion, this study evidenced a current minimal incidence of acute HDV hepatitis in Italy with a shift of cases toward an older age, reflecting the impact of the vaccination campaign against-HBV. Intravenous drug use and household contact with an HBsAg positive carrier are no longer efficient modes of HDV transmission. The low proportion of acute HBsAg positive hepatitis tested for anti-Delta needs more alert, particularly among subjects belonging to risk groups. The growing proportion of acute HDV cases among foreigners requires monitoring in the years to come.

These features, even if generated in a given country, may be of interest even for other developed countries.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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APPENDIX

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