Progress Report

The changing pattern of hepatitis B virus infection over the past three decades in Italy

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Abstract

By the end of 1970s, Italy was a country at medium endemic level of hepatitis B virus infection, with wide geographical differences; intrafamilial transmission was the major mode by which infection spread; hepatitis B e antigen positivity and hepatitis Delta positivity were frequently detected in hepatitis B surface antigen chronic carriers; a high proportion of subjects with chronic liver disease resulted as hepatitis B surface antigen positive. Three decades apart, the picture was completely changed, as documented by several surveys. Nowadays, Italy is a country at very low endemic level of hepatitis B, without geographical differences; the infection is mostly sexually transmitted; hepatitis B e antigen positivity and hepatitis Delta positivity are rarely detected in hepatitis B surfaces antigen chronic carriers; a low proportion of subjects with chronic liver disease result hepatitis B surface antigen positive. These important changes may be due to both non-specific (i.e. improvement in socio-demographic features) and specific (i.e. a comprehensive vaccination program against hepatitis B) preventive measures.

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The epidemiology of hepatitis B virus (HBV) infection has widely changed over the past three decades in Italy. Several factors have played a role: improvement in socio-economic conditions, better standard of hygiene, reduced family size, educational campaign against HIV infection and finally the introduction, in the year 1991, of the compulsory vaccination by law against HBV for all newborns starting at 3 months of age and for all 12-year-old subjects.

The changes have been documented by seroepidemiological surveys in the general population, by multicentric studies recruiting patients hospitalised for chronic liver diseases, by the national surveillance system for specific acute viral hepatitis (SEIEVA) and by the national statistic of deaths (ISTAT).

Finding are herein reported and commented.

First, to better understand the dynamics of the epidemiology of HBV infection, it should be pointed out how the pool of chronic hepatitis B surface antigen (HBsAg) carriers gathers in a given population. The risk of becoming an HBsAg chronic carrier after acute HBV infection is inversely related to the age at primary infection slowing down from early childhood to late adolescence [1]. With the availability of serological tests for IgM anti-HBc (the reliable marker for differentiating recent from past HBV infection), it has been firmly shown that acute clinical hepatitis B in adults rarely (<1%) leads to the chronic carrier state, unless some degree of immune deficiency exists [2]. These figures suggest that the pool of chronic HBsAg carriers is likely to have arisen from childhood infections.

By the end of the 1970s, the main characteristics of HBV infection in Italy were:

- a medium endemic level (prevalence of HBsAg in the general population >2%);
- wide geographical differences in the prevalence of chronic HBsAg carriers (much higher in southern regions);
- high proportion of HBcAg positivity among HBsAg positive subjects;
Delta infection frequently detected in HBsAg-positive subjects; intrafamilial transmission as the major mode of infection spread; high proportion of HBsAg positivity among subjects with chronic liver diseases.

A seroepidemiological survey performed among the general population of 3–19-year-olds in five Italian regions during the second half of 1980s showed important changes[3]. Subjects were selected by a systematic cluster sampling procedure from those attending kindergartens, primary, junior and high schools, respectively. Out of 7800 selected people, 7405 (95%) accepted to participate. To date, this is the largest study ever performed in these age groups among the general population in a western country. The sampling procedure adopted and the very high participation rate assured validity to the observed findings. The results were unexpected: the overall prevalence of HBsAg was as low as 0.6%, that of any HBV marker was only 2.8%.

These findings indicated that in Italy exposure to HBV infection at a young age was low, suggesting a shift towards a low level of endemicity. Moreover, because the pool of chronic HBsAg carriers is likely to have arisen from childhood infection, the observed 0.6% rate of HBsAg prevalence represented the true future picture of HBsAg prevalence in the Italian population some years later even in absence of any potential vaccination programme against HBV.

The decline was well documented in the city of Naples: in 1988, the prevalence of HBsAg among children 7–12-year-old attending a primary school was 0.8%, a rate much lower than the 2.1% observed in the same school and in the same age-groups in 1980[4]. Similarly, comparing the results of survey conducted on national sample of recruits in 1981 and in 1990, the HBsAg prevalence dropped from 3.4% to 1.6% in 9 years[5].

The more limited exposure to HBV infection was a consequence of the considerable improvement of socio-economic conditions and decreased family size over the previous years. The importance of socio-demographic features in the spread of HBV infection was clearly demonstrated in the survey involving children and teenagers[3]: subjects who’s father had less than 6 years of schooling had a 2.3-fold risk (95% CI 1.5–3.4), while those belonging to a household of six or more under one roof had a 1.7-fold risk (95% CI 1.2–2.4) of previous exposure to HBV infection. Therefore, changes of these features over the course of time may have affected the dynamics of HBV infection.

Surveys performed in the second half of the 1990s among all age groups of the general population in some towns of different Italian regions further confirmed the decline of HBV infection. In all these surveys, initially planned to assess the prevalence of hepatitis C virus (HCV) infection, subjects were selected from the census by a random sampling procedure. The results showed in each area studied an HBsAg prevalence lower than 1% [6–9], without geographical differences (Table 1).

Findings from a recent survey in 79 Italian hospitals scattered all over the country were in agreement with results in the general population. Among nearly 10,000 subjects observed for chronic liver diseases during a 6-month period of enrolment, only 10% were HBsAg-positive (13.4% considering the presence of other risk factors such as anti-HCV positivity or risky alcohol intake)[10] (Fig. 1). Low HBsAg prevalence was documented both in chronic hepatitis (12.2%)[11] and in liver cirrhosis cases (13.0%) [12]. The changing pattern of HBV-related cases over time was clearly documented in chronic hepatitis cases, as multicentric studies had been performed in the past on this topic. HBsAg prevalence was 60.7% among patients enrolled from 1976 to 1981[13], 44% in 1980[4], 34.2% in 1989[4] and 12.2% in 2001 [11] (Table 2). Comparing HBV-related cases in the period 1975–1985[15] with those in 2001 [11], two additional changes can be observed: a decrease in HBeAg-positive cases (from 58.4% to 16.6%) and in anti-Delta-positive cases (from 14.6% to 7.0%).

Even among subjects with hepatocellular carcinoma (HCC) the prevalence of HBsAg was found to be as low as 11.5% [16], a rate much lower than the 30.5% observed prevalence lower than 1% [6–9], without geographical differences (Table 1).

Table 1 Prevalence of HBsAg in the general population in some Italian towns

<table>
<thead>
<tr>
<th>Town (region)</th>
<th>No. of subjects</th>
<th>HBsAg prevalence (%)</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valenzano (Lazio)</td>
<td>681</td>
<td>1.0</td>
<td>1994</td>
<td>[6]</td>
</tr>
<tr>
<td>Serafe (Calabria)</td>
<td>1352</td>
<td>0.8</td>
<td>1996</td>
<td>[7]</td>
</tr>
<tr>
<td>Buonarbergo (Campania)</td>
<td>488</td>
<td>0.2</td>
<td>1997</td>
<td>[8]</td>
</tr>
<tr>
<td>Camporeale (Sicilia)</td>
<td>721</td>
<td>0.7</td>
<td>1999</td>
<td>[9]</td>
</tr>
</tbody>
</table>

Table 2 Temporal trend of HBsAg prevalence among chronic hepatitis cases in Italy

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of subjects</th>
<th>HBsAg prevalence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>1134</td>
<td>61.0</td>
<td>[13]</td>
</tr>
<tr>
<td>1980</td>
<td>501</td>
<td>44.0</td>
<td>[14]</td>
</tr>
<tr>
<td>1989</td>
<td>608</td>
<td>34.2</td>
<td>[14]</td>
</tr>
<tr>
<td>2001</td>
<td>6210</td>
<td>12.2</td>
<td>[13]</td>
</tr>
</tbody>
</table>
Cirrhosis mortality has strongly declined from 1969 to 2000 (Fig. 2), mostly reflecting the fall in HBV-related cases. However, with the recent advances in supporting therapies of non-HCC complications of cirrhosis, such as prevention and treatment of variceal bleeding and management of ascites, the life expectancy of subjects with cirrhosis has increased. As a consequence these subjects are at greater risk to die because of HCC (Fig. 2) or because of other causes [18]. In any case, the increased time trend mortality rate for HCC may only partially explain the much higher decreased time trend mortality rate for liver cirrhosis.

The spread of human immunodeficiency virus (HIV) infection in Italy from the half of 1980s has affected to some extent the dynamics of HBV infection. Undoubtedly, the educational campaign against HIV infection strongly suggesting the use of condom for occasional sexual intercourses and the avoidance of sharing glass syringes for intravenous drug users has contributed to the reduction of HBV spread. On the other hand, acute HBV infection in HIV-positive subjects more likely leads to chronic HBsAg carrier state than in HIV-negative subjects.

In 1991, the HB vaccine became compulsory by law in Italy for 3-month-old infants and for 12-year-old subjects. The comprehensive immunisation programme further contributed to the downward trend of acute hepatitis B incidence, particularly in subjects 15–24-year-old [19]. However, the fall was more evident before than after the introduction of compulsory vaccination against hepatitis B (Fig. 3), reflecting the improved socio-economic and sanitary conditions in the country. In a national survey of 113,230 teenagers during the period 1993–1994, the HB vaccine coverage was as good as 93.6%; wide geographical differences were observed: 97.9% in the North, 96.6% in the Centre, but only 65.1% in the South [20]. However, a better (83.3%) HB vaccine coverage...
was found among teenagers in an ad hoc survey carried out in the city of Naples, the largest metropolitan area in the South of Italy [21].

Data from the national surveillance system specific for acute viral hepatitis (SEIEV A) provide information on the modes of transmission of hepatitis viruses in Italy. Nowadays, acute hepatitis B in Italy is mostly a sexually transmitted disease, as more than half of the cases report two or more sexual partners in the period of 6 months before onset of the disease (Fig. 4). The efficiency of HBV transmission is the strongest for being a household contact with a positive HBsAg carrier (OR 5.7; 95% CI 3.8–8.6) (Table 3). It should be emphasised that nearly one-third of the cases occurring in households of positive HBsAg carriers were aware of the carrier condition of the cohabitants. Despite the fact that the vaccine is strongly recommended and offered free of charge in this high-risk category, these subjects were not vaccinated [19]. These subjects should be made aware of the risk of HBV transmission in the family setting and be actively offered the vaccine.

The important role of beauty treatment in the spread of parenterally transmitted hepatitis viruses in Italy has been recently shown [22]. The estimates of the population attributable risk indicate that nearly 15% of all acute HBV cases (17.4% in males) occurring in 15–55-year-old subjects not exposed to intravenous drug use or blood transfusion in Italy are due to beauty treatments [22]. Because beauty treatments are becoming increasingly common in the western world and are practised across many social and age groups, it may be expected that the proportion of cases of acute HBV due to such exposure will increase in the years to come.

All the above reported findings show a completely different picture of HBV infection three decades apart. At the beginning of the year 2000 the main characteristics of HBV infection in Italy were:

- a low endemic level (prevalence of HBsAg in the general population <2%);
- no geographical differences in HBsAg prevalence;
- low proportion of HBeAg positivity among HBsAg-positive subjects;
- Delta infection rarely detected in HBsAg-positive subjects;
- sexual transmission as main source of exposure;
- low proportion of HBsAg positivity among subjects with chronic liver diseases.

Further changes may occur in the future because of the increasing immigration flow of people from developing world, where the HBsAg prevalence rate is generally higher. Immigrants from such areas may promote the spread of HBV,

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Table 3

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR adjusted</th>
<th>95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>4.4</td>
<td>1.4–14.1</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>2.4</td>
<td>1.7–3.3</td>
</tr>
<tr>
<td>Other parenteral exposure</td>
<td>2.0</td>
<td>1.7–2.4</td>
</tr>
<tr>
<td>Dental therapy</td>
<td>1.4</td>
<td>1.2–1.7</td>
</tr>
<tr>
<td>I.V. drug use</td>
<td>4.6</td>
<td>3.1–6.8</td>
</tr>
<tr>
<td>Household HBsAg+ carrier</td>
<td>5.7</td>
<td>3.8–8.6</td>
</tr>
<tr>
<td>≥2 sexual partners</td>
<td>1.6</td>
<td>1.3–2.0</td>
</tr>
</tbody>
</table>

HAV cases have been used as control group. SEIEVA 2000–2003.

a Adjusted for age, sex, educational level, area of residence and for all listed variables.
b Piercing, tattoo, manicure, pedicure.
c Age >14 years.
especially by sexual route. Particular attention should be addressed to pregnant women from the developing world. A recent survey [23] has shown that they have much higher HBsAg carrier rate (5.9%) than Italian pregnant women; but, unfortunately, they are twofold less likely than Italian pregnant women to adhere to HBsAg screening, mostly for lack of interpretation or translation facilities. On the other hand, once they are screened, 100% of offspring of those resulted HBsAg-positive are given appropriate immunisation. Because pregnant women represent the reservoir in the natural cycle of HBsAg carriage (Fig. 5), efforts should be attempted to increase compliance with antenatal HBsAg screening in women coming from developing countries. Otherwise the reduction of the size of the carrier reservoir and the control of HBV spread may not be achieved.

In conclusion, the epidemiology of HBV infection has completely changed in Italy over the last three decades. The interaction of specific (i.e. the comprehensive vaccination program) with non-specific (i.e. improvement in socioeconomic features) preventive measures has caused the dramatic fall observed. The lesson from the Italian experience may represent a model for other countries.

Conflict of interest statement
None declared.

References


