

# Changing Epidemiology of HCV and HBV Infections in Northern Italy

## *A Survey in the General Population*

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**Aim:** To evaluate the hepatitis B virus (HBV) and the hepatitis C virus (HCV) epidemiology in the general population of Northern Italy, a cohort of 965 subjects, all residents (including 47 immigrants), were anonymously tested for HBV and HCV infections.

**Material and Methods:** Serum samples were assayed for anti-HCV and anti-HBV markers by enzyme-linked immunosorbent assay and for HCV-RNA by polymerase chain reaction, and the positive cases were genotyped. HBsAg-positive cases were assayed for HBeAg/anti-HBe, whereas HBsAg negatives were tested for both anti-HBc and anti-HBs.

**Results:** The overall prevalence of anti-HCV was 2.6%, with a bimodal distribution characterized by the highest prevalence (12%) in subjects over 75 years old. None of the subjects under 25 years old was anti-HCV positive. Anti-HCV positivity was similar in males and females (2.4% vs. 2.7%). HCV-RNA was positive in 40% of cases and genotype 1 was the most common. The HBsAg prevalence was 1%, with a significant difference according to country of origin (0.8% in Italian subjects vs. 6.4% in immigrants,  $P = 0.01$ ). HBsAg positivity increased significantly with age ( $R^2 = 0.57$ ,  $P < 0.02$ ). The overall percentages for the prevalence of isolated anti-HBs, anti-HBs+/anti-HBc+, and isolated anti-HBc were 23.8%, 8.4%, and 4.2%, respectively.

**Conclusions:** Our study provides a new picture of HCV and HBV epidemiology in Northern Italy, with these features: (1) a cohort effect showing a reduction of HCV infection in the

elderly, possible due to age-related mortality; (2) an unchanged overall prevalence of HBV infection, despite continuing immigration of subjects from endemic countries.

**Key Words:** HBV, HCV, epidemiology, general population, immigrants

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It has been estimated that about 123 million people have hepatitis C virus (HCV) worldwide and the burden of hepatitis B virus (HBV) infection is even higher, with high rates of morbidity and mortality.<sup>1,2</sup> In Italy, the prevalence of HCV infection in the general population ranges from 2% in the north to 4% in the south, and increases with age.<sup>3–7</sup> This figure was also confirmed in elderly people from our geographical area.<sup>8</sup> As for the HBV infection, in Italy the introduction of mass vaccination campaigns for risk groups, in the beginning of the 80s, and for all newborn babies from 1991 onwards, has significantly reduced the incidence of acute hepatitis B in Italy in the last decade.<sup>9,10</sup> Similar figures have been reported for the incidence of acute hepatitis C.<sup>11</sup> Accordingly, a progressive decline in the prevalence of both B and C infections has been reported in Southern Italy.<sup>12</sup> It must be stressed, however, that the last decade has seen a sizable influx of immigrants from Africa and the eastern countries ([www.demo.istat.it](http://www.demo.istat.it)), where the prevalence of hepatitis B is particularly high. Whether the immigration can have an impact on hepatitis virus epidemiology in Italy remains to be seen.

Knowing the prevalence of HBV and HCV in the general population is crucial for anticipating their future impact on the health system and for ensuring an adequate allocation of financial resources. The aim of this study was to evaluate the epidemiology of HBV and HCV infection in the general population in the north east of Italy.

## MATERIALS AND METHODS

### Study Population

In Vicenza, an industrialized city of Northeast Italy with 108,281 inhabitants, a broken sewer pipe allowed

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water from the local river to enter the aqueduct in 2002. Overall, 670 (22%) of the 3006 individuals (all living in the same quarter), who were exposed to the contaminated water, reported gastrointestinal symptoms. Among the measures taken to deal with the situation was the local authorities' decision to vaccinate the population exposed against hepatitis A. A month later, a blood test for hepatitis A virus (HAV) was offered to the subjects who had been vaccinated.<sup>13</sup> In all, 965 subjects (452 men and 513 women, mean age  $42.1 \pm 22.2$  y) agreed to be tested. This cohort represented 0.9% of the total population of the city and was statistically representative of the population living in Vicenza in term of sex and age distribution. Information about country of origin, age, and sex were collected from each subject and were provided by the local health authorities. Of the 965 (452 men and 513 women) subjects tested, 918 were Italians and 47 (4.9%) were immigrants (mean age  $27.7 \pm 15.5$  y) from the following countries: Eastern Europe 59.6%; Western Europe 2.1%; sub-Saharan Africa 27.7%; Asia 4.2%; and South America 6.4%. No cases of hepatitis A were recorded at the HAV test or in the follow-up. After HAV testing, the serum samples were divided into 2 aliquots and stored at  $-30^{\circ}\text{C}$  for future analyses. They were subsequently and anonymously, in accordance with the guidelines of the local health authorities, tested for HCV and HBV markers. All serum samples were assayed for anti-HCV and anti-HBV markers by ELISA (Bio-Rad, Marnes-la-Coquette, France). HBsAg-positive samples were tested for HBeAg/anti-HBe, whereas HBsAg-negative samples were tested for anti-HBc and anti-HBs (Bio-Rad, Marnes-la-Coquette France). The anti-HCV positive cases were then tested for HCV-RNA and were HCV genotyped. HCV-RNA was detected using a nested reverse-transcription polymerase chain reaction with primers in the 5' noncoding region with a detection limit of 100 copies/mL.<sup>14</sup> HCV genotypes were tested by nested polymerase chain reaction using genotype-specific primers of the core region<sup>15</sup> and were classified according to the system proposed by Simmonds et al.<sup>16</sup>

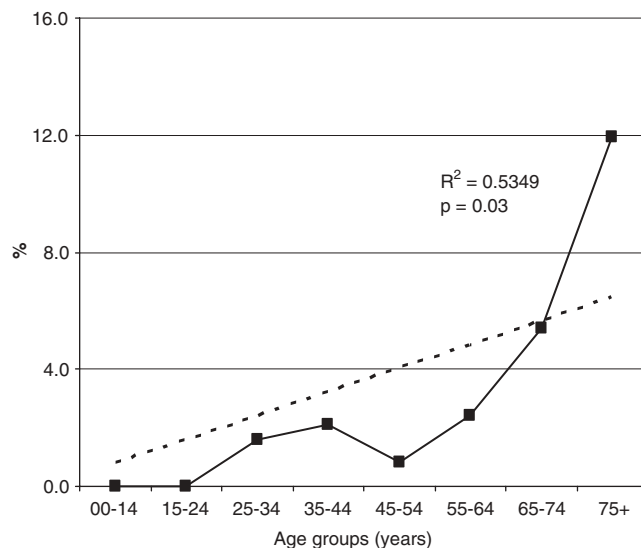
### Statistical Analyses

Data analyses were performed using the  $\chi^2$  test (uncorrected and Fisher exact test) and Student *t* test, as appropriate. A *P* value of  $\leq 0.05$  was considered significant and an odds ratio with a 95% confidence interval was calculated. Regression analyses were performed between age and markers of infection. For comparing Italians with immigrants, to eliminate age and sex confounding factors, we extracted a randomized sample of Italians (as a control group) and immigrants (as cases) in the ratio 1:2. The analyses were carried out using the Statistical Package for the Social Sciences (SPSS, Chicago, IL).

## RESULTS

### HCV Study

A total of 25 individuals (2.6%) were anti-HCV positive; 11/452 (2.4%) were men, and 14/513 (2.7%)



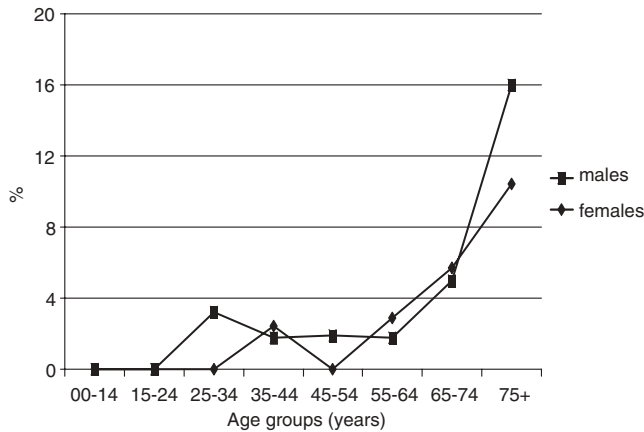
**FIGURE 1.** Prevalence of anti-HCV according to the age groups.

were women (*P* = NS). None of the immigrants were anti-HCV positive. Overall, the prevalence of anti-HCV increased from 0% among subjects under 24 to 12% among those aged 75 years and above ( $R^2 = 0.53$ , *P* = 0.03), in a bimodal manner. In particular, the seroprevalence of anti-HCV showed a first peak among subjects aged from 25 to 44 years, followed by a sharp increase in subjects aged over 50 years (Fig. 1). Concerning the first peak, an interesting difference was observed between men and women; in the male group, the highest prevalence was seen in subjects aged 25 to 34; whereas in the female group it was among the 35 to 44 years old (Fig. 2). Moreover, anti-HCV prevalence was higher in men than in women in the over-75-years age bracket (16.0% vs. 10.4%, *P* = NS) (Fig. 2). Of the 25 anti-HCV positive individuals, 10 (40%) were HCV-RNA positive. They were all over 60 years old and 60% of them were men. The most frequently detected genotype was 1b (70%); 2a was detected in 1 subject (10%); 2 genotypes coexisted in 2 individuals (1b/2b and 1a/2c, respectively). No sex-related differences were found in the distribution of genotypes.

### HBV Study

Ten individuals (1%) were HBsAg-positive, with a trend directly correlating with age ( $R^2 = 0.57$ , *P* = 0.02) and the highest prevalence (2.2%) was reached in the subjects aged 65 to 74 years old (Fig. 3). No significant differences emerged between men and women [5/452 (1.1%) vs. 5/513 (0.9%), respectively, *P* = NS]. Among the HBsAg-positive cases, only 1 was found to be HBeAg-positive.

The overall prevalence of isolated anti-HBs was 23.8%. Anti-HBs was found in 63.4% of the individuals who were under 14 years of age, and in 78.7% of those between 15 and 24; whereas, the prevalence of anti-HBs was 7%, 4%, and 9% in the 25 to 34, 35 to 44, and 45 to

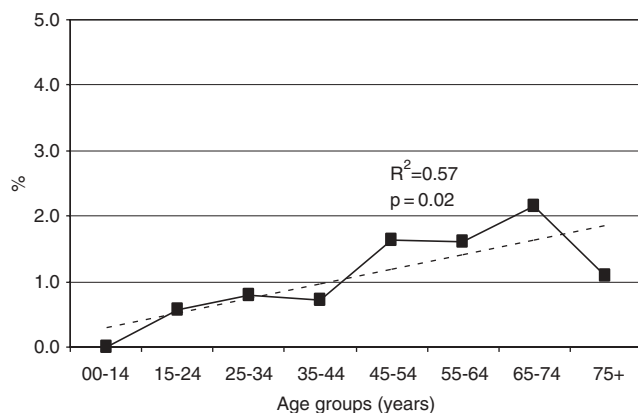


**FIGURE 2.** Prevalence of anti-HCV according to the age groups and sex.

54 year-old age groups, respectively. In the older groups, the prevalence of isolated anti-HBs was below 3% (Fig. 4).

Overall, the prevalence of anti-HBs in the subjects with over 24 years was 110/707 (15.6%). Markers of past exposure, anti-HBs+anti-HBc and isolated anti-HBc, showed a prevalence of 8.4% and 4%, respectively; both markers increased progressively with age, reaching 17.8% and 16%, respectively, in subjects over 65 years (Fig. 4). None of the subjects tested were found to be coinfectd with both HBV and HCV.

The prevalence of both the HCV and HBV serum markers was analyzed in the subgroup of immigrants (47 subjects, 4.9% of the overall sample), the majority of whom came from Eastern Europe (59.6%) and Africa (27.7%); 2 from Asia (4.2%); and 3 from South America (6.4%). The mean age of the immigrants was 27.7 ± 15 years. None of them was anti-HCV positive. The distribution of serum markers among the immigrants and Italians is shown in Table 1. A comparison was drawn between the immigrants and the whole sample of Italians, and also with a 1:2 sample of immigrants and Italians, matched for sex and age (n = 94). The prevalence of HBsAg and of any marker of HBV was



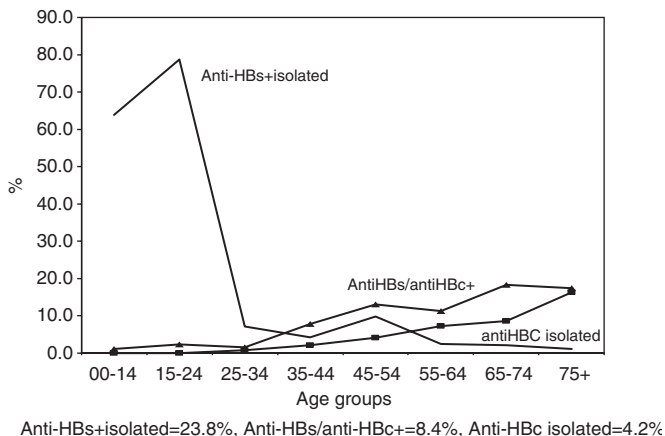
**FIGURE 3.** Prevalence of HBsAg according to the age groups.

significantly higher in immigrants than in native Italians. No significant difference emerged regarding the prevalence of anti-HBs alone in the 3 groups.

### DISCUSSION

Our study was performed in a selected quarter of Vicenza, a city in the northeast of Italy, situated in an area with a high socioeconomic level, where the unemployment rate is much lower than the national average (2.5% vs. 8%). The economy is generally based on small industries, so the influx of immigrants is high. Immigrants in the entire Vicenza province constitute 9.1% of the resident population. According to official statistics, the number of immigrants, recorded in Vicenza city when the samples were collected, was 4926. This represented 4.5% of the whole population ([www.provincia.vicenza.it/economia/statistica/files/cifrepopstranieriarea.pdf](http://www.provincia.vicenza.it/economia/statistica/files/cifrepopstranieriarea.pdf)). Overall, we have anonymously tested for HBV and HCV viruses in 965 subjects: 918 (95%) were Italians and 47 (4.9%) immigrants. The cohort of subjects we studied reflects the real distribution of the population of the city as a whole and one of the strengths of our findings is that the screening was done for other reasons, as described above. The picture obtained represents the real epidemiology of hepatitis viruses in Vicenza. The main limitations of our study, on the other hand, are the lack of information on the risk factors for acquiring blood-borne transmitted hepatitis viruses and the lack of clinical information (particularly liver function test levels).

The results of our study show a 2.6% prevalence of anti-HCV and a 1% prevalence of HBsAg in the general population. These rates indicate an appreciable change in the epidemiology of these infections in recent years. The overall prevalence of anti-HCV (2.6%) is lower than that in previous studies—even in those conducted in Northern Italy, which has a lower prevalence of HCV than the south. The majority of the studies on the general population in Italy were performed in the 90s.<sup>3-7</sup> In the most important study performed in Southern Italy and published in 1997 by Guadagnino et al,<sup>6</sup> the overall prevalence of anti-HCV was 12.6%, ranging from 1.3% in people under 30 years of age to 33% in those over 60 years of age. The prevalence of anti-HCV recorded in our study is even lower than in the Dionysos Study performed between 1991 and 1993 in 2 different towns in Northern Italy, which recorded an overall prevalence of 3.2% and with a different age distribution.<sup>4</sup> One of the relevant findings is the bimodal trend of the anti-HCV curve. As expected, the highest peak is in the over-75-year age group, with an anti-HCV of 12%. A much smaller peak (2.1%) occurs in the age group 35 to 44 years, and it may reflect other modes of transmission, that is, intravenous drug abuse and new risk factors of transmission (tattoos and piercing), typical of the younger generation. This is consistent with the data reported by Mariano et al,<sup>17</sup> who demonstrated that, for young Italian people, even after excluding intravenous drug users and receivers of blood transfusions, the population attributable risk for beauty



**FIGURE 4.** Prevalence of HBV antibodies in Vicenza general population.

treatments represents 11.5% of all acute HCV cases. The high peak in the geriatric population is still lower than that among general population in all previous studies. This may reflect a cohort effect due to an epidemic of HCV infection after the Second World War, as has already been reported<sup>3-7,12,18,19</sup> (Table 2). The prevalence we found in the geriatric population was comparable with that reported by Bellentani et al,<sup>4</sup> and by Campello et al.<sup>20</sup> However, in the first study the oldest age group considered was 56 to 65 years, and, in the latter, the group of subjects over 65 years old was underrepresented (48 subjects), as stated by the same authors. Overall, no significant differences were found between men and women (the prevalence of anti-HCV was 2.4% and 2.7%, respectively), but in the over-75-year age group, the prevalence of anti-HCV was much higher in men (16%) than in women (10.4%). Although not statistically significant, this finding is in contrast to those in with all the previous studies in the general population, which had found that the prevalence of HCV was higher among women in the older age groups<sup>4-6</sup>; but it is perfectly in line with a case-control study published by Chiaramonte et al<sup>18</sup> on chronically HCV-infected patients in the same geographical area. In this latter study, anti-HCV in patients over 60 was significantly associated with prior use of nondisposable syringes and with a history of tuberculosis treated in closed communities; both these risk factors were more common in males than in female

patients. The higher trend in men could also reflect a cohort effect in the past, when there was a higher rate of chronic HCV infection in men. However, locally acting risk factors cannot be excluded when explaining the differences found in different studies.

No HCV infection was found in subjects under 25 years of age, suggesting that exposure to the virus is rare in this age group. This finding was confirmed by other reports also.<sup>4,21,22</sup> Notably, no particular HCV reduction programme was adopted in Vicenza before the study was carried out. The absence of HCV infection in young people may be explained by the low rate of vertical and intrafamilial transmission,<sup>23,24</sup> but the decreasing prevalence of HCV in younger individuals can also be attributed to a general improvement in their socioeconomic status and to the impact of AIDS campaigns and HCV screening in blood donors. As mentioned above, the high socioeconomic level of Vicenza may represent “in se” another possible explanation for the low prevalence of infection.

We found a 40% prevalence of HCV-RNA in anti-HCV positive subjects. This is much lower than the 75% reported by Guadagnino et al<sup>6</sup> in Southern Italy, or the 72% and 71.8% reported by Bellentani et al<sup>4</sup> and Campello et al,<sup>20</sup> respectively, in Northern Italy. Our rate of HCV-RNA is much more similar, however, to those reported in recent studies, which has put the range between 53% and 63%.<sup>5,25,26</sup> All the viremic subjects were 60 years or older. The low proportion of HCV-RNA positive subjects in our study may have been due either to the spontaneous clearance of the virus or to the effect of antiviral therapy. However, the lack of this clinical information does not allow us to get conclusive information about this point. Another possible explanation could be that storing the serum samples for a relatively long period before testing may have decreased the rate of HCV-RNA positivity in them.

Because the majority of the studies on the anti-HCV positive cases were over 60, in the years to come the majority of the patients (in our area at least) will be much older than who have been treated seen in our wards and clinics so far. This reinforces the hypothesis that the prevalence of HCV will drop significantly over the next 2 decades. In industrialized countries, the residual risk of HCV transmission by transfusion is very low; so future new cases of HCV infection could be limited to intravenous drug abusers, and to people acquiring the

**TABLE 1.** Comparison Between Prevalence of HCV and HBV Markers in Vicenza (Northern Italy) Residents and Immigrant Residents (Case-control Evaluation)

	Immigrants (N = 47) (%)	Italians (N = 918) (%)	P	OR (95% CI)	Cohort (n = 94) (%)	P**	OR (95% CI)
Anti-HCV	0.0	2.7	NS	—	1.1	NS	—
HBsAg	6.4	0.8	0.01	8.88 (1.75-39.9)	0.0	0.03	—
HBV any markers	25.5	13	0.01	2.33 (1.10-4.76)	1.1	0.0001	31.89 (4.04-80.7)
Anti-HBs alone	31.9	23.4	NS	1.53 (0.78-3.00)	40.4	NS	0.69 (0.31-1.54)

Random cohort matched by sex and age (ratio 1:2); any HBV markers: at least one of HBV markers (excluding isolated anti-HBs). CI indicates confidence intervals; OR, odd ratio, calculated comparing Italians versus immigrants.

**TABLE 2.** Prevalence of Anti-HCV in General Population in Italy

Authors	Place Where the Study was Performed	Year of the Study	Subjects Studied		Overall Prevalence of Anti-HCV (%)	Prevalence of Anti-HCV in Old Subjects Years (%)
			N	Age Range (y)		
Bellentani et al <sup>4</sup>	Campogalliano (Modena) and Cormons (Gorizia)	1991-1993	6917	12-65	3.2	56-65 115/1384 (8.3%)
Stroffolini et al <sup>19</sup>	Valentano (Viterbo)	1994	681	6-70	8.4	> 60 16/88 (18.4%)
Guadagnino et al <sup>6</sup>	Sarsale (Catanzaro)	1996	1352	7-91	12.6	≥ 60 123/372 (33.1%)
Maio et al <sup>5</sup>	Buonalbergo (Napoli)	1997	488	6-87	16.2	≥ 60 53/126 (42.1%)
Di Stefano et al <sup>7</sup>	Camporeale (Palermo)	1999-2000	721	10-90	10.4	≥ 60 48/141 (34%)
Pendino et al <sup>12</sup>	Cittanova (Reggio Calabria)	2002-2003	1645	12-95	6.5	≥ 70 (16.7%)*
Fabris et al (present study)	Vicenza	2002	965	0-90	2.6	> 60 18/219 (8.2%) > 70 12/120 (10.0%)

\*Number of anti-HCV positive subjects and the total number of subjects in this subgroup have not been reported in the manuscript.

infection from beauty treatments, injection injuries, or from other marginal risk factors, such as nosocomial and vertical transmission.

As far as HBV infection is concerned, the study showed a 1% HBsAg seroprevalence, confirming previous results in the general population, in which the HBsAg prevalence has ranged from 0.2%<sup>5</sup> to 1.3%.<sup>4,19</sup> We also found a low prevalence of anti-HBs/anti-HBc, indicating a limited circulation of HBV in our geographical area. These results reflect epidemiologic changes in HBV in recent times, confirmed by the marked reduction in the incidence of new acute events in the last 20 years. In fact, the National Surveillance System (SEIEVA) indicated that, in 2004, the incidence of acute hepatitis B has dropped from 12 to 1.4 per 100,000 population ([www.epicentro.iss.it/problemi/epatite/seieva.htm](http://www.epicentro.iss.it/problemi/epatite/seieva.htm)). Such a different epidemiologic picture has been explained by the better sanitation standards, the effects of HIV and hepatitis prevention campaigns, and the mass vaccination campaigns introduced in 1991.<sup>9</sup> The effect of the vaccination campaigns is demonstrated by the high rate of anti-HBs prevalence observed in young adults. Given the good compliance with vaccination schemes in our region, new cases of HBV infection can confidently be predicted to further decrease in years to come.

The prevalence of HBV infection that we found in the immigrants (6.4%) was significantly higher than that in Italian residents, but was lower than expected.<sup>27</sup> This may be explained by the small sample size and the relatively low proportion of immigrants from sub-Saharan Africa.

Immigrants from underdeveloped countries should be considered as a risk group for HBV infection, owing to the high rate of circulation of the infection (6.4%), but the risk of transmission to the general population is restricted to the subjects not yet covered by active immunization.

It is consequently essential to maintain the ongoing vaccination policy (HBV vaccination in all newborn and in adults belonging to particular risk groups, such as homosexuals and intravenous drug users).

In conclusion, our study has provided a new picture of HCV and HBV epidemiology in Northern Italy: (1) in particular, a cohort effect, showing a reduction in HCV infection in old age is possibly due to age-related mortality; (2) an unchanged overall prevalence of HBV infection is seen in the general population of Northern Italy, despite the continuing immigration of subjects from endemic countries. The latter aspect reinforces, once again, the idea that it is crucial to maintain the ongoing prevention strategy.

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